Clinical trial results:
A 104 week clinical trial comparing long term glycaemic control of insulin degludec/liraglutide (IDegLira) versus insulin glargine therapy in subjects with type 2 diabetes mellitus

Summary

EudraCT number	2014-005639-15
Trial protocol	GB HU SK CZ NO PL IT
Global end of trial date	03 October 2018

Results information

Result version number	v1 (current)
This version publication date	19 October 2019
First version publication date	19 October 2019

Trial information

Trial identification

Sponsor protocol code	NN9068-4228

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02501161
WHO universal trial number (UTN)	U1111-1165-3914

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, +1 8668677178, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, +1 8668677178, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2018
Global end of trial reached?	Yes
Global end of trial date	03 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare long-term glycaemic control of IDegLira vs. IGlar in insulin naïve subjects with type 2 diabetes mellitus (T2DM) inadequately controlled with oral anti-diabetic drug OAD(s).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice, including archiving of essential documents and FDA 21 CFR 312.120.

Background therapy:

All subjects were continued on pre-trial OAD(s) except dipeptidyl peptidase-4 inhibitors (DPP-4i) and glinides, which were discontinued at randomisation. Pre-trial OADs allowed were: biguanides, sulphonylurea, glinides, pioglitazone, and DPP4-inhibitors, though glinides and DPP4-inhibitors were not allowed as monotherapy or in combination. When trial product (IDegLira or IGlar) was added to sulphonylurea therapy, a reduction in the dose of sulphonylurea was to be considered based on glycaemic response.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	08 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 78
Country: Number of subjects enrolled	Czech Republic: 30
Country: Number of subjects enrolled	United Kingdom: 70
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	India: 92
Country: Number of subjects enrolled	Israel: 50
Country: Number of subjects enrolled	Italy: 60
Country: Number of subjects enrolled	Mexico: 104
Country: Number of subjects enrolled	Norway: 32
Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Russian Federation: 81
Country: Number of subjects enrolled	Slovakia: 42
Country: Number of subjects enrolled	Turkey: 63
Country: Number of subjects enrolled	United States: 152
Country: Number of subjects enrolled	South Africa: 89

Worldwide total number of subjects	1012
EEA total number of subjects	303

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	780
From 65 to 84 years	232
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 130 sites in Argentina (4), Czech Republic (4), Hungary (5), India (11), Israel (8), Italy (7), Mexico (4), Norway (7), Poland (3), Russian Federation (8), Slovakia (5), South Africa (10), Turkey (8), United Kingdom (9) and United States (37).

Pre-assignment

Screening details:

Trial design: Subjects were randomised in a 1:1 manner to receive either IDegLira or IGlar as an adjunct to oral anti-diabetic drugs (OADs).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Insulin degludec/liraglutide

Arm description:

Subjects received subcutaneous (s.c.) injection of Insulin degludec/liraglutide (IDegLira) once daily in dose escalation manner up to 104 weeks.

Arm type	Experimental
Investigational medicinal product name	Insulin degludec liraglutide
Investigational medicinal product code	
Other name	Xultophy®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received s.c. injection of IDegLira once daily up to 104 weeks. Subjects received 10 dose steps (10 units IDeg/0.36 milligrams [mg] liraglutide) initially. The dose was then escalated twice weekly until the fasting plasma glucose (FPG) target between 4.0−5.0 millimoles per liter (mmol/L) (72−90 milligrams per deciliter [mg/dL]) was reached. The maximum dose was 50 dose steps (50 units IDeg/1.8 mg liraglutide).

Arm title	Insulin glargine

Arm description:

Subjects received s.c. injection of Insulin glargine (IGlar) once daily up to 104 weeks.

Arm type	Active comparator
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	
Other name	Lantus®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received s.c. injection of IGlar once daily up to 104 weeks. Subjects received 10 units of IGlar initially. The dose was then escalated twice weekly until the FPG target between 4.0−5.0 mmol/L (72−90 mg/dL) was reached.

Number of subjects in period 1	Insulin degludec/liraglutide	Insulin glargine
Started	506	506
Exposed	506	504
Completed	484	481
Not completed	22	25
Consent withdrawn by subject	10	15
Adverse event, non-fatal	2	6
Unspecified	3	-
Lost to follow-up	7	4

Baseline characteristics

Reporting groups	
Reporting group title	Insulin degludec/liraglutide
Reporting group description:	
Subjects received subcutaneous (s.c.) injection of Insulin degludec/liraglutide (IDegLira) once daily in dose escalation manner up to 104 weeks.	
Reporting group title	Insulin glargine
Reporting group description:	
Subjects received s.c. injection of Insulin glargine (IGlar) once daily up to 104 weeks.	

Reporting group values	Insulin degludec/liraglutide	Insulin glargine	Total
Number of subjects	506	506	1012
Age categorical Units: Subjects			
18<= to <40 years	30	29	59
40<= to <65 years	363	358	721
65<= to <75 years	102	107	209
75<= years	11	12	23
Age Continuous Units: Years			
arithmetic mean	56.8	56.4	
standard deviation	± 10.0	± 10.1	-
Sex: Female, Male Units: Subjects			
Female	226	231	457
Male	280	275	555

End points

End points reporting groups

Reporting group title	Insulin degludec/liraglutide
Reporting group description:	
Subjects received subcutaneous (s.c.) injection of Insulin degludec/liraglutide (IDegLira) once daily in dose escalation manner up to 104 weeks.	

Reporting group title	Insulin glargine
Reporting group description:	
Subjects received s.c. injection of Insulin glargine (IGlar) once daily up to 104 weeks.	

Primary: Time from randomisation to inadequate glycaemic control and need for treatment intensification, defined as a glycosylated haemoglobin (HbA1c) of ≥7.0% at 2 consecutive visits from week 26, including week 26 if HbA1c was ≥7% at week 12

End point title	Time from randomisation to inadequate glycaemic control and need for treatment intensification, defined as a glycosylated haemoglobin (HbA1c) of ≥7.0% at 2 consecutive visits from week 26, including week 26 if HbA1c was ≥7% at week 12

End point description:

Inadequate glycaemic control and need for treatment intensification was defined as HbA1c of 7.0% or greater at 2 consecutive visits from week 26, including week 26 if HbA1c≥7% at week 12. Time was analysed using stratified log-rank test where treatment, baseline HbA1c group and previous OAD treatment were included as strata in the model. The variable "baseline HbA1c group" was a dichotomised baseline HbA1c variable with 2 categories: HbA1c<8.5% or HbA1c≥8.5% and "previous OAD treatment" was a categorical variable with 2 categories: SU±OAD(s) (SU users) or OAD(s) (Non-SU users). 25%, median (50%) and 75% percentiles for the cumulative distribution function were obtained from Kaplan-Meier survival function. Results are based on full analysis set (FAS) consisted of all randomised subjects. Number of subjects analyzed = number of subjects with available data. 99999 indicates the estimated data was not available as the proportion was not reached within study period.

End point type	Primary

End point timeframe:

Up to 104 weeks

End point values	Insulin degludec/liraglutide	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	506	506		
Units: Weeks				
median (inter-quartile range (Q1-Q3))				
Baseline HbA1c <8.5% + Non-SU users	99999 (104.0 to 99999)	104.3 (38.1 to 99999)		
Baseline HbA1c <8.5% + SU users	106.7 (89.9 to 99999)	90.3 (26.4 to 105.1)		
Baseline HbA1c >=8.5% + Non-SU users	99999 (39.7 to 99999)	64.6 (26.1 to 105.1)		
Baseline HbA1c >=8.5% + SU users	104.0 (26.4 to 99999)	26.6 (26.1 to 91.1)		

Statistical analyses

Statistical analysis title	Insulin degludec/liraglutide vs Insulin glargine

Statistical analysis description:

Test for no treatment difference was based on using a stratified log-rank test where treatment, baseline HbA1c group and pre-trial OAD treatment group were included as strata in the model.

Comparison groups	Insulin degludec/liraglutide v Insulin glargine
Number of subjects included in analysis	1012
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Stratified log-rank test

Secondary: Time from randomisation to an HbA1c > 6.5% at 2 consecutive visits

End point title	Time from randomisation to an HbA1c > 6.5% at 2 consecutive visits

End point description:

Time to HbA1c>6.5% at 2 consecutive visits is defined as time from randomization to HbA1c>6.5% at 2 consecutive visits from week 26 including week 26 if HbA1c>6.5% at week 12. Time was analysed using stratified log-rank test where treatment, baseline HbA1c group and previous OAD treatment were included as strata in the model. The variable "baseline HbA1c group" was a dichotomised baseline HbA1c variable with 2 categories: HbA1c<8.5% or HbA1c≥8.5% and the variable "previous OAD treatment" was a categorical variable with 2 categories: SU±OAD(s) (SU users) or OAD(s) (Non-SU users). 25%, median (50%) and 75% percentiles for the cumulative distribution function were obtained from the Kaplan-Meier survival function. Results are based on FAS consisted of all randomised subjects. Number of subjects analyzed = number of subjects with available data. 99999 indicates the estimated data was not available as the proportion was not reached within study period.

End point type	Secondary

End point timeframe:

From week 26

End point values	Insulin degludec/liraglutide	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	506	506		
Units: Weeks				
median (inter-quartile range (Q1-Q3))				
Baseline HbA1c <8.5% + Non-SU users	99999 (52.1 to 99999)	64.1 (26.1 to 104.3)		
Baseline HbA1c <8.5% + SU users	90.1 (27.0 to 99999)	26.6 (26.1 to 89.9)		
Baseline HbA1c >=8.5% + Non-SU users	64.1 (26.1 to 99999)	26.6 (26.1 to 90.1)		

Baseline HbA1c >=8.5% + SU users	52.1 (26.1 to 104.1)	26.1 (26.1 to 38.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in HbA1c

End point title	Change from baseline in HbA1c

End point description:

Change in HbA1c from baseline (week 0) to week 26 is presented. Results are based on the FAS which consisted of all randomised subjects. Number of subjects analysed = number of subjects with available data.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Insulin degludec/liraglutide	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	481	466		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)	-1.99 (± 1.14)	-1.69 (± 1.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in body weight

End point title	Change from baseline in body weight

End point description:

Change in body weight from baseline (week 0) to week 26 is presented. Results are based on the FAS which consisted of all randomised subjects. Number of subjects analysed = number of subjects with available data.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Insulin degludec/liraglutide	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	481	466		
Units: Kilogram (kg)				
arithmetic mean (standard deviation)				
Week 26	0.5 (± 3.3)	2.2 (± 3.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in fasting plasma glucose (FPG)

End point title	Change from baseline in fasting plasma glucose (FPG)

End point description:

Change in FPG from baseline (week 0) at week 26 is presented. Results are based on the FAS which consisted of all randomised subjects. Number of subjects analysed = number of subjects with available data.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Insulin degludec/liraglutide	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	461		
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Week 26	-3.97 (± 3.06)	-3.79 (± 3.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in 9-point Self-measured plasma glucose (SMPG) profile (individual points in the profile)

End point title	Change from baseline in 9-point Self-measured plasma glucose (SMPG) profile (individual points in the profile)

End point description:

Subjects measured plasma glucose values using the blood glucose meter at 9 time points: before breakfast, 90 min after start of breakfast, before lunch, 90 minutes after start of lunch, before dinner, 90 min after start of dinner, bedtime, at 4:00 am and before breakfast the following day. SMPG-9-point profile (individual points in the profile) at week 26 is presented. Results are based on the FAS which consisted of all randomised subjects. Number of subjects analysed = number of subjects with available data.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Insulin degludec/liraglutide	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	506	506		
Units: mmol/L				
arithmetic mean (standard deviation)				
Before breakfast (n=437,413)	5.59 (± 1.57)	5.58 (± 1.58)		
90 minutes after breakfast (n=425,409)	8.34 (± 2.62)	8.76 (± 2.68)		
Before lunch (n=435,407)	6.03 (± 2.00)	6.43 (± 2.24)		
90 minutes after lunch (n=433,407)	8.02 (± 2.32)	8.79 (± 2.64)		
Before dinner (n=434,408)	6.67 (± 2.26)	6.91 (± 2.35)		
90 minutes after dinner (n=428,406)	8.31 (± 2.47)	9.10 (± 2.70)		
Bedtime (n=423,398)	7.48 (± 2.42)	8.13 (± 2.68)		
At 4:00 a.m. (n=419,398)	5.72 (± 1.55)	5.91 (± 1.99)		
Before breakfast the following day (n=433,403)	5.53 (± 1.37)	5.56 (± 1.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin dose

End point title	Insulin dose

End point description:

Insulin dose after 26 weeks of treatment is presented. Results are based on the safety analysis set (SAS) included all participants receiving at least 1 dose of the investigational product (IDegLira) or comparator (IGlar). Number of subjects analysed = number of subjects with available data.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Insulin degludec/liraglutide	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	449		
Units: Units				
arithmetic mean (standard deviation)				
Week 26	34.6 (± 13.4)	48.6 (± 28.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Responder (yes/no): HbA1c < 7.0%

End point title	Responder (yes/no): HbA1c < 7.0%

End point description:

Percentage of subjects who achieved HbA1c < 7.0% at week 26 and week 104 is presented. Results are based on the FAS which consisted of all randomised subjects. Number of subjects analysed = number of subjects with available data.

End point type	Secondary

End point timeframe:

After 26 and 104 weeks of treatment

End point values	Insulin degludec/liraglutide	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	506	506		
Units: Percentage of subjects				
number (not applicable)				
Week 26: Yes	78.7	55.7		
Week 26: No	21.3	44.3		
Week 104: Yes	55.5	28.5		
Week 104: No	44.5	71.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Responder (yes/no): HbA1c ≤ 6.5%

End point title	Responder (yes/no): HbA1c ≤ 6.5%

End point description:

Percentage of subjects who achieved HbA1c ≤ 6.5% at week 26 and week 104 is presented. Results are based on the FAS which consisted of all randomised subjects. Number of subjects analysed = number of subjects with available data.

End point type	Secondary

End point timeframe:

After 26 and 104 weeks of treatment

End point values	Insulin degludec/liraglutide	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	506	506		
Units: Percentage of subjects				
number (not applicable)				
Week 26: Yes	63.6	35.4		
Week 26: No	36.4	64.6		
Week 104: Yes	43.3	21.7		
Week 104: No	56.7	78.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes

End point title	Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes

End point description:

Severe or BG confirmed symptomatic hypoglycaemia is defined as an episode that is severe according to the ADA classification or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. Hypoglycaemic episodes were defined as treatment-emergent if the onset of the episode occurred on or after the first day of trial product administration, and no later than 7 calendar days after the last day on trial product. Number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 and 104 weeks of treatment is presented. Results are based on the SAS included all participants receiving at least 1 dose of the investigational product (IDegLira) or comparator (IGlar). Number of subjects analysed = number of subjects with available data.

End point type	Secondary

End point timeframe:

During 26 and 104 weeks of treatment

End point values	Insulin degludec/liraglutide	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	506	504		
Units: Episodes				
During 26 weeks of treatment	143	261		
During 104 weeks of treatment	319	642		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Weeks 0-104 (treatment period) + 7 days follow-up-1 + 30 days follow-up-2

Adverse event reporting additional description:

All presented AEs are TEAEs. A TEAE was defined as an event that had onset date on or after the first day of exposure to trial product and no later than 7 days after the last day of trial product administration. Results are based on the SAS which included all subjects receiving at least one dose of trial product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Insulin degludec/liraglutide

Reporting group description:

Subjects received s.c. injection of IDegLira once daily up to 104 weeks. The maximum dose was 50 dose steps (50 units IDeg/1.8 mg liraglutide).

Reporting group title	Insulin glargine

Reporting group description:

Subjects received s.c. injection of IGlar once daily up to 104 weeks.

Serious adverse events	Insulin degludec/liraglutide	Insulin glargine	
Total subjects affected by serious adverse events			
subjects affected / exposed	60 / 506 (11.86%)	43 / 504 (8.53%)	
number of deaths (all causes)	2	5	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 506 (0.00%)	2 / 504 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign hepatic neoplasm			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer metastatic			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			

subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 506 (0.40%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	3 / 506 (0.59%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	2 / 506 (0.40%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasoconstriction			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary arterial stent insertion			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Percutaneous coronary intervention			

subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tympanoplasty			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 506 (0.40%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 506 (0.20%)	2 / 504 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 506 (0.20%)	2 / 504 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung perforation			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Electrocardiogram abnormal			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 506 (0.59%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gun shot wound			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ilium fracture			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nerve injury			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial reocclusion			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory failure			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory fume inhalation disorder			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	2 / 506 (0.40%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 506 (0.20%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stab wound			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			

subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	3 / 506 (0.59%)	2 / 504 (0.40%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina unstable			
subjects affected / exposed	4 / 506 (0.79%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 506 (0.00%)	2 / 504 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 506 (0.00%)	2 / 504 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiac failure			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			

subjects affected / exposed	1 / 506 (0.20%)	2 / 504 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 506 (0.00%)	2 / 504 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 506 (0.40%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			

subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 506 (0.40%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			

subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular degeneration			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroduodenitis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	3 / 506 (0.59%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	2 / 506 (0.40%)	3 / 504 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	2 / 506 (0.40%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 506 (0.20%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal pain			
subjects affected / exposed	2 / 506 (0.40%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	4 / 506 (0.79%)	3 / 504 (0.60%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryocystitis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 506 (0.59%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	2 / 506 (0.40%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 506 (0.20%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 506 (0.00%)	2 / 504 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	0 / 506 (0.00%)	1 / 504 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 506 (0.20%)	0 / 504 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Insulin degludec/liraglutide	Insulin glargine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	206 / 506 (40.71%)	156 / 504 (30.95%)	
Nervous system disorders			
Headache			
subjects affected / exposed	58 / 506 (11.46%)	45 / 504 (8.93%)	
occurrences (all)	98	89	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	39 / 506 (7.71%)	12 / 504 (2.38%)	
occurrences (all)	52	14	
Nausea			
subjects affected / exposed	31 / 506 (6.13%)	8 / 504 (1.59%)	
occurrences (all)	39	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	24 / 506 (4.74%)	29 / 504 (5.75%)	
occurrences (all)	27	36	
Back pain			
subjects affected / exposed	25 / 506 (4.94%)	27 / 504 (5.36%)	
occurrences (all)	30	40	
Infections and infestations			
Influenza			
subjects affected / exposed	36 / 506 (7.11%)	28 / 504 (5.56%)	
occurrences (all)	46	38	
Nasopharyngitis			

subjects affected / exposed	57 / 506 (11.26%)	44 / 504 (8.73%)	
occurrences (all)	71	53	
Upper respiratory tract infection			
subjects affected / exposed	28 / 506 (5.53%)	36 / 504 (7.14%)	
occurrences (all)	30	44	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2016	1) Clarification of inclusion criteria, concerning OAD treatments allowed in the trial. 2) Low FPG should be reported as Clinical Laboratory Adverse Event not AE. 3) New process of drug accountability. 4)Visit specific diary covering visit 13-14
01 February 2017	1) Minimum mandatory safety text updated. 2) Clarifications concerning distribution of human insulin results, storage of abnormal haematology samples and MACE definition. 3) '(x)' removed from pregnancy test in flowchart.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported