Clinical trial results:
Effect and safety of liraglutide 3.0 mg in subjects with overweight or obesity and type 2 diabetes mellitus treated with basal insulin

Summary

EudraCT number	2015-005619-33
Trial protocol	DE IT
Global end of trial date	25 September 2018

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019

Trial information

Trial identification

Sponsor protocol code	NN8022-4272

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02963922
WHO universal trial number (UTN)	U1111-1177-4903

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, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, 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	04 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 September 2018
Global end of trial reached?	Yes
Global end of trial date	25 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm superiority of liraglutide 3.0 mg vs. placebo, as an adjunct to a reduced-calorie diet and increased physical activity, on weight loss effectiveness in subjects with overweight or obesity and T2DM treated with a basal insulin and up to 2 OAD medications (metformin, glitazone, SGLT-2 inhibitor, alpha glucosidase inhibitor, glinide or sulphonylurea).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, ICH GCP and FDA 21 CFR 312.120. In addition, the 21 Code of Federal Regulations, parts 312, 50, and 56 were followed.

Background therapy:

The following products were regarded as non-investigational medicinal products (non-IMPs) in this trial: Oral antidiabetic drugs (OADs) and insulin. OADs: Subjects were allowed to take the following OADs throughout the treatment period: Any approved and marketed metformin, glitazone, SGLT-2 inhibitor, alpha glucosidase inhibitor, glinide or sulphonylurea product or combination products.

Evidence for comparator:

Not applicable

Actual start date of recruitment	06 February 2017
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	Canada: 44
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Italy: 31
Country: Number of subjects enrolled	Mexico: 44
Country: Number of subjects enrolled	Turkey: 51
Country: Number of subjects enrolled	United States: 152
Worldwide total number of subjects	396
EEA total number of subjects	83

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)	293
From 65 to 84 years	103
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 53 sites in Canada (7), Germany (7), Israel (6), Italy (4), Mexico (2), Turkey (7) and United States (20).

Pre-assignment

Screening details:

Subjects were randomised in a 1:1 manner to receive either liraglutide or placebo as an adjunct to a reduced-calorie diet and increased physical activity as part of a comprehensive lifestyle intervention program.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Liraglutide and placebo were visually identical in order to ensure double-blinding in the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Liraglutide 3.0 mg

Arm description:

Subjects received liraglutide subcutaneous injections for 56 weeks. The starting dose was 0.6 milligrams (mg) for the first week. The dose was then escalated in weekly increments of 0.6 mg until the maintenance dose of 3.0 mg was reached after 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	Saxenda®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide was administered once daily by subcutaneous injection irrespective of the timing of meals for 56 weeks. Subjects received 0.6 mg liraglutide during the first week. The dose was escalated in weekly increments of 0.6 mg until the maintenance dose of 3.0 mg was reached after 4 weeks.

Arm title	Placebo

Arm description:

Subjects received matching placebo once daily by subcutaneous injection for 56 weeks. Dose escalation for placebo matched that of liraglutide.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo was administered once daily by subcutaneous injection irrespective of the timing of meals for 56 weeks. Dose escalation for placebo matched that of liraglutide.

Number of subjects in period 1	Liraglutide 3.0 mg	Placebo
Started	198	198
Completed	166	168
Not completed	32	30
Adverse event, non-fatal	15	6
Protocol deviation	6	6
Unclassified	8	14
Lost to follow-up	2	3
Lack of efficacy	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Liraglutide 3.0 mg
Reporting group description:	
Subjects received liraglutide subcutaneous injections for 56 weeks. The starting dose was 0.6 milligrams (mg) for the first week. The dose was then escalated in weekly increments of 0.6 mg until the maintenance dose of 3.0 mg was reached after 4 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo once daily by subcutaneous injection for 56 weeks. Dose escalation for placebo matched that of liraglutide.	

Reporting group values	Liraglutide 3.0 mg	Placebo	Total
Number of subjects	198	198	396
Age Categorical			
Units: Subjects			
Adults (18- <65 years)	151	142	293
From 65- <75 years	42	48	90
75- <85 years	5	8	13
Age Continuous			
Units: years			
arithmetic mean	55.9	57.6	
standard deviation	± 11.3	± 10.4	-
Gender Categorical			
Units: Subjects			
Female	108	99	207
Male	90	99	189
Body weight			
Units: Kilograms (kg)			
arithmetic mean	100.6	98.9	
standard deviation	± 20.8	± 19.9	-

End points

End points reporting groups

Reporting group title	Liraglutide 3.0 mg

Reporting group description:

Subjects received liraglutide subcutaneous injections for 56 weeks. The starting dose was 0.6 milligrams (mg) for the first week. The dose was then escalated in weekly increments of 0.6 mg until the maintenance dose of 3.0 mg was reached after 4 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo once daily by subcutaneous injection for 56 weeks. Dose escalation for placebo matched that of liraglutide.

Primary: Change in body weight (%)

End point title	Change in body weight (%)

End point description:

Change in body weight from baseline (week 0) to week 56 was evaluated based on full analysis set (FAS) in-trial data and on-drug data. FAS includes all randomised subjects. In-trial observation period: the uninterrupted time interval from the date of randomisation until and including the date of the follow-up visit or date of last contact. On-drug observation period: includes all time intervals in which subjects are considered to be on treatment from the date of first trial product administration to 7 days (or 14 days for adverse events [AEs]) after the final trial product administration, excluding potential off-treatment time intervals triggered by at least 7 consecutive missed doses (or 14 consecutive missed doses for AEs). 'n' is the number of subjects (subjects with available data) analysed for the respective reporting group.

End point type	Primary

End point timeframe:

From baseline to week 56

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	198		
Units: Percentage of body weight				
arithmetic mean (standard deviation)				
In-trial observation period (n=191,193)	-6.0 (± 6.0)	-1.5 (± 5.4)		
On-drug observation period (n=163,168)	-6.5 (± 5.8)	-1.7 (± 5.2)		

Statistical analyses

Statistical analysis title	Liraglutide 3.0 mg vs Placebo

Statistical analysis description:

Analysis of in-trial data with missing observations imputed from placebo arm based on jump to reference multiple (x100) imputation approach. Week 56 responses were analysed using an analysis of covariance model with treatment, body mass index (BMI) groups and sex as factors and baseline body weight as covariate. The treatment policy estimand evaluated treatment effect (liraglutide 3.0 mg vs placebo) at week 56 for all randomised subjects regardless of premature discontinuation of trial product.

Comparison groups	Placebo v Liraglutide 3.0 mg
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-4.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.48
upper limit	-3.16
Variability estimate	Standard error of the mean
Dispersion value	0.59

Statistical analysis title	Liraglutide 3.0 mg vs Placebo

Statistical analysis description:

Analysis of on-drug before first drug discontinuation date using a mixed model for repeated measurements with treatment, BMI groups and sex as factors and baseline body weight as covariate, all nested within visit. The hypothetical estimand evaluated the treatment effect (liraglutide 3.0 mg vs placebo) for all randomised subjects assuming that all subjects remained on trial product (on-treatment principle).

Comparison groups	Liraglutide 3.0 mg v Placebo
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed model for repeated measurements
Parameter estimate	Treatment difference
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	-3.91
Variability estimate	Standard error of the mean
Dispersion value	0.61

Primary: Proportion of subjects losing at least 5% of baseline body weight

End point title	Proportion of subjects losing at least 5% of baseline body weight

End point description:

The estimated percentage of subjects losing at least 5% of baseline (week 0) body weight at week 56 was presented based on FAS in-trial data and on-drug data. In-trial observation period: the uninterrupted time interval from the date of randomisation until and including the date of the follow-up visit or date of last contact. On-drug observation period: includes all time intervals in which participants are considered to be on treatment from the date of first trial product administration to 7 days (or 14 days for adverse events [AEs]) after the final trial product administration, excluding potential off-

treatment time intervals triggered by at least 7 consecutive missed doses (or 14 consecutive missed doses for AEs). 'n' is the number of subjects (subjects with available data) analysed for the respective reporting group.

End point type	Primary

End point timeframe:

Week 56

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	198		
Units: Percentage of subjects				
number (not applicable)				
In-trial observation period (n=191,193)	51.80	23.98		
On-drug observation period (n=195,197)	56.92	21.83		

Statistical analyses

Statistical analysis title	Liraglutide 3.0 mg vs Placebo

Statistical analysis description:

Analysis of in-trial data with missing observations imputed from the placebo arm based on a jump to reference multiple (x100) imputation approach. Week 56 responses were analysed using a logistic regression model with treatment, BMI groups and sex as factors and baseline body weight as covariate.

Comparison groups	Liraglutide 3.0 mg v Placebo
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.19
upper limit	5.31

Statistical analysis title	Liraglutide 3.0 mg vs Placebo

Statistical analysis description:

Analysis of on-drug before first drug discontinuation date using a mixed model for repeated measurements with treatment, BMI groups and sex as factors and baseline body weight as covariate, all nested within visit. The MMRM was used to classify responders and analysed with a logistic regression with treatment as the only factor.

Comparison groups	Liraglutide 3.0 mg v Placebo

Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed model for repeated measurements
Parameter estimate	Odds ratio (OR)
Point estimate	4.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.04
upper limit	7.36

Secondary: Proportion of subjects losing more than 10% of baseline body weight

End point title	Proportion of subjects losing more than 10% of baseline body weight

End point description:

The estimated percentage of subjects losing more than 10% of baseline (week 0) body weight at week 56 was presented based on FAS in-trial data and on-drug data. In-trial observation period: the uninterrupted time interval from the date of randomisation until and including the date of the follow-up visit or date of last contact. On-drug observation period: includes all time intervals in which participants are considered to be on treatment from the date of first trial product administration to 7 days (or 14 days for adverse events [AEs]) after the final trial product administration, excluding potential off-treatment time intervals triggered by at least 7 consecutive missed doses (or 14 consecutive missed doses for AEs). 'n' is the number of subjects (subjects with available data) analysed for the respective reporting group.

End point type	Secondary

End point timeframe:

Week 56

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	198		
Units: Percentage of subjects				
number (not applicable)				
In-trial observation period (n=191,193)	22.77	6.55		
On-drug observation period (n=195,197)	22.56	5.58		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in waist circumference

End point title	Change in waist circumference

End point description:

Change in waist circumference from baseline (week 0) to week 56 was presented based on FAS in-trial data and on-drug data. In-trial observation period: the uninterrupted time interval from the date of randomisation until and including the date of the follow-up visit or date of last contact. On-drug observation period: includes all time intervals in which subjects are considered to be on treatment from the date of first trial product administration to 7 days (or 14 days for AEs) after the final trial product administration, excluding potential off-treatment time intervals triggered by at least 7 consecutive missed doses (or 14 consecutive missed doses for AEs). 'n' is the number of subjects (subjects with available data) analysed for the respective reporting group.

End point type	Secondary

End point timeframe:

From baseline to week 56

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	198		
Units: Centimeters (cm)				
arithmetic mean (standard deviation)				
In-trial observation period (n=189,193)	-5.40 (± 6.06)	-2.60 (± 5.72)		
On-drug observation period (n=163,168)	-5.71 (± 6.05)	-2.78 (± 5.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HbA1c

End point title	Change in HbA1c

End point description:

Change in glycosylated haemoglobin (HbA1c) from baseline (week 0) to week 56 was presented based on FAS in-trial data and on-drug data. In-trial observation period: the uninterrupted time interval from the date of randomisation until and including the date of the follow-up visit or date of last contact. On-drug observation period: includes all time intervals in which subjects are considered to be on treatment from the date of first trial product administration to 7 days (or 14 days for AEs) after the final trial product administration, excluding potential off-treatment time intervals triggered by at least 7 consecutive missed doses (or 14 consecutive missed doses for AEs). 'n' is the number of subjects (subjects with available data) analysed for the respective reporting group.

End point type	Secondary

End point timeframe:

From baseline to week 56

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	198		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)				
In-trial observation period (n=187,188)	-1.1 (± 1.2)	-0.5 (± 1.2)		
On-drug observation period (n=160,164)	-1.2 (± 1.1)	-0.7 (± 1.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose

End point title	Change in fasting plasma glucose

End point description:

Change from baseline (week 0) in fasting plasma glucose (FPG) was presented based on FAS in-trial data and on-drug data. In-trial observation period: the uninterrupted time interval from the date of randomisation until and including the date of the follow-up visit or date of last contact. On-drug observation period: includes all time intervals in which subjects are considered to be on treatment from the date of first trial product administration to 7 days (or 14 days for AEs) after the final trial product administration, excluding potential off-treatment time intervals triggered by at least 7 consecutive missed doses (or 14 consecutive missed doses for AEs). 'n' is the number of subjects (subjects with available data) analysed for the respective reporting group.

End point type	Secondary

End point timeframe:

From baseline to week 56

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	198		
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
In-trial observation period (n=187,188)	-0.91 (± 3.13)	-0.68 (± 3.04)		
On-drug observation period (n=162,165)	-1.05 (± 3.08)	-0.96 (± 2.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Short Form-36 (SF-36) v2.0 acute, physical functioning score

End point title	Change in Short Form-36 (SF-36) v2.0 acute, physical functioning score

End point description:

SF-36 is a 36-item patient-reported survey of patient health that measures the subject's overall health-related quality of life (HRQoL). SF-36v2™ questionnaire measured the HRQoL on 8 domains on individual scale ranges. The scores 0-100 (where higher scores indicated a better HRQoL) from the SF-36 were converted to norm-based scores to enable a direct interpretation in relation to the distribution of the scores in the 2009 U.S. general population. A norm-based score of 50 corresponds to the mean score and 10 corresponds to the standard deviation of the 2009 U.S. general population. Change from baseline (week 0) in SF-36 physical functioning score was presented based on FAS in-trial data and on-drug data. A positive change score indicates an improvement since baseline. 'n' is the number of subjects (subjects with available data) analysed for the respective reporting group.

End point type	Secondary

End point timeframe:

From baseline to week 56

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	198		
Units: Score on a scale				
arithmetic mean (standard deviation)				
In-trial observation period (n=186,187)	2.5 (± 7.9)	2.6 (± 7.3)		
On-drug observation period (n=161,167)	2.9 (± 7.8)	2.5 (± 7.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Impact of Weight on Quality of Life-Lite for Clinical Trial Version (IWQoL-Lite for CT), physical function domain (5-items) score

End point title	Change in Impact of Weight on Quality of Life-Lite for Clinical Trial Version (IWQoL-Lite for CT), physical function domain (5-items) score

End point description:

IWQoL-Lite for CT is a modified version of an instrument designed to assess weight-related quality of life. The scores ranged between 0-100 where higher scores indicated a better quality of life. A positive change score indicates an improvement since baseline. The endpoint was presented based on FAS in-trial data and on-drug data. In-trial observation period: the uninterrupted time interval from the date of randomisation until and including the date of the follow-up visit or date of last contact. On-drug observation period: includes all time intervals in which subjects are considered to be on treatment from the date of first trial product administration to 7 days (or 14 days for AEs) after the final trial product administration, excluding potential off-treatment time intervals triggered by at least 7 consecutive missed doses (or 14 consecutive missed doses for AEs). 'n' is the number of subjects (subjects with available data) analysed for the respective reporting group.

End point type	Secondary

End point timeframe:

From baseline to week 56

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	198		
Units: Score on a scale				
arithmetic mean (standard deviation)				
In-trial observation period (n=186,187)	7.3 (± 22.5)	6.8 (± 21.5)		
On-drug observation period (n=161,167)	8.2 (± 20.9)	6.5 (± 21.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of first dose of trial product (week 0) to end of treatment (week 56) + post treatment follow-up of 30 days.

Adverse event reporting additional description:

Evaluation of safety was based on SAS comprised of all randomised subjects who received at least one dose of trial product.
AEs with onset during the on-treatment period were considered treatment-emergent.
'Number of deaths causally related to treatment' is the data considered to present under 'total number of deaths resulting from adverse events'.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Liraglutide 3.0 mg

Reporting group description:

Subjects received liraglutide subcutaneous injections for 56 weeks. The starting dose was 0.6 milligrams (mg) for the first week. The dose was then escalated in weekly increments of 0.6 mg until the maintenance dose of 3.0 mg was reached after 4 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo once daily by subcutaneous injection for 56 weeks. Dose escalation for placebo matched that of liraglutide.

Serious adverse events	Liraglutide 3.0 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 195 (8.21%)	19 / 197 (9.64%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			

subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid adenoma			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral vascular disorder			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Lipoma excision			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (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			
Pleural effusion			

subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Amylase increased			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metaphyseal corner fracture			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpericardiotomy syndrome			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention postoperative			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 195 (0.00%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Relapsing-remitting multiple sclerosis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulum			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peptic ulcer			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (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			
Intervertebral disc disorder			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 195 (1.03%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (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			
Cellulitis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Liraglutide 3.0 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	162 / 195 (83.08%)	141 / 197 (71.57%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 195 (2.05%)	12 / 197 (6.09%)	
occurrences (all)	4	14	
Nervous system disorders			

Dizziness			
subjects affected / exposed	13 / 195 (6.67%)	7 / 197 (3.55%)	
occurrences (all)	18	7	
Headache			
subjects affected / exposed	29 / 195 (14.87%)	29 / 197 (14.72%)	
occurrences (all)	36	47	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 195 (7.18%)	10 / 197 (5.08%)	
occurrences (all)	18	11	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	11 / 195 (5.64%)	8 / 197 (4.06%)	
occurrences (all)	17	11	
Abdominal pain upper			
subjects affected / exposed	12 / 195 (6.15%)	8 / 197 (4.06%)	
occurrences (all)	17	9	
Constipation			
subjects affected / exposed	28 / 195 (14.36%)	17 / 197 (8.63%)	
occurrences (all)	36	21	
Diarrhoea			
subjects affected / exposed	45 / 195 (23.08%)	30 / 197 (15.23%)	
occurrences (all)	77	54	
Dyspepsia			
subjects affected / exposed	12 / 195 (6.15%)	5 / 197 (2.54%)	
occurrences (all)	13	5	
Gastrooesophageal reflux disease			
subjects affected / exposed	10 / 195 (5.13%)	2 / 197 (1.02%)	
occurrences (all)	12	2	
Nausea			
subjects affected / exposed	58 / 195 (29.74%)	23 / 197 (11.68%)	
occurrences (all)	105	27	
Vomiting			
subjects affected / exposed	32 / 195 (16.41%)	12 / 197 (6.09%)	
occurrences (all)	53	13	
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain			
subjects affected / exposed	7 / 195 (3.59%)	10 / 197 (5.08%)	
occurrences (all)	7	12	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 195 (6.15%)	24 / 197 (12.18%)	
occurrences (all)	14	37	
Back pain			
subjects affected / exposed	13 / 195 (6.67%)	12 / 197 (6.09%)	
occurrences (all)	13	17	
Osteoarthritis			
subjects affected / exposed	6 / 195 (3.08%)	12 / 197 (6.09%)	
occurrences (all)	9	13	
Pain in extremity			
subjects affected / exposed	16 / 195 (8.21%)	19 / 197 (9.64%)	
occurrences (all)	17	21	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	15 / 195 (7.69%)	5 / 197 (2.54%)	
occurrences (all)	15	5	
Influenza			
subjects affected / exposed	12 / 195 (6.15%)	22 / 197 (11.17%)	
occurrences (all)	14	26	
Nasopharyngitis			
subjects affected / exposed	42 / 195 (21.54%)	36 / 197 (18.27%)	
occurrences (all)	48	49	
Sinusitis			
subjects affected / exposed	9 / 195 (4.62%)	10 / 197 (5.08%)	
occurrences (all)	11	11	
Upper respiratory tract infection			
subjects affected / exposed	24 / 195 (12.31%)	29 / 197 (14.72%)	
occurrences (all)	32	37	
Urinary tract infection			
subjects affected / exposed	7 / 195 (3.59%)	19 / 197 (9.64%)	
occurrences (all)	12	22	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	19 / 195 (9.74%) 24	5 / 197 (2.54%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 January 2017	Key changes: 1. Addition of bicarbonate as a part of the biochemistry laboratory assessment 2. Updated the wording in reporting of insulin dose and transcription of insulin dose to eCRF 3. Updated the time period of an eye examination performed prior to randomisation.
18 April 2017	Key changes: 1. Clarification of the criteria to allow two additional oral antidiabetic drug (OAD) classes- alpha glucosidase inhibitors and glinides 2. Clarification of the criteria to continue on their standard insulin treatment.
09 April 2018	Key changes: 1. Included the Short-form 36 (SF-36) 2.0 questionnaire as a confirmatory secondary endpoint 2. Systolic blood pressure has been added as a supportive secondary endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported