Clinical trial results:
The efficacy and safety of liraglutide as adjunct therapy to insulin in the treatment of type 1 diabetes.
A 52-week randomised, treat-to-target, placebo-controlled, double-blinded, parallelgroup, multinational, multi-centre trial

Summary

EudraCT number	2012-003580-21
Trial protocol	SE FI IE NL GB NO PL BE
Global end of trial date	04 June 2015

Results information

Result version number	v1 (current)
This version publication date	08 June 2016
First version publication date	08 June 2016

Trial information

Trial identification

Sponsor protocol code	NN9211-3919

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01836523
WHO universal trial number (UTN)	U1111-1133-0590

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Global Clinical Registry (GCR, 1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR, 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	10 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 June 2015
Global end of trial reached?	Yes
Global end of trial date	04 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the efficacy of liraglutide as adjunct to insulin treatment on glycaemic control, and to confirm the superiority of liraglutide treatment compared to placebo, both adjunct to insulin treatment, with regard to reduction in total daily insulin dose and body weight loss, after 52 weeks of treatment in subjects with established type 1 diabetes with inadequate glycaemic control.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 64th WMA General Assembly, Fortaleza. 1 Oct 2013. 2013) and ICH Good Clinical Practice (International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Good Clinical Practice. 01-May-1996) and 21 CFR 312.120 (Food and Drug Administration. FDA Code Federal Regulations. 21 CFR 312.120. Foreign clinical studies not conducted under an IND. 4 Jan 2008).

Background therapy:

Subjects' pre-trial insulin treatment was considered background medication.

Evidence for comparator:

Not applicable

Actual start date of recruitment	25 November 2013
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	Australia: 51
Country: Number of subjects enrolled	Argentina: 73
Country: Number of subjects enrolled	Belgium: 33
Country: Number of subjects enrolled	Canada: 99
Country: Number of subjects enrolled	Finland: 49
Country: Number of subjects enrolled	France: 102
Country: Number of subjects enrolled	Germany: 88
Country: Number of subjects enrolled	Ireland: 31
Country: Number of subjects enrolled	Israel: 52
Country: Number of subjects enrolled	Netherlands: 37
Country: Number of subjects enrolled	Norway: 30
Country: Number of subjects enrolled	Poland: 60
Country: Number of subjects enrolled	Sweden: 42
Country: Number of subjects enrolled	Ukraine: 41
Country: Number of subjects enrolled	United Kingdom: 85

Country: Number of subjects enrolled	United States: 473
Country: Number of subjects enrolled	Russian Federation: 52
Worldwide total number of subjects	1398
EEA total number of subjects	557

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)	1321
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 177 sites in 17 countries:
Argentina: 6, Australia: 5, Belgium: 4, Canada: 14, Germany: 8, Finland: 6, France: 13, United Kingdom: 10, Ireland: 5, Israel: 6, Netherlands: 6, Norway: 5, Poland: 5, Russia: 5, Sweden: 4, Ukraine: 5, United States: 70.

Pre-assignment

Screening details:

Eligible subjects were randomised in a 3:3:3:1:1:1 manner to receive liraglutide (0.6 mg, 1.2 mg or 1.8 mg) or placebo (0.1 mL, 0.2 mL or 0.3 mL), both adjunct to insulin treatment.

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	Investigator, Subject

Blinding implementation details:

Treatment allocation was blinded to all subjects, investigators and Novo Nordisk. The evaluations performed by the independent EAC and CMC committees were also based on blinded data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Liraglutide 0.6 mg

Arm description:

Subjects received liraglutide 0.6 mg once daily (OD) subcutaneously for 52 weeks in addition to their pre-trial insulin treatment.

Arm type	Experimental
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	Victoza®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide 0.6 mg, to be administered any time of the day and irrespective of meals. It was recommended that the time of injection was consistent throughout the trial.

Arm title	Liraglutide 1.2 mg

Arm description:

Subjects received liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment.

Arm type	Experimental
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	Victoza®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide 1.2 mg, to be administered any time of the day and irrespective of meals. It was recommended that the time of injection was consistent throughout the trial.

Arm title	Liraglutide 1.8 mg

Arm description:

Liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously for 2 weeks (weeks 2-4) followed by 1.8 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment.

Arm type	Experimental
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	Victoza®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide 1.8 mg, to be administered any time of the day and irrespective of meals. It was recommended that the time of injection was consistent throughout the trial.

Arm title	Placebo

Arm description:

Subjects received placebo (matched to liraglutide 0.6, 1.2 and 1.8 mg) OD subcutaneously as an add-on to their pre-trial insulin treatment.
Placebo 0.1 mL (placebo matched to liraglutide 0.6 mg): Subjects received 0.1 mL liraglutide placebo for 52 weeks.
Placebo 0.2 mL (placebo matched to liraglutide 1.2 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL up to week 52.
Placebo 0.3 mL (placebo matched to liraglutide 1.8 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL for next 2 weeks and 0.3 mL up to week 52.
All the 3 placebo doses were pooled for data analysis.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo (0.1 mL, 02 mL or 0.3 mL), to be administered any time of the day and irrespective of meals. It was recommended that the time of injection was consistent throughout the trial.

Number of subjects in period 1	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg
Started	351	350	349
Exposed	350	348	347
Completed	300	265	258
Not completed	51	85	91
Adverse event, non-fatal	15	41	49
Unclassified	17	28	19
Protocol deviation	6	3	2
Met Withdrawal Criteria	13	13	21

Number of subjects in period 1	Placebo
Started	348
Exposed	348

Completed	274
Not completed	74
Adverse event, non-fatal	14
Unclassified	29
Protocol deviation	4
Met Withdrawal Criteria	27

Baseline characteristics

Reporting groups	
Reporting group title	Liraglutide 0.6 mg
Reporting group description:	
Subjects received liraglutide 0.6 mg once daily (OD) subcutaneously for 52 weeks in addition to their pre-trial insulin treatment.	
Reporting group title	Liraglutide 1.2 mg
Reporting group description:	
Subjects received liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment.	
Reporting group title	Liraglutide 1.8 mg
Reporting group description:	
Liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously for 2 weeks (weeks 2-4) followed by 1.8 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo (matched to liraglutide 0.6, 1.2 and 1.8 mg) OD subcutaneously as an add-on to their pre-trial insulin treatment. Placebo 0.1 mL (placebo matched to liraglutide 0.6 mg): Subjects received 0.1 mL liraglutide placebo for 52 weeks. Placebo 0.2 mL (placebo matched to liraglutide 1.2 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL up to week 52. Placebo 0.3 mL (placebo matched to liraglutide 1.8 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL for next 2 weeks and 0.3 mL up to week 52. All the 3 placebo doses were pooled for data analysis.	

Reporting group values	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg
Number of subjects	351	350	349
Age categorical Units: Subjects			
Age Continuous			
Number of subjects analysed for this parameter=350 (liraglutide 0.6 mg), 346 (liraglutide 1.2 mg), 346 (liraglutide 1.8 mg) and 347 (placebo).			
Units: years			
arithmetic mean	43.6	43.9	43.7
standard deviation	± 12.78	± 13.06	± 13.33
Gender, Male/Female Units: Subjects			
Female	186	179	181
Male	164	167	165
Data not used for this summary	1	4	3
Glycosylated haemoglobin (HbA1c)			
Number of subjects analysed for this parameter=350 (liraglutide 0.6 mg), 346 (liraglutide 1.2 mg), 346 (liraglutide 1.8 mg) and 347 (placebo).			
Units: percentage of glycosylated haemoglobin			
arithmetic mean	8.18	8.16	8.14
standard deviation	± 0.738	± 0.779	± 0.74
Body weight			
Number of subjects analysed for this parameter=350 (liraglutide 0.6 mg), 346 (liraglutide 1.2 mg), 346			

(liraglutide 1.8 mg) and 347 (placebo).			
Units: kg			
arithmetic mean	86.54	85.39	86.27
standard deviation	± 17.338	± 17.21	± 17.321
Total daily actual insulin dose - continuous subcutaneous insulin infusion			
Total insulin daily dose of subjects who were on continuous subcutaneous insulin infusion treatment. Number of subjects analysed=69 (liraglutide 0.6 mg), 99 (liraglutide 1.2 mg), 113 (liraglutide 1.8 mg), 95 (Placebo).			
Units: units			
geometric mean	52.97	50.73	50.46
full range (min-max)	13.8 to 137.1	19.7 to 160.5	8.7 to 150.2
Total daily actual insulin dose - multiple daily injections			
Total insulin daily dose of subjects who were on multiple daily insulin injection treatment. Number of subjects analysed=277 (liraglutide 0.6 mg), 242 (liraglutide 1.2 mg), 227 (liraglutide 1.8 mg), 250 (Placebo).			
Units: units			
geometric mean	59.54	59.61	62.52
full range (min-max)	22.9 to 181.6	16 to 282.5	16.4 to 271.3

Reporting group values	Placebo	Total	
Number of subjects	348	1398	
Age categorical			
Units: Subjects			

Age Continuous			
Number of subjects analysed for this parameter=350 (liraglutide 0.6 mg), 346 (liraglutide 1.2 mg), 346 (liraglutide 1.8 mg) and 347 (placebo).			
Units: years			
arithmetic mean	43.4		
standard deviation	± 12.57	-	
Gender, Male/Female			
Units: Subjects			
Female	180	726	
Male	167	663	
Data not used for this summary	1	9	
Glycosylated haemoglobin (HbA1c)			
Number of subjects analysed for this parameter=350 (liraglutide 0.6 mg), 346 (liraglutide 1.2 mg), 346 (liraglutide 1.8 mg) and 347 (placebo).			
Units: percentage of glycosylated haemoglobin			
arithmetic mean	8.15		
standard deviation	± 0.728	-	
Body weight			
Number of subjects analysed for this parameter=350 (liraglutide 0.6 mg), 346 (liraglutide 1.2 mg), 346 (liraglutide 1.8 mg) and 347 (placebo).			
Units: kg			
arithmetic mean	86.41		
standard deviation	± 17.768	-	
Total daily actual insulin dose - continuous subcutaneous insulin infusion			
Total insulin daily dose of subjects who were on continuous subcutaneous insulin infusion treatment. Number of subjects analysed=69 (liraglutide 0.6 mg), 99 (liraglutide 1.2 mg), 113 (liraglutide 1.8 mg),			

95 (Placebo).			
Units: units geometric mean full range (min-max)	 49.18 3.9 to 176.1	 -	
Total daily actual insulin dose - multiple daily injections			
Total insulin daily dose of subjects who were on multiple daily insulin injection treatment. Number of subjects analysed=277 (liraglutide 0.6 mg), 242 (liraglutide 1.2 mg), 227 (liraglutide 1.8 mg), 250 (Placebo).			
Units: units geometric mean full range (min-max)	 62.42 20.3 to 230	 -	

End points

End points reporting groups

Reporting group title	Liraglutide 0.6 mg
Reporting group description:	
Subjects received liraglutide 0.6 mg once daily (OD) subcutaneously for 52 weeks in addition to their pre-trial insulin treatment.	
Reporting group title	Liraglutide 1.2 mg
Reporting group description:	
Subjects received liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment.	
Reporting group title	Liraglutide 1.8 mg
Reporting group description:	
Liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously for 2 weeks (weeks 2-4) followed by 1.8 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo (matched to liraglutide 0.6, 1.2 and 1.8 mg) OD subcutaneously as an add-on to their pre-trial insulin treatment. Placebo 0.1 mL (placebo matched to liraglutide 0.6 mg): Subjects received 0.1 mL liraglutide placebo for 52 weeks. Placebo 0.2 mL (placebo matched to liraglutide 1.2 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL up to week 52. Placebo 0.3 mL (placebo matched to liraglutide 1.8 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL for next 2 weeks and 0.3 mL up to week 52. All the 3 placebo doses were pooled for data analysis.	

Primary: Change from baseline in HbA1c

End point title	Change from baseline in HbA1c
End point description:	
Change from baseline in HbA1C at week 52. Missing values were handled by using a mixed model for repeated measurements (MMRM). Full analysis set (FAS) included all randomised subjects who received at least one dose and had any post-randomisation data. Five subjects, who started the study, were excluded because of no exposure to study drug and 4 subjects were excluded because of non-availability of post-baseline data. Number of subjects analysed=subjects with any post-baseline HbA1c data.	
End point type	Primary
End point timeframe:	
After 52 weeks of treatment	

End point values	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	312	305	324
Units: percentage of glycosylated haemoglobin				
arithmetic mean (standard deviation)	-0.45 (± 0.741)	-0.5 (± 0.767)	-0.54 (± 0.729)	-0.34 (± 0.707)

Statistical analyses

Statistical analysis title	Liraglutide 1.8 mg vs Placebo

Statistical analysis description:

Analysis was performed using MMRMs where all post-baseline measurements for the specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as the dependent variable, and visit, treatment, country and the stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate.

Comparison groups	Liraglutide 1.8 mg v Placebo
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	-0.07

Notes:

[1] - Non-inferiority was concluded if the upper bound of 95% confidence interval was <0.3.

Statistical analysis title	Liraglutide 1.2 mg vs Placebo

Statistical analysis description:

Analysis was performed using MMRMs where all post-baseline measurements for the specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as the dependent variable, and visit, treatment, country and the stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate.

Comparison groups	Liraglutide 1.2 mg v Placebo
Number of subjects included in analysis	636
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	-0.03

Notes:

[2] - Non-inferiority was concluded if the upper bound of 95% confidence interval was <0.3.

Statistical analysis title	Liraglutide 0.6 mg vs Placebo

Statistical analysis description:

Analysis was performed using MMRMs where all post-baseline measurements for the specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as the dependent variable, and visit, treatment, country and the stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate.

Comparison groups	Liraglutide 0.6 mg v Placebo
Number of subjects included in analysis	658
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.03

Notes:

[3] - Non-inferiority was concluded if the upper bound of 95% confidence interval was <0.3.

Primary: Change from baseline in body weight

End point title	Change from baseline in body weight

End point description:

Change from baseline in body weight at week 52. Missing values were handled by using a MMRM. Analysis was performed on full analysis set. Number of subjects analysed=subjects with any post-baseline body weight data.

End point type	Primary

End point timeframe:

After 52 weeks of treatment

End point values	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	324	300	298	311
Units: kg				
arithmetic mean (standard deviation)	-1.34 (± 4.183)	-2.73 (± 4.524)	-4.02 (± 4.873)	0.94 (± 3.828)

Statistical analyses

Statistical analysis title	Liraglutide 1.8 mg vs Placebo

Statistical analysis description:

Analysis was performed using MMRMs where all post-baseline measurements for the specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as the dependent variable, and visit, treatment, country and the stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate.

Comparison groups	Liraglutide 1.8 mg v Placebo
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.65
upper limit	-4.16

Statistical analysis title	Liraglutide 1.2 mg vs Placebo

Statistical analysis description:

Analysis was performed using MMRMs where all post-baseline measurements for the specific variable from planned visits up to week 52 and obtained no later than 7 days after withdrawal from treatment were entered as the dependent variable, and visit, treatment, country and the stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate.

Comparison groups	Liraglutide 1.2 mg v Placebo
Number of subjects included in analysis	611
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-3.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.29
upper limit	-2.81

Statistical analysis title	Liraglutide 0.6 mg vs Placebo

Statistical analysis description:

Analysis was performed using MMRMs where all post-baseline measurements for the specific variable from planned visits up to week 52 and obtained no later than 7 days after withdrawal from treatment were entered as the dependent variable, and visit, treatment, country and the stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate.

Comparison groups	Liraglutide 0.6 mg v Placebo

Number of subjects included in analysis	635
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-2.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.91
upper limit	-1.47

Primary: Change from baseline in total daily insulin dose

End point title	Change from baseline in total daily insulin dose

End point description:

Change from baseline in total daily insulin dose at week 52. Change from baseline was represented in terms of ratio to baseline for insulin dose i.e. Total daily insulin dose at week 52/total daily insulin dose at baseline. Missing values were handled by using a MMRM. Full analysis set. Number of subjects analysed=subjects with any post-baseline total insulin daily dose data.

End point type	Primary

End point timeframe:

After 52 weeks of treatment

End point values	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	337	328	331	341
Units: ratio				
geometric mean (geometric coefficient of variation)	1.04 (± 23.75)	0.98 (± 26.66)	0.95 (± 24.21)	1.04 (± 26.69)

Statistical analyses

Statistical analysis title	Liraglutide 1.8 mg vs Placebo

Statistical analysis description:

Analysis was done using MMRMs where all post-baseline measurements for specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as dependent variable, and visit, treatment, country and stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate. The measurements were log-transformed before analysis

Comparison groups	Liraglutide 1.8 mg v Placebo

Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	0.96

Statistical analysis title	Liraglutide 0.6 mg vs Placebo

Statistical analysis description:

Analysis was done using MMRMs where all post-baseline measurements for specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as dependent variable, and visit, treatment, country and stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate. The measurements were log-transformed before analysis

Comparison groups	Liraglutide 0.6 mg v Placebo
Number of subjects included in analysis	678
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9615
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.04

Statistical analysis title	Liraglutide 1.2 mg vs Placebo

Statistical analysis description:

Analysis was done using MMRMs where all post-baseline measurements for specific variable from planned visits up to week 52 and obtained no later than 1 day after withdrawal from treatment were entered as dependent variable, and visit, treatment, country and stratification variable (4 levels: HbA1c < 8.5% and ≥8.5%, each intersected by BMI≤27 kg/m2 and >27 kg/m2) were included as fixed factors and the corresponding baseline value as covariate. The measurements were log-transformed before analysis

Comparison groups	Liraglutide 1.2 mg v Placebo

Number of subjects included in analysis	669
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0148
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	0.99

Secondary: Number of treatment-emergent symptomatic hypoglycaemic episodes

End point title	Number of treatment-emergent symptomatic hypoglycaemic episodes

End point description:

This is a confirmatory secondary endpoint. Symptomatic hypoglycaemic episodes were defined as episodes that were:
1) Severe according to the American Diabetes Association (ADA) classification
OR
2) Self-monitoring of plasma glucose value of < 3.1 mmol/L, with symptoms consistent with hypoglycaemia.
ADA classification of severe hypoglycemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions.
A treatment emergent episode is defined as an episode with onset date (or increase in severity) on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment.
The safety analysis set included all randomised subjects exposed to at least one dose of liraglutide or placebo.

End point type	Secondary

End point timeframe:

During 52 weeks of treatment

End point values	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	350	348	347	348
Units: episodes	4954	4602	4614	3654

Statistical analyses

Statistical analysis title	Liraglutide 1.8 mg vs Placebo

Statistical analysis description:

The endpoint was analysed using a negative binomial regression model with a log-link function and the log of the time period in which an occurrence of a hypoglycaemic episode was considered treatment emergent as offset. The model included fixed factors (treatment, country, stratification group) and a covariate (baseline HbA1c). The actual number of subjects in this analysis was 693 instead of 695.

Comparison groups	Liraglutide 1.8 mg v Placebo

Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0081
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	1.59

Statistical analysis title	Liraglutide 1.2 mg vs Placebo

Statistical analysis description:

The endpoint was analysed using a negative binomial regression model with a log-link function and the log of the time period in which an occurrence of a hypoglycaemic episode was considered treatment emergent as offset. The model included fixed factors (treatment, country, stratification group) and a covariate (baseline HbA1c). The actual number of subjects in this analysis was 693 instead of 696.

Comparison groups	Liraglutide 1.2 mg v Placebo
Number of subjects included in analysis	696
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0219
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.55

Statistical analysis title	Liraglutide 0.6 mg vs Placebo

Statistical analysis description:

The endpoint was analysed using a negative binomial regression model with a log-link function and the log of the time period in which an occurrence of a hypoglycaemic episode was considered treatment emergent as offset. The model included fixed factors (treatment, country, stratification group) and a covariate (baseline HbA1c). The actual number of subjects in this analysis was 697 instead of 698.

Comparison groups	Liraglutide 0.6 mg v Placebo
Number of subjects included in analysis	698
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1079
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	1.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.43

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 52 weeks

Adverse event reporting additional description:

A treatment emergent adverse event is defined as an event with onset date (or increase in severity) on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Liraglutide 0.6 mg

Reporting group description:

Subjects received liraglutide 0.6 mg once daily (OD) subcutaneously for 52 weeks in addition to their pre-trial insulin treatment.

Reporting group title	Liraglutide 1.2 mg

Reporting group description:

Subjects received liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment.

Reporting group title	Liraglutide 1.8 mg

Reporting group description:

Liraglutide 0.6 mg OD subcutaneously for 2 weeks followed by 1.2 mg OD subcutaneously for 2 weeks (weeks 2-4) followed by 1.8 mg OD subcutaneously up to week 52 in addition to their pre-trial insulin treatment.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo (matched to liraglutide 0.6, 1.2 and 1.8 mg) OD subcutaneously an add-on to their pre-trial insulin treatment. All the 3 placebo doses pooled together for data analysis.
Placebo 0.1 mL (placebo matched to liraglutide 0.6 mg): Subjects received 0.1 mL liraglutide placebo for 52 weeks.
Placebo 0.2 mL (placebo matched to liraglutide 1.2 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL up to week 52.
Placebo 0.3 mL (placebo matched to liraglutide 1.8 mg): Subjects received 0.1 mL for 2 weeks followed by 0.2 mL for next 2 weeks and 0.3 mL up to week 52.

Serious adverse events	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 350 (10.00%)	36 / 348 (10.34%)	29 / 347 (8.36%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			

subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangioma of bone			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive lobular breast carcinoma			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Popliteal artery entrapment syndrome			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Obesity surgery			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toe amputation			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cyst			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar inflammation			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression suicidal			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Biopsy prostate			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Suture related complication			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Melkersson-Rosenthal syndrome			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myocardial infarction			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocarditis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic seizure			
subjects affected / exposed	1 / 350 (0.29%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic unconsciousness			
subjects affected / exposed	5 / 350 (1.43%)	3 / 348 (0.86%)	6 / 347 (1.73%)
occurrences causally related to treatment / all	4 / 5	1 / 3	3 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vertigo positional			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular oedema			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinopathy			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 350 (0.29%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pancreatitis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal prolapse			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder prolapse			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dupuytren's contracture			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal pain			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site infection			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis externa			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis streptococcal			

subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal cyst			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	3 / 347 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			

subjects affected / exposed	0 / 350 (0.00%)	1 / 348 (0.29%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	3 / 350 (0.86%)	1 / 348 (0.29%)	3 / 347 (0.86%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	3 / 350 (0.86%)	3 / 348 (0.86%)	3 / 347 (0.86%)
occurrences causally related to treatment / all	0 / 5	1 / 4	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperosmolar hyperglycaemic state			
subjects affected / exposed	0 / 350 (0.00%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	3 / 350 (0.86%)	7 / 348 (2.01%)	5 / 347 (1.44%)
occurrences causally related to treatment / all	3 / 4	6 / 8	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 350 (0.29%)	0 / 348 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 348 (10.92%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemangioma of bone			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Papillary thyroid cancer			
subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral vascular disorder			
subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Popliteal artery entrapment syndrome			

subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Obesity surgery			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Toe amputation			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cyst			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 348 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillar inflammation				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Alcoholism				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Completed suicide				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	1 / 348 (0.29%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Depression suicidal				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Panic attack				
subjects affected / exposed	1 / 348 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				

subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Biopsy prostate			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Foot fracture			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament rupture			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Post procedural haemorrhage				
subjects affected / exposed	1 / 348 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suture related complication				
subjects affected / exposed	1 / 348 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Melkersson-Rosenthal syndrome				
subjects affected / exposed	1 / 348 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 348 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Angina pectoris				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 348 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Coronary artery disease				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocarditis				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrospinal fluid leakage				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemic seizure				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemic unconsciousness				
subjects affected / exposed	6 / 348 (1.72%)			
occurrences causally related to treatment / all	5 / 7			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	1 / 348 (0.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				

Vertigo			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vertigo positional			
subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Macular oedema			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinopathy			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Large intestine polyp			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Nausea			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal prolapse			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Urticaria			
subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder prolapse			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bursitis			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dupuytren's contracture			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Joint effusion				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal column stenosis				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abscess				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abscess limb				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	2 / 348 (0.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	0 / 348 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis infective				

subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Incision site infection			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infectious mononucleosis			
subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Otitis externa			

subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis streptococcal			
subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pilonidal cyst			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subcutaneous abscess			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound infection			

subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	2 / 348 (0.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperosmolar hyperglycaemic state			
subjects affected / exposed	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	13 / 348 (3.74%)		
occurrences causally related to treatment / all	9 / 16		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	259 / 350 (74.00%)	263 / 348 (75.57%)	282 / 347 (81.27%)
Nervous system disorders			
Headache			
subjects affected / exposed	56 / 350 (16.00%)	46 / 348 (13.22%)	49 / 347 (14.12%)
occurrences (all)	78	85	119
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	17 / 350 (4.86%)	22 / 348 (6.32%)	18 / 347 (5.19%)
occurrences (all)	18	24	21
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	20 / 350 (5.71%)	16 / 348 (4.60%)	29 / 347 (8.36%)
occurrences (all)	32	20	41
Constipation			
subjects affected / exposed	17 / 350 (4.86%)	28 / 348 (8.05%)	26 / 347 (7.49%)
occurrences (all)	20	30	28
Diarrhoea			
subjects affected / exposed	41 / 350 (11.71%)	50 / 348 (14.37%)	64 / 347 (18.44%)
occurrences (all)	52	69	92
Dyspepsia			
subjects affected / exposed	26 / 350 (7.43%)	27 / 348 (7.76%)	38 / 347 (10.95%)
occurrences (all)	37	41	48
Nausea			
subjects affected / exposed	112 / 350 (32.00%)	141 / 348 (40.52%)	172 / 347 (49.57%)
occurrences (all)	146	196	271
Vomiting			
subjects affected / exposed	24 / 350 (6.86%)	44 / 348 (12.64%)	64 / 347 (18.44%)
occurrences (all)	26	58	106
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 350 (4.00%)	7 / 348 (2.01%)	10 / 347 (2.88%)
occurrences (all)	14	8	12

Oropharyngeal pain			
subjects affected / exposed	15 / 350 (4.29%)	22 / 348 (6.32%)	28 / 347 (8.07%)
occurrences (all)	17	24	32
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	15 / 350 (4.29%)	22 / 348 (6.32%)	18 / 347 (5.19%)
occurrences (all)	17	24	19
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	12 / 350 (3.43%)	6 / 348 (1.72%)	18 / 347 (5.19%)
occurrences (all)	14	6	24
Gastroenteritis			
subjects affected / exposed	21 / 350 (6.00%)	15 / 348 (4.31%)	29 / 347 (8.36%)
occurrences (all)	25	17	32
Influenza			
subjects affected / exposed	29 / 350 (8.29%)	17 / 348 (4.89%)	25 / 347 (7.20%)
occurrences (all)	32	26	28
Nasopharyngitis			
subjects affected / exposed	105 / 350 (30.00%)	81 / 348 (23.28%)	83 / 347 (23.92%)
occurrences (all)	175	124	145
Sinusitis			
subjects affected / exposed	24 / 350 (6.86%)	17 / 348 (4.89%)	16 / 347 (4.61%)
occurrences (all)	35	22	21
Upper respiratory tract infection			
subjects affected / exposed	33 / 350 (9.43%)	23 / 348 (6.61%)	43 / 347 (12.39%)
occurrences (all)	37	37	59
Urinary tract infection			
subjects affected / exposed	18 / 350 (5.14%)	14 / 348 (4.02%)	20 / 347 (5.76%)
occurrences (all)	28	21	26
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	31 / 350 (8.86%)	43 / 348 (12.36%)	64 / 347 (18.44%)
occurrences (all)	32	45	70
Hyperglycaemia			
subjects affected / exposed	17 / 350 (4.86%)	17 / 348 (4.89%)	22 / 347 (6.34%)
occurrences (all)	29	26	38

Hypoglycaemia			
subjects affected / exposed	26 / 350 (7.43%)	13 / 348 (3.74%)	20 / 347 (5.76%)
occurrences (all)	32	18	37

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	224 / 348 (64.37%)		
Nervous system disorders			
Headache			
subjects affected / exposed	40 / 348 (11.49%)		
occurrences (all)	77		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 348 (4.60%)		
occurrences (all)	18		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 348 (2.30%)		
occurrences (all)	9		
Constipation			
subjects affected / exposed	9 / 348 (2.59%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	38 / 348 (10.92%)		
occurrences (all)	50		
Dyspepsia			
subjects affected / exposed	8 / 348 (2.30%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	42 / 348 (12.07%)		
occurrences (all)	52		
Vomiting			
subjects affected / exposed	21 / 348 (6.03%)		
occurrences (all)	26		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	21 / 348 (6.03%)		
occurrences (all)	24		
Oropharyngeal pain			
subjects affected / exposed	13 / 348 (3.74%)		
occurrences (all)	15		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	16 / 348 (4.60%)		
occurrences (all)	16		
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	8 / 348 (2.30%)		
occurrences (all)	10		
Gastroenteritis			
subjects affected / exposed	15 / 348 (4.31%)		
occurrences (all)	21		
Influenza			
subjects affected / exposed	24 / 348 (6.90%)		
occurrences (all)	30		
Nasopharyngitis			
subjects affected / exposed	85 / 348 (24.43%)		
occurrences (all)	130		
Sinusitis			
subjects affected / exposed	21 / 348 (6.03%)		
occurrences (all)	31		
Upper respiratory tract infection			
subjects affected / exposed	40 / 348 (11.49%)		
occurrences (all)	58		
Urinary tract infection			
subjects affected / exposed	11 / 348 (3.16%)		
occurrences (all)	15		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 348 (1.72%)		
occurrences (all)	6		

Hyperglycaemia subjects affected / exposed occurrences (all)	17 / 348 (4.89%) 28		
Hypoglycaemia subjects affected / exposed occurrences (all)	24 / 348 (6.90%) 35		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2013	1) Correcting a discrepancy between the wording of the key exclusion criteria in the summary section and the exclusion criteria stated in the protocol so the text is in alignment. 2) The model for calculating within-subject variability in self-measured fasting plasma glucose for insulin dose titration was simplified to employ a fewer number of parameters. 3) A discrepancy in the wording of the MESI regarding administration of an accidental overdose in the protocol and Appendix were corrected.
26 February 2014	1) Further instruction/clarification was added to ensure that the insulin dose was reduced correctly when trial drug was started. 2) Endpoints of hypoglycaemia were slightly revised. The endpoint hypoglycaemia with concurrent presence of both hypoglycaemic symptoms and low glucose value was added. 3) Severe hypoglycaemic events were to undergo independent review to evaluate if the event was a severe hypoglycaemic event. It was decided to follow the same set-up and present the severe hypoglycaemic events to the EAC as described in the current protocol for other MESI requiring event adjudication. 4) Statistical consideration was updated in regards to the definition of the hypoglycaemic events. A figure illustrating the updated ADA definition of hypoglycaemic events was included. 5) An Investigator Portal was used to exchange documents between Novo Nordisk and the sites. Text regarding the Investigator Portal was added to provide clarification for sites. 6) Changes in the protocol were made for clarification and consistency purposes. The rationale for adjudicating the MESIs Fatal. Acute Coronory Syndrome and Cerebrovascular events was updated to clarify that this was performed in all Novo Nordisk trials with Victoza®.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported