Clinical trial results:
Efficacy and safety of semaglutide once-weekly versus exenatide ER 2.0 mg once-weekly as add-on to 1-2 oral antidiabetic drugs (OADs) in subjects with type 2 diabetes

Summary

EudraCT number	2012-004826-92
Trial protocol	IT DE NL FI GR GB HR
Global end of trial date	13 July 2015

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	NN9535-3624

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01885208
WHO universal trial number (UTN)	U1111-1135-8647

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 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 July 2015
Global end of trial reached?	Yes
Global end of trial date	13 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of semaglutide 1.0 mg once-weekly versus exenatide extended release (ER) 2.0 mg once-weekly on glycaemic control after 56 weeks of treatment

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice and FDA 21 CFR 312.50 and 56.

Background therapy:

The following compounds (1-2 OADs) were considered as background medication:
• Metformin
• Thiazolidinedione (TZD)
• Sulfonylureas (SU)
Metformin: doses ≥ 1500 mg or maximum tolerated dose. TZD and SU: doses ≥ half of maximum dose allowed according to national label.
Subjects upon inclusion continued pre-trial background medication throughout the entire trial. The background medication were maintained at the stable, pre-trial dose and frequency during the whole treatment period unless rescue medication was needed or if the subject had unacceptable hypoglycaemia on a background of SUs in which case the dose of SU was reduced.

Evidence for comparator:

Not applicable

Actual start date of recruitment	02 December 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	Serbia: 57
Country: Number of subjects enrolled	Argentina: 72
Country: Number of subjects enrolled	Switzerland: 19
Country: Number of subjects enrolled	United States: 313
Country: Number of subjects enrolled	Netherlands: 40
Country: Number of subjects enrolled	United Kingdom: 39
Country: Number of subjects enrolled	Croatia: 49
Country: Number of subjects enrolled	Finland: 23
Country: Number of subjects enrolled	France: 45
Country: Number of subjects enrolled	Germany: 54
Country: Number of subjects enrolled	Greece: 39
Country: Number of subjects enrolled	Italy: 59

Worldwide total number of subjects	809
EEA total number of subjects	348

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)	614
From 65 to 84 years	195
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 138 sites in 12 countries, Argentina: 4 sites; Croatia: 5 sites; Finland: 5 sites; France: 7 sites; Germany: 7 sites; Greece: 5 sites; Italy: 6 sites; Netherlands: 8 sites; Serbia: 5 sites; Switzerland: 5 sites; United Kingdom: 6 sites; and United States: 75 sites.

Pre-assignment

Screening details:

Not applicable

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Semaglutide 1.0 mg once-weekly

Arm description:

Subjects randomised to semaglutide followed a fixed dose-escalation regimen, starting with once-weekly doses of 0.25 mg for 4 weeks, then escalated to doses of 0.5 mg once weekly for 4 weeks, and finally escalated to 1.0 mg once weekly (maximum dose). Doses were not changed during the trial after the maintenance dose was reached.

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

Dosage and administration details:

Semaglutide 1.34 mg/mL, solution for injection, 1.5 mL pre-filled PDS290 pen-injector, one test pen per subject was given at the screening visit to ensure subject`s willingness and ability to self-inject. The test pen contained semaglutide placebo, solution for injection, 1.5 mL prefilled PDS290 pen-injector and was to be administered once. Subjects were instructed in administration of subcutaneous (s.c.) injection and the investigator documented whether direction for use (DFU) was given orally and/or in writing.

Arm title	Exenatide ER 2.0 mg once-weekly

Arm description:

Subjects on exenatide ER 2.0 mg were treated with the same 2.0 mg dose throughout the trial.

Arm type	Active comparator
Investigational medicinal product name	Exenatide
Investigational medicinal product code	
Other name	Bydureon
Pharmaceutical forms	Powder and solvent for prolonged-release suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Exenatide ER (Bydureon®), one vial of 2 mg exenatide extended-release for injectable suspension for s.c. injection, one pre-filled syringe of 0.65 mL solvent, one vial connector, and two injection needles (one spare) were given at the screening visit. Subjects were instructed in administration of s.c. injection and the investigator documented whether DFU was given orally and/or in writing.

Number of subjects in period 1	Semaglutide 1.0 mg once-weekly	Exenatide ER 2.0 mg once-weekly
Started	404	405
Premature discontinuation of treatment	82 [1]	85 [2]
Completed	374	369
Not completed	30	36
Not completed	30	36

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number represents only those participants who prematurely discontinued the treatment. However, subjects who prematurely discontinued treatment were allowed to continue participation in the trial.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number represents only those participants who prematurely discontinued the treatment. However, subjects who prematurely discontinued treatment were allowed to continue participation in the trial.

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide 1.0 mg once-weekly
Reporting group description:	
Subjects randomised to semaglutide followed a fixed dose-escalation regimen, starting with once-weekly doses of 0.25 mg for 4 weeks, then escalated to doses of 0.5 mg once weekly for 4 weeks, and finally escalated to 1.0 mg once weekly (maximum dose). Doses were not changed during the trial after the maintenance dose was reached.	
Reporting group title	Exenatide ER 2.0 mg once-weekly
Reporting group description:	
Subjects on exenatide ER 2.0 mg were treated with the same 2.0 mg dose throughout the trial.	

Reporting group values	Semaglutide 1.0 mg once-weekly	Exenatide ER 2.0 mg once-weekly	Total
Number of subjects	404	405	809
Age categorical			
Units: Subjects			
Age continuous			
The number of subjects analysed in the semaglutide and exenatide arms was 404 and 405, respectively.			
Units: years			
arithmetic mean	56.4	56.7	
standard deviation	± 10.3	± 11.1	-
Gender categorical			
The number of subjects analysed in the semaglutide and exenatide arms was 404 and 405, respectively.			
Units: Subjects			
Female	185	177	362
Male	219	228	447
Glycated haemoglobin (HbA1c)			
The number of subjects analysed in the semaglutide and exenatide arms was 404 and 405, respectively.			
Units: Percantage of glycated haemoglobin			
arithmetic mean	8.36	8.33	
standard deviation	± 0.95	± 0.96	-
Body weight			
The number of subjects analysed in the semaglutide and exenatide arms was 404 and 405, respectively.			
Units: kilogram(s)			
arithmetic mean	96.21	95.37	
standard deviation	± 22.5	± 20.46	-
Fasting Plasma Glucose			
The number of subjects analysed in the semaglutide and exenatide arms was 383 and 384, respectively.			
Units: mg/dL			
arithmetic mean	190.5	187.5	
standard deviation	± 48.06	± 49.41	-
Systolic blood pressure			
The number of subjects analysed in the semaglutide and exenatide arms was 404 and 404, respectively.			
Units: mm Hg			
arithmetic mean	133.35	133.66	
standard deviation	± 14.87	± 14.25	-
Diastolic blood pressure			

The number of subjects analysed in the semaglutide and exenatide arms was 404 and 404, respectively.			
Units: mm Hg			
arithmetic mean	80.23	79.57	
standard deviation	± 8.67	± 8.8	-
Patient-reported outcome: Diabetes Treatment Satisfaction Questionnaire (DTSQ)			
The result presented is the 'Treatment Satisfaction' summary score, which is the sum of 6 of the 8 items of the DTSQs questionnaire. The number of subjects analysed in the semaglutide and exenatide arms was 403 and 405, respectively.			
Units: Units on a scale			
arithmetic mean	27.35	27.23	
standard deviation	± 6.55	± 6.62	-

End points

End points reporting groups

Reporting group title	Semaglutide 1.0 mg once-weekly

Reporting group description:

Subjects randomised to semaglutide followed a fixed dose-escalation regimen, starting with once-weekly doses of 0.25 mg for 4 weeks, then escalated to doses of 0.5 mg once weekly for 4 weeks, and finally escalated to 1.0 mg once weekly (maximum dose). Doses were not changed during the trial after the maintenance dose was reached.

Reporting group title	Exenatide ER 2.0 mg once-weekly

Reporting group description:

Subjects on exenatide ER 2.0 mg were treated with the same 2.0 mg dose throughout the trial.

Primary: Change in HbA1c

End point title	Change in HbA1c

End point description:

Change in HbA1c from baseline to week 56. The full analysis set (FAS) included all randomised subjects who had received at least one dose of randomised semaglutide 1.0 mg or exenatide ER 2.0 mg.

End point type	Primary

End point timeframe:

From baseline to week 56

End point values	Semaglutide 1.0 mg once-weekly	Exenatide ER 2.0 mg once-weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	405		
Units: Percentage of glycated haemoglobin				
least squares mean (standard error)	-1.54 (± 0.06)	-0.92 (± 0.06)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The post-baseline responses were analysed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

Comparison groups	Semaglutide 1.0 mg once-weekly v Exenatide ER 2.0 mg once-weekly

Number of subjects included in analysis	809
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.44

Notes:

[1] - Non-inferiority was concluded if the upper limit of the two-sided 95% confidence interval for the estimated treatment difference between semaglutide 1.0 mg and exenatide ER 2.0 mg was below the pre-specified non-inferiority margin (0.3 %).

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The post-baseline responses were analysed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

Comparison groups	Semaglutide 1.0 mg once-weekly v Exenatide ER 2.0 mg once-weekly
Number of subjects included in analysis	809
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.44

Notes:

[2] - Superiority was concluded if the upper limit of the two-sided 95% confidence interval for the estimated treatment difference between semaglutide 1.0 mg and exenatide ER 2.0 mg was below the pre-specified superiority margin (0 %).

Secondary: Change in body weight

End point title	Change in body weight

End point description:

The full analysis set (FAS) included all randomised subjects who had received at least one dose of randomised semaglutide 1.0 mg or exenatide ER 2.0 mg.

End point type	Secondary

End point timeframe:

From baseline to week 56

End point values	Semaglutide 1.0 mg once-weekly	Exenatide ER 2.0 mg once-weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	405		
Units: kilograms				
least squares mean (standard error)	-5.63 (± 0.29)	-1.85 (± 0.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (FPG)

End point title	Change in fasting plasma glucose (FPG)

End point description:

The full analysis set (FAS) included all randomised subjects who had received at least one dose of randomised semaglutide 1.0 mg or exenatide ER 2.0 mg.

End point type	Secondary

End point timeframe:

From baseline to week 56

End point values	Semaglutide 1.0 mg once-weekly	Exenatide ER 2.0 mg once-weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	405		
Units: mg/dL				
least squares mean (standard error)	-51.22 (± 2.36)	-36.1 (± 2.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in diastolic blood pressure

End point title	Change in diastolic blood pressure

End point description:

The full analysis set (FAS) included all randomised subjects who had received at least one dose of randomised semaglutide 1.0 mg or exenatide ER 2.0 mg.

End point type	Secondary

End point timeframe:

From baseline to week 56

End point values	Semaglutide 1.0 mg once-weekly	Exenatide ER 2.0 mg once-weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	405		
Units: mm Hg				
least squares mean (standard error)	-1 (± 0.45)	-0.1 (± 0.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in systolic blood pressure

End point title	Change in systolic blood pressure

End point description:

The full analysis set (FAS) included all randomised subjects who had received at least one dose of randomised semaglutide 1.0 mg or exenatide ER 2.0 mg.

End point type	Secondary

End point timeframe:

From baseline to week 56

End point values	Semaglutide 1.0 mg once-weekly	Exenatide ER 2.0 mg once-weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	405		
Units: mm Hg				
least squares mean (standard error)	-4.6 (± 0.68)	-2.23 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Patient reported outcome (PRO) questionnaire Diabetes Treatment Satisfaction Questionnaire status (DTSQs)

End point title	Change in Patient reported outcome (PRO) questionnaire Diabetes Treatment Satisfaction Questionnaire status (DTSQs)

End point description:

The DTSQs questionnaire was used to assess subjects’ treatment satisfaction. This questionnaire contained 8 components and evaluated the diabetes treatment (including insulin, tablets and/or diet) in terms of convenience, flexibility and general feelings regarding towards the treatment. The result presented is the 'Treatment Satisfaction' summary score, which is the sum of 6 of the 8 items of the

DTSQs questionnaire. The full analysis set (FAS) included all randomised subjects who had received at least one dose of randomised semaglutide 1.0 mg or exenatide ER 2.0 mg.

End point type	Secondary

End point timeframe:

From baseline to week 56

End point values	Semaglutide 1.0 mg once-weekly	Exenatide ER 2.0 mg once-weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	405		
Units: Units on a scale				
least squares mean (standard error)	4.98 (± 0.26)	3.96 (± 0.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects who achieve HbA1c ≤6.5% (48 mmol/mol) American Association of Clinical Endocrinologists (AACE) target (yes/no)

End point title	Subjects who achieve HbA1c ≤6.5% (48 mmol/mol) American Association of Clinical Endocrinologists (AACE) target (yes/no)

End point description:

The endpoint considered HbA1c ≤6.5% (48 mmol/mol) as per the AACE (American Association of Clinical Endocrinologists) target. The full analysis set (FAS) included all randomised subjects who had received at least one dose of randomised semaglutide 1.0 mg or exenatide ER 2.0 mg.

End point type	Secondary

End point timeframe:

After 56 weeks' treatment

End point values	Semaglutide 1.0 mg once-weekly	Exenatide ER 2.0 mg once-weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	405		
Units: Subjects				
Yes	190	89		
No	214	316		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First day of exposure to trial product and until week 61

Adverse event reporting additional description:

The 'on-treatment' overview includes treatment-emergent adverse events with onset at or after the date of the first trial product dose and before or at the date of the last trial product dose plus 5 weeks plus the 7 days visit window for the end-of-treatment follow-up visit (=42 days).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	exenatide ER 2.0 mg

Reporting group description:

Subjects on exenatide ER 2.0 mg were treated with the same dose throughout the trial.

Reporting group title	semaglutide 1.0 mg

Reporting group description:

Subjects randomised to semaglutide followed a fixed dose-escalation regimen, starting with doses of 0.25 mg for 4 weeks, then escalated to doses of 0.5 mg for 4 weeks, and finally escalated to 1.0 mg (maximum dose). Doses were not changed during the trial after the maintenance dose was reached.

Serious adverse events	exenatide ER 2.0 mg	semaglutide 1.0 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 405 (5.93%)	38 / 404 (9.41%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign renal neoplasm			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 405 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Castleman's disease			

subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer stage I			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Follicular thyroid cancer			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ablation			

subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary arterial stent insertion			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery bypass			
subjects affected / exposed	0 / 405 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus removal			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical failure			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
HIV test positive			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Spinal compression fracture			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
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 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
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	3 / 405 (0.74%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			

subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery insufficiency			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 405 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 405 (0.00%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 405 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal colic			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal disorder			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 405 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 405 (0.49%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 405 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			

subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
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	exenatide ER 2.0 mg	semaglutide 1.0 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	187 / 405 (46.17%)	194 / 404 (48.02%)	
Investigations			
Lipase increased			
subjects affected / exposed	49 / 405 (12.10%)	41 / 404 (10.15%)	
occurrences (all)	64	51	
Nervous system disorders			
Headache			
subjects affected / exposed	39 / 405 (9.63%)	38 / 404 (9.41%)	
occurrences (all)	65	81	
General disorders and administration site conditions			
Injection site nodule			
subjects affected / exposed	49 / 405 (12.10%)	0 / 404 (0.00%)	
occurrences (all)	55	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	34 / 405 (8.40%)	46 / 404 (11.39%)	
occurrences (all)	58	86	
Constipation			

subjects affected / exposed	21 / 405 (5.19%)	26 / 404 (6.44%)	
occurrences (all)	26	28	
Dyspepsia			
subjects affected / exposed	19 / 405 (4.69%)	27 / 404 (6.68%)	
occurrences (all)	23	33	
Nausea			
subjects affected / exposed	48 / 405 (11.85%)	90 / 404 (22.28%)	
occurrences (all)	70	159	
Vomiting			
subjects affected / exposed	25 / 405 (6.17%)	29 / 404 (7.18%)	
occurrences (all)	40	37	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	38 / 405 (9.38%)	39 / 404 (9.65%)	
occurrences (all)	51	46	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 405 (5.19%)	32 / 404 (7.92%)	
occurrences (all)	24	34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2014	Update of the hypoglycaemic definition and endpoint in this connection, rescue medication criteria, statistical analysis and other minor corrections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported