Clinical trial results:
Efficacy and safety of semaglutide once-weekly versus placebo in drug-naïve subjects with type 2 diabetes

Summary

EudraCT number	2013-000632-94
Trial protocol	IT GB
Global end of trial date	08 May 2015

Results information

Result version number	v1 (current)
This version publication date	20 May 2016
First version publication date	20 May 2016

Trial information

Trial identification

Sponsor protocol code	NN9535-3623

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02054897
WHO universal trial number (UTN)	U1111-1139-3090

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	22 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 May 2015
Global end of trial reached?	Yes
Global end of trial date	08 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate superiority of once-weekly dosing of two dose levels of semaglutide versus placebo on glycaemic control after 30 weeks of treatment in drug-naïve subjects with type 2 diabetes

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice, EN ISO 14155 Part 1 and 2 and FDA 21 CFR 312.120

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	03 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Canada: 39
Country: Number of subjects enrolled	Japan: 61
Country: Number of subjects enrolled	Mexico: 33
Country: Number of subjects enrolled	Russian Federation: 52
Country: Number of subjects enrolled	South Africa: 26
Country: Number of subjects enrolled	United States: 124
Worldwide total number of subjects	387
EEA total number of subjects	52

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)	317
From 65 to 84 years	69
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

There were 72 sites in 8 countries that randomised subjects: Canada: 7 sites; Italy: 6 sites; Japan: 5 sites; Mexico: 2 sites; Russian Federation: 8 sites; South Africa: 8 sites; United Kingdom: 4 sites; United States: 32 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	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Semaglutide and placebo were supplied in similar 1.5 mL pre-filled PDS290 pen-injector and were by all means visually identical and were packed and labelled to fulfil the requirements for double blind procedures. Furthermore, equal volumes of semaglutide and placebo were administered during treatment ensuring blinding within dose-level.

Arms

Are arms mutually exclusive?	Yes
Arm title	Semaglutide 0.5 mg

Arm description:

Subjects were given 0.25 mg semaglutide once weekly for 4 weeks followed by 0.5 mg semaglutide once weekly for the remaining 26 weeks of the treatment period.

Arm type	Experimental
Investigational medicinal product name	Semaglutide B 1.34 mg/ml PDS290
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were given 0.25 mg semaglutide once weekly for 4 weeks followed by 0.5 mg semaglutide once weekly for the remaining 26 weeks of the treatment period. Administered subcutaneously (s.c., under the skin).

Arm title	Semaglutide 1.0 mg

Arm description:

Subjects were given 0.25 mg semaglutide once weekly for 4 weeks, 0.5 mg semaglutide once weekly for the next 4 weeks followed by 1.0 mg semaglutide once weekly for the remaining 22 weeks of the treatment period.

Arm type	Experimental
Investigational medicinal product name	Semaglutide B 1.34 mg/ml PDS290
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were given 0.25 mg semaglutide once weekly for 4 weeks, 0.5 mg semaglutide once weekly for the next 4 weeks followed by 1.0 mg semaglutide once weekly for the remaining 22 weeks of the treatment period. Administered subcutaneously (s.c., under the skin).

Arm title	Placebo

Arm description:

Subjects randomised to either of the 2 different placebo arms, i.e., placebo 0.5 mg arm or placebo 1.0 mg arm. These 2 placebo arms were pooled together for data analysis.
a. Placebo 0.5 mg arm: Subjects were given 0.25 mg placebo once weekly for 4 weeks followed by 0.5 mg placebo once weekly for the remaining 26 weeks of the treatment period.
b. Placebo 1.0 mg arm: Subjects were given 0.25 mg placebo once weekly for 4 weeks, 0.5 mg placebo once weekly for the next 4 weeks followed by 1.0 mg placebo once weekly for the remaining 22 weeks of the treatment period.

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 0.5 mg arm: Subjects were given 0.25 mg placebo once weekly for 4 weeks followed by 0.5 mg placebo once weekly for the remaining 26 weeks of the treatment period. Administered subcutaneously (s.c., under the skin).
Placebo 1.0 mg arm: Subjects were given 0.25 mg placebo once weekly for 4 weeks, 0.5 mg placebo once weekly for the next 4 weeks followed by 1.0 mg placebo once weekly for the remaining 22 weeks of the treatment period. Administered subcutaneously (s.c., under the skin).

Number of subjects in period 1	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo
Started	128	130	129
Completed	119	123	117
Not completed	9	7	12
Lost to follow-up	4	2	7
Missing follow-up information	3	5	3
Withdrawal by subject	2	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide 0.5 mg
Reporting group description:	
Subjects were given 0.25 mg semaglutide once weekly for 4 weeks followed by 0.5 mg semaglutide once weekly for the remaining 26 weeks of the treatment period.	
Reporting group title	Semaglutide 1.0 mg
Reporting group description:	
Subjects were given 0.25 mg semaglutide once weekly for 4 weeks, 0.5 mg semaglutide once weekly for the next 4 weeks followed by 1.0 mg semaglutide once weekly for the remaining 22 weeks of the treatment period.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomised to either of the 2 different placebo arms, i.e., placebo 0.5 mg arm or placebo 1.0 mg arm. These 2 placebo arms were pooled together for data analysis. a. Placebo 0.5 mg arm: Subjects were given 0.25 mg placebo once weekly for 4 weeks followed by 0.5 mg placebo once weekly for the remaining 26 weeks of the treatment period. b. Placebo 1.0 mg arm: Subjects were given 0.25 mg placebo once weekly for 4 weeks, 0.5 mg placebo once weekly for the next 4 weeks followed by 1.0 mg placebo once weekly for the remaining 22 weeks of the treatment period.	

Reporting group values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo
Number of subjects	128	130	129
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54.6	52.7	53.9
standard deviation	± 11.1	± 11.9	± 11
Gender categorical Units: Subjects			
Female	68	50	59
Male	60	80	70
HbA1c Units: Percentage			
arithmetic mean	8.09	8.12	7.95
standard deviation	± 0.89	± 0.81	± 0.85
Fasting plasma glucose Units: mmol/L			
arithmetic mean	9.66	9.9	9.68
standard deviation	± 2.77	± 2.5	± 2.77
Body weight Units: kilogram(s)			
arithmetic mean	89.81	96.87	89.05
standard deviation	± 22.96	± 25.59	± 22.16
Diastolic blood pressure Units: mmHg			
arithmetic mean	79.52	79.25	79.14
standard deviation	± 9.06	± 8.52	± 8.39

Systolic blood pressure Units: mmHg			
arithmetic mean	127.87	128.89	129.57
standard deviation	± 13.15	± 12.92	± 13.5

Reporting group values	Total		
Number of subjects	387		
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	177		
Male	210		
HbA1c Units: Percentage			
arithmetic mean			
standard deviation	-		
Fasting plasma glucose Units: mmol/L			
arithmetic mean			
standard deviation	-		
Body weight Units: kilogram(s)			
arithmetic mean			
standard deviation	-		
Diastolic blood pressure Units: mmHg			
arithmetic mean			
standard deviation	-		
Systolic blood pressure Units: mmHg			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Semaglutide 0.5 mg

Reporting group description:

Subjects were given 0.25 mg semaglutide once weekly for 4 weeks followed by 0.5 mg semaglutide once weekly for the remaining 26 weeks of the treatment period.

Reporting group title	Semaglutide 1.0 mg

Reporting group description:

Subjects were given 0.25 mg semaglutide once weekly for 4 weeks, 0.5 mg semaglutide once weekly for the next 4 weeks followed by 1.0 mg semaglutide once weekly for the remaining 22 weeks of the treatment period.

Reporting group title	Placebo

Reporting group description:

Subjects randomised to either of the 2 different placebo arms, i.e., placebo 0.5 mg arm or placebo 1.0 mg arm. These 2 placebo arms were pooled together for data analysis.
a. Placebo 0.5 mg arm: Subjects were given 0.25 mg placebo once weekly for 4 weeks followed by 0.5 mg placebo once weekly for the remaining 26 weeks of the treatment period.
b. Placebo 1.0 mg arm: Subjects were given 0.25 mg placebo once weekly for 4 weeks, 0.5 mg placebo once weekly for the next 4 weeks followed by 1.0 mg placebo once weekly for the remaining 22 weeks of the treatment period.

Primary: Change in HbA1c

End point title	Change in HbA1c

End point description:

Change in HbA1c from baseline to week 30. Full analysis set (FAS) included all randomised subjects who had received at least 1 dose of randomised semaglutide or placebo. Missing data imputed from a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

End point type	Primary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	130	129	
Units: Percentage				
arithmetic mean (standard deviation)	-1.47 (± 1.02)	-1.56 (± 1.26)	0 (± 0.9)	

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

For the primary HbA1c endpoint, superiority was planned to be tested for semaglutide 1.0 mg versus placebo. Superiority for change in HbA1c was claimed if the upper limit of the 2-sided 95% CI for the estimated difference was below 0%.

Comparison groups	Semaglutide 1.0 mg v Placebo
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.81
upper limit	-1.25

Notes:

[1] - 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.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

For the primary HbA1c endpoint, superiority was planned to be tested for semaglutide 0.5 mg versus placebo, if superiority for semaglutide 1.0 mg was concluded. Superiority for change in HbA1c was claimed if the upper limit of the 2-sided 95% CI for the estimated difference was below 0%.

Comparison groups	Semaglutide 0.5 mg v Placebo
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	-1.15

Notes:

[2] - 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.

Secondary: Change in body weight.

End point title	Change in body weight.

End point description:

Change in body weight from baseline to week 30. Full analysis set (FAS) included all randomised subjects who had received at least 1 dose of randomised semaglutide or placebo. Missing data imputed from a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	130	129	
Units: kilogram(s)				
arithmetic mean (standard deviation)	-3.68 (± 4.03)	-4.67 (± 5.19)	-0.89 (± 3.46)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Fasting plasma glucose

End point title	Change in Fasting plasma glucose

End point description:

Change in Fasting plasma glucose from baseline to week 30. Full analysis set (FAS) included all randomised subjects who had received at least 1 dose of randomised semaglutide or placebo. Missing data imputed from a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	125	129	127	
Units: mmol/L				
arithmetic mean (standard deviation)	-2.41 (± 2.55)	-2.39 (± 2.74)	-0.55 (± 2.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in systolic and diastolic blood pressure

End point title	Change in systolic and diastolic blood pressure

End point description:

Change in systolic and diastolic blood pressure from baseline to week 30. Full analysis set (FAS) included all randomised subjects who had received at least 1 dose of randomised semaglutide or placebo. Missing data imputed from a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

End point type	Secondary

End point timeframe:

From baseline to week 30.

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	130	129	
Units: mmHg				
arithmetic mean (standard deviation)				
Systolic blood pressure	-2.29 (± 12.58)	-2.74 (± 11.58)	-2.01 (± 11.23)	
Diastolic blood pressure	-0.73 (± 6.88)	0.22 (± 7.6)	0.6 (± 7.59)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects who achieve (yes/no): HbA1c below 7.0% (53 mmol/mol) American Diabetes Association target

End point title	Subjects who achieve (yes/no): HbA1c below 7.0% (53 mmol/mol) American Diabetes Association target

End point description:

Percentage of subjects who achieve (yes/no): HbA1c below 7.0% (53 mmol/mol) American Diabetes Association target after 30 weeks' treatment. Full analysis set (FAS) included all randomised subjects who had received at least 1 dose of randomised semaglutide or placebo. Missing data imputed from a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

End point type	Secondary

End point timeframe:

After 30 weeks' treatment

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	130	129	
Units: percentage				
number (not applicable)				
Yes	74.2	72.3	24.8	
No	25.8	27.7	75.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects who achieve (yes/no): HbA1c equal to or below 6.5% (48 mmol/mol) American Association of Clinical Endocrinologists target

End point title	Subjects who achieve (yes/no): HbA1c equal to or below 6.5% (48 mmol/mol) American Association of Clinical Endocrinologists target

End point description:

Percentage of subjects who achieve (yes/no): HbA1c below 6.5% (48 mmol/mol) American Diabetes Association target after 30 weeks' treatment. Full analysis set (FAS) included all randomised subjects who had received at least 1 dose of randomised semaglutide or placebo. Missing data imputed from a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

End point type	Secondary

End point timeframe:

After 30 weeks' treatment

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	130	129	
Units: Percentage				
number (not applicable)				
Yes	59.4	60	13.2	
No	40.6	40	86.8	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first trial product dose (visit 2) till the date of the end-of-treatment follow-up visit (visit 11) or on the date of the last trial product dose plus 42 days (5 weeks plus the 7 days visit window).

Adverse event reporting additional description:

Safety analysis set (SAS) included all randomised subjects who had received at least 1 dose of randomised semaglutide or placebo.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Semaglutide 0.5 mg

Reporting group description:

Subjects were given 0.25 mg semaglutide once weekly for 4 weeks followed by 0.5 mg semaglutide once weekly for the remaining 26 weeks of the treatment period.

Reporting group title	Placebo

Reporting group description:

Subjects randomised to either of the 2 different placebo arms, i.e., placebo 0.5 mg arm or placebo 1.0 mg arm. These 2 placebo arms were pooled together for data analysis.
a. Placebo 0.5 mg arm: Subjects were given 0.25 mg placebo once weekly for 4 weeks followed by 0.5 mg placebo once weekly for the remaining 26 weeks of the treatment period.
b. Placebo 1.0 mg arm: Subjects were given 0.25 mg placebo once weekly for 4 weeks, 0.5 mg placebo once weekly for the next 4 weeks followed by
1.0 mg placebo once weekly for the remaining 22 weeks of the treatment period.

Reporting group title	Semaglutide 1.0 mg

Reporting group description:

Subjects were given 0.25 mg semaglutide once weekly for 4 weeks, 0.5 mg semaglutide once weekly for the next 4 weeks followed by 1.0 mg semaglutide once weekly for the remaining 22 weeks of the treatment period.

Serious adverse events	Semaglutide 0.5 mg	Placebo	Semaglutide 1.0 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 128 (5.47%)	5 / 129 (3.88%)	7 / 130 (5.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 128 (0.78%)	0 / 129 (0.00%)	0 / 130 (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
Prostate cancer			

subjects affected / exposed	0 / 128 (0.00%)	0 / 129 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Coronary revascularisation			
subjects affected / exposed	0 / 128 (0.00%)	0 / 129 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric bypass			
subjects affected / exposed	0 / 128 (0.00%)	0 / 129 (0.00%)	2 / 130 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	0 / 128 (0.00%)	1 / 129 (0.78%)	0 / 130 (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
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 128 (0.78%)	0 / 129 (0.00%)	0 / 130 (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			
Mental disorder			
subjects affected / exposed	1 / 128 (0.78%)	0 / 129 (0.00%)	0 / 130 (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
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	0 / 128 (0.00%)	0 / 129 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	0 / 128 (0.00%)	0 / 129 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 129 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 128 (0.78%)	0 / 129 (0.00%)	0 / 130 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 128 (0.00%)	1 / 129 (0.78%)	0 / 130 (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			
Gastric haemorrhage			
subjects affected / exposed	0 / 128 (0.00%)	1 / 129 (0.78%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 128 (0.78%)	0 / 129 (0.00%)	0 / 130 (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
Oesophagitis			
subjects affected / exposed	1 / 128 (0.78%)	0 / 129 (0.00%)	0 / 130 (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
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	1 / 128 (0.78%)	0 / 129 (0.00%)	0 / 130 (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
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 128 (0.00%)	0 / 129 (0.00%)	1 / 130 (0.77%)
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 and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 128 (0.00%)	1 / 129 (0.78%)	0 / 130 (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			
Cystitis			
subjects affected / exposed	1 / 128 (0.78%)	0 / 129 (0.00%)	0 / 130 (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
Encephalitis			
subjects affected / exposed	1 / 128 (0.78%)	0 / 129 (0.00%)	0 / 130 (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
Lobar pneumonia			
subjects affected / exposed	1 / 128 (0.78%)	0 / 129 (0.00%)	0 / 130 (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
Subcutaneous abscess			
subjects affected / exposed	0 / 128 (0.00%)	1 / 129 (0.78%)	0 / 130 (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

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

Non-serious adverse events	Semaglutide 0.5 mg	Placebo	Semaglutide 1.0 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 128 (41.41%)	27 / 129 (20.93%)	47 / 130 (36.15%)
Investigations			
Lipase increased			
subjects affected / exposed	8 / 128 (6.25%)	5 / 129 (3.88%)	5 / 130 (3.85%)
occurrences (all)	10	5	5
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 128 (11.72%)	8 / 129 (6.20%)	9 / 130 (6.92%)
occurrences (all)	43	13	18
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 128 (6.25%)	1 / 129 (0.78%)	5 / 130 (3.85%)
occurrences (all)	9	2	5
Diarrhoea			
subjects affected / exposed	16 / 128 (12.50%)	3 / 129 (2.33%)	14 / 130 (10.77%)
occurrences (all)	27	3	19
Dyspepsia			
subjects affected / exposed	7 / 128 (5.47%)	3 / 129 (2.33%)	5 / 130 (3.85%)
occurrences (all)	13	3	5
Nausea			
subjects affected / exposed	26 / 128 (20.31%)	10 / 129 (7.75%)	31 / 130 (23.85%)
occurrences (all)	44	12	46
Vomiting			
subjects affected / exposed	5 / 128 (3.91%)	2 / 129 (1.55%)	9 / 130 (6.92%)
occurrences (all)	11	2	15
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 128 (4.69%)	7 / 129 (5.43%)	6 / 130 (4.62%)
occurrences (all)	7	9	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2014	The main objective was to update the definition of hypoglycaemia and to include an additional hypoglycaemic endpoint on severe or BG-confirmed symptomatic hypoglycaemic episodes and associated statistical analysis and minor updates for general clarification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported