Clinical trial results:
Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes and moderate renal impairment. A 26-week randomised, double-blind, placebo-controlled trial

Summary

EudraCT number	2015-005326-19
Trial protocol	SE DK FI PL GB
Global end of trial date	15 May 2018

Results information

Result version number	v1 (current)
This version publication date	30 May 2019
First version publication date	30 May 2019

Trial information

Trial identification

Sponsor protocol code	NN9924-4234

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02827708
WHO universal trial number (UTN)	U1111-1176-9230

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 April 2018
Global end of trial reached?	Yes
Global end of trial date	15 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of once daily dosing of 14 mg oral semaglutide versus placebo, both in combination with metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin on glycaemic control in subjects with type 2 diabetes mellitus and moderate renal impairment.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013), ICH Good Clinical Practice, including archiving of essential documents, (1996) and 21 CFR 312.120.

Background therapy:

Subjects were to continue their following listed pre-trial antidiabetic medications for the entire treatment period (week 1 - 26): metformin and/or sulphonylurea, basal insulin alone or metformin in combination with basal insulin.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	20 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	Israel: 21
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Russian Federation: 126
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 36
Country: Number of subjects enrolled	United States: 94
Worldwide total number of subjects	324
EEA total number of subjects	83

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	65
From 65 to 84 years	251
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 8 countries (107 sites screened/88 randomised subjects), as follows: Denmark: 7/4; Finland: 7/7; Israel: 7/6; Poland: 2/2; Russian Federation: 19/18; Sweden: 6/4; United Kingdom: 9/7; United States (US):50/40. In addition, 10 sites in the US were approved by the institutional review board, but didn't randomise any subject

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:

The trial was double blinded and the clinical study group and the investigator remained blinded throughout the trial. The blinding was to be maintained until the database had been released for statistical analysis after database lock. The trial products (oral semaglutide 3, 7 and 14 mg as well as placebo) were manufactured as visually identical tablets for oral administration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Oral semaglutide 14 mg

Arm description:

Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 1 to 26: 3 mg from week 1 to 4, 7 mg from week 5 to 8 and 14 mg from week 9 to 26.

Arm type	Experimental
Investigational medicinal product name	Semaglutide 3 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Semaglutide 3 mg tablets were to be taken from week 1 to 4, once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The trial product could be taken with up to half a glass of water (approximately 120 mL/4 fluid ounces) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could only be taken 30 minutes after administration of trial product.

Investigational medicinal product name	Semaglutide 7 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Semaglutide 7 mg tablets were to be taken from week 5 to 8, once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The trial product could be taken with up to half a glass of water (approximately 120 mL/4 fluid ounces) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could only be taken 30 minutes after administration of trial product.

Investigational medicinal product name	Semaglutide 14 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Semaglutide 14 mg tablets were to be taken from week 9 to 26, once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The trial product could be taken with up to half a glass of water (approximately 120 mL/4 fluid ounces) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could only be taken 30 minutes after administration of trial product.

Arm title	Placebo

Arm description:

Subjects were to take oral semaglutide placebo tablets once daily from week 1 to 26.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Semaglutide placebo tablets were to be taken from week 1 – 26, once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The trial product could be taken with up to half a glass of water (approximately 120 mL/4 fluid ounces) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could only be taken 30 minutes after administration of trial product.

Number of subjects in period 1	Oral semaglutide 14 mg	Placebo
Started	163	161
Completed	158	156
Not completed	5	5
Adverse event, serious fatal	1	2
Consent withdrawn by subject	1	2
Lost to follow-up	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Oral semaglutide 14 mg
Reporting group description:	
Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 1 to 26: 3 mg from week 1 to 4, 7 mg from week 5 to 8 and 14 mg from week 9 to 26.	
Reporting group title	Placebo
Reporting group description:	
Subjects were to take oral semaglutide placebo tablets once daily from week 1 to 26.	

Reporting group values	Oral semaglutide 14 mg	Placebo	Total
Number of subjects	163	161	324
Age Categorical Units: Subjects			
Adults (18-64 years)	26	39	65
From 65-84 years	130	121	251
85 years and over	7	1	8
Age Continuous Units: years			
arithmetic mean	71	70	
standard deviation	± 8	± 8	-
Gender Categorical Units: Subjects			
Female	80	88	168
Male	83	73	156
Glycosylated haemoglobin (HbA1c) Units: Percentage of HbA1c			
arithmetic mean	8.0	7.9	
standard deviation	± 0.7	± 0.7	-

End points

End points reporting groups

Reporting group title	Oral semaglutide 14 mg
Reporting group description:	
Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 1 to 26: 3 mg from week 1 to 4, 7 mg from week 5 to 8 and 14 mg from week 9 to 26.	
Reporting group title	Placebo
Reporting group description:	
Subjects were to take oral semaglutide placebo tablets once daily from week 1 to 26.	

Primary: Change in glycosylated haemoglobin (HbA1c) (In-trial observation period)

End point title	Change in glycosylated haemoglobin (HbA1c) (In-trial observation period)
End point description:	
Change from baseline (week 0) in HbA1c was evaluated at week 26. Results are based on the in-trial observation period, which was the time period from when a subject was randomised until the final scheduled visit, including any period after initiation of rescue medication and/or premature discontinuation of trial product. Population analysed: The full analysis set (FAS), which comprised all randomised subjects. Number of subjects analysed = number of subjects with available data.	
End point type	Primary
End point timeframe:	
From baseline to week 26	

End point values	Oral semaglutide 14 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	155		
Units: Percentage-point of HbA1c				
arithmetic mean (standard deviation)	-1.1 (± 1.0)	-0.2 (± 0.9)		

Statistical analyses

Statistical analysis title	Oral semaglutide 14 mg versus Placebo
Statistical analysis description:	
The analysis was based on a pattern mixture model using multiple imputation to impute missing week-26 data, assuming that such data were missing at random. The imputed data sets were analysed using an analysis of covariance (ANCOVA) model with treatment, region, stratification factors and the interaction between the two stratification factors as categorical fixed effects and the baseline HbA1c value as a covariate.	
Comparison groups	Oral semaglutide 14 mg v Placebo

Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.6

Notes:

[1] - This hypothesis was controlled for multiplicity. The estimated treatment effect includes the effect of any rescue medication and any effect after premature trial product discontinuation (treatment policy estimand). Number of subjects included in analysis = Number of subjects in the FAS, who contributed to the analysis (N = 324).

Primary: Change in glycosylated haemoglobin (HbA1c) (On-treatment without rescue medication observation period)

End point title	Change in glycosylated haemoglobin (HbA1c) (On-treatment without rescue medication observation period)

End point description:

Change from baseline (week 0) in HbA1c was evaluated at week 26. Results are based on the on treatment without rescue medication observation period, which was the time period when a subject was on treatment with trial product, excluding any period after initiation of rescue medication and/or premature trial product discontinuation. Population analysed: The FAS. Number of subjects analysed = number of subjects with available data.

End point type	Primary

End point timeframe:

From baseline to week 26

End point values	Oral semaglutide 14 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	127		
Units: Percentage-point of HbA1c				
arithmetic mean (standard deviation)	-1.2 (± 0.9)	-0.1 (± 0.9)		

Statistical analyses

Statistical analysis title	Oral semaglutide 14 mg versus Placebo

Statistical analysis description:

The analysis was based on a mixed model for repeated measurements (MMRM) that assumed data to be missing at random. The analysis included all scheduled post-baseline measurements up to and including week 26 as dependent variables. The independent effects were treatment, stratification factors, the interaction between the two stratification factors and region as categorical fixed effects and the baseline value as a covariate, all nested within visit.

Comparison groups	Oral semaglutide 14 mg v Placebo

Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.8

Notes:

[2] - This hypothesis was not controlled for multiplicity. The estimated treatment effect excludes the effect of any rescue medication and any effect after premature trial product discontinuation (hypothetical estimand). Number of subjects included in analysis = Number of subjects in the FAS, who contributed to the analysis (N = 324).

Secondary: Change in body weight (kg) (In-trial observation period)

End point title	Change in body weight (kg) (In-trial observation period)

End point description:

Change from baseline (week 0) in body weight was evaluated at week 26. Results are based on the in-trial observation period. Population analysed: The FAS. Number of subjects analysed = number of subjects with available data.

End point type	Secondary

End point timeframe:

From baseline to week 26

End point values	Oral semaglutide 14 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	155		
Units: Kg				
arithmetic mean (standard deviation)	-3.5 (± 3.8)	-0.9 (± 2.9)		

Statistical analyses

Statistical analysis title	Oral semaglutide 14 mg versus Placebo

Statistical analysis description:

The analysis was based on a pattern mixture model using multiple imputation to impute missing week-26 data, assuming that such data were missing at random. The imputed data sets were analysed using an ANCOVA model with treatment, region, stratification factors and the interaction between the two stratification factors as categorical fixed effects and the baseline body weight value as a covariate.

Comparison groups	Oral semaglutide 14 mg v Placebo

Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	-1.8

Notes:

[3] - This hypothesis was controlled for multiplicity. The estimated treatment effect includes the effect of any rescue medication and any effect after premature trial product discontinuation (treatment policy estimand). Number of subjects included in analysis = Number of subjects in the FAS, who contributed to the analysis (N = 323).

Secondary: Change in body weight (kg) (On-treatment without rescue medication observation period)

End point title	Change in body weight (kg) (On-treatment without rescue medication observation period)

End point description:

Change from baseline (week 0) in body weight was evaluated at week 26. Results are based on the on treatment without rescue medication observation period. Population analysed: The FAS. Number of subjects analysed = number of subjects with available data.

End point type	Secondary

End point timeframe:

From baseline to week 26

End point values	Oral semaglutide 14 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	127		
Units: Kg				
arithmetic mean (standard deviation)	-3.9 (± 3.6)	-0.9 (± 2.9)		

Statistical analyses

Statistical analysis title	Oral semaglutide 14 mg versus Placebo

Statistical analysis description:

The analysis was based on a MMRM that assumed data to be missing at random. The analysis included all scheduled post-baseline measurements up to and including week 26 as dependent variables. The independent effects were treatment, stratification factors, the interaction between the two stratification factors and region as categorical fixed effects and the baseline value as a covariate, all nested within visit.

Comparison groups	Oral semaglutide 14 mg v Placebo

Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	-1.9

Notes:

[4] - This hypothesis was not controlled for multiplicity. The estimated treatment effect excludes the effect of any rescue medication and any effect after premature trial product discontinuation (hypothetical estimand). Number of subjects included in analysis = Number of subjects in the FAS, who contributed to the analysis (N = 323).

Secondary: Change in fasting plasma glucose

End point title	Change in fasting plasma glucose

End point description:

Change from baseline (week 0) in fasting plasma glucose (FPG) was evaluated at week 26. Results are based on the in-trial observation period. Population analysed: The FAS. Number of subjects analysed = number of subjects with available data.

End point type	Secondary

End point timeframe:

From baseline to week 26

End point values	Oral semaglutide 14 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	151		
Units: mmol/L				
arithmetic mean (standard deviation)	-1.58 (± 2.96)	-0.34 (± 3.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: HbA1c <7.0% (53 mmol/mol) American Diabetes Association target (yes/no)

End point title	HbA1c <7.0% (53 mmol/mol) American Diabetes Association target (yes/no)

End point description:

Subjects who achieved (yes/no) HbA1c <7.0% (American Diabetes Association (ADA) target), was evaluated at week 26. Results are based on the in-trial observation period. Population analysed: The FAS. Number of subjects analysed = number of subjects with available data.

End point type	Secondary

End point timeframe:

After week 26

End point values	Oral semaglutide 14 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	155		
Units: Subjects				
Yes	89	35		
No	65	120		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent adverse events during exposure to trial product

End point title	Number of treatment-emergent adverse events during exposure to trial product

End point description:

Treatment emergent adverse events (TEAEs) were recorded during the exposure to trial products. Adverse events (AEs) with onset during the on-treatment observation period were considered treatment-emergent. On-treatment observation period: Time period when a subject was on treatment with trial product, including any period after initiation of rescue medication. Population analysed: The safety analysis set, which included all randomised subjects who received at least one dose of trial product.

End point type	Secondary

End point timeframe:

Assessed up to approximately 31 weeks

End point values	Oral semaglutide 14 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	161		
Units: Events	463	331		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product

End point title	Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product

End point description:

Treatment emergent severe or blood glucose-confirmed confirmed symptomatic hypoglycaemic episodes were recorded during exposure to trial products. Hypoglycaemic episodes with onset during the on-treatment observation period were considered treatment-emergent. Severe hypoglycaemia was defined as an episode requiring assistance of another person to actively administer carbohydrate or glucagon, or take other corrective actions. BG-confirmed symptomatic hypoglycaemia: Confirmed by a glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. Population analysed: The safety analysis set.

End point type	Secondary

End point timeframe:

Assessed up to approximately 31 weeks

End point values	Oral semaglutide 14 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	161		
Units: Episodes	17	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 1 – 31 (26 weeks treatment period + 5 weeks follow-up period).

Adverse event reporting additional description:

Results are based on the safety analysis set. All presented AEs are TEAEs which were recorded during the exposure to trial products. Adverse events (AEs) with onset during the on-treatment observation period were considered treatment-emergent.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects were to take oral semaglutide placebo tablets once daily from week 1 to 26.

Reporting group title	Oral semaglutide 14 mg

Reporting group description:

Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 1 to 26: 3 mg from week 1 to 4, 7 mg from week 5 to 8 and 14 mg from week 9 to 26.

Serious adverse events	Placebo	Oral semaglutide 14 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 161 (10.56%)	17 / 163 (10.43%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malignant melanoma in situ			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
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			
Pyrexia			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
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			

Animal bite			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb crushing injury			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 161 (0.00%)	2 / 163 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina unstable			

subjects affected / exposed	0 / 161 (0.00%)	2 / 163 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 161 (0.62%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dysarthria			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient global amnesia			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
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	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Eyelid ptosis			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 161 (0.62%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myalgia			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arteriosclerotic gangrene			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected bite			

subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site abscess			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 163 (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	1 / 161 (0.62%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 161 (0.00%)	1 / 163 (0.61%)	
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	Placebo	Oral semaglutide 14 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 161 (19.88%)	75 / 163 (46.01%)	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 161 (4.97%)	10 / 163 (6.13%)	
occurrences (all)	21	13	

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 161 (3.73%)	19 / 163 (11.66%)	
occurrences (all)	6	23	
Diarrhoea			
subjects affected / exposed	6 / 161 (3.73%)	17 / 163 (10.43%)	
occurrences (all)	16	24	
Dyspepsia			
subjects affected / exposed	2 / 161 (1.24%)	16 / 163 (9.82%)	
occurrences (all)	2	20	
Nausea			
subjects affected / exposed	12 / 161 (7.45%)	31 / 163 (19.02%)	
occurrences (all)	12	38	
Vomiting			
subjects affected / exposed	2 / 161 (1.24%)	19 / 163 (11.66%)	
occurrences (all)	2	29	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 161 (5.59%)	1 / 163 (0.61%)	
occurrences (all)	9	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 161 (0.00%)	11 / 163 (6.75%)	
occurrences (all)	0	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2016	1) Additional eye examinations and fundus photography or dilated fundoscopy at end of trial and after premature discontinuation of trial product. 2) Fundoscopy requires pharmacological dilation of both pupils. 3) Eye examination category added as supportive secondary endpoint. 4) Diabetic retinopathy and related complications added as adverse events requiring additional data collection. 5) Addition of 'Diabetic retinopathy complications' subsection to "Benefit risk assessment of the trial" section of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported