Clinical trial results:
Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only. A 26-week, randomised, double-blind, placebo-controlled trial.

Summary

EudraCT number	2015-005622-19
Trial protocol	BG CZ
Global end of trial date	08 December 2017

Results information

Result version number	v1 (current)
This version publication date	23 December 2018
First version publication date	23 December 2018

Trial information

Trial identification

Sponsor protocol code	NN9924-4233

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02906930
WHO universal trial number (UTN)	U1111-1177-5112
Other trial identifiers	Japanese trial registration: JapicCTI-163384

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	20 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 October 2017
Global end of trial reached?	Yes
Global end of trial date	08 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) vs once-daily placebo on glycaemic control in subjects with type 2 diabetes treated with diet and exercise only.

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:

Not applicable

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	Bulgaria: 35
Country: Number of subjects enrolled	Czech Republic: 28
Country: Number of subjects enrolled	Japan: 116
Country: Number of subjects enrolled	Mexico: 76
Country: Number of subjects enrolled	Algeria: 60
Country: Number of subjects enrolled	Russian Federation: 88
Country: Number of subjects enrolled	Serbia: 33
Country: Number of subjects enrolled	Turkey: 54
Country: Number of subjects enrolled	United States: 213
Worldwide total number of subjects	703
EEA total number of subjects	63

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	560
From 65 to 84 years	143
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 93 sites in 9 countries as follows: Algeria (4), Bulgaria (3), Czech Republic (5), Japan (6), Mexico (2), Russian Federation (9), Serbia (3), Turkey (7), and United States: 53 sites screened/48 sites randomised subjects.

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 data base lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Oral semaglutide 3 mg

Arm description:

Subjects were to receive oral semaglutide 3 mg tablets once daily from week 0 to week 26.

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

Dosage and administration details:

Semaglutide was administered once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. Semaglutide was required to be taken with up to half a glass of water (approximately 120 mL/4 fluid oz) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could be taken 30 minutes after administration of trial product

Arm title	Oral semaglutide 7 mg

Arm description:

Subjects were to receive oral semaglutide 3 mg tablets once daily from week 0 to week 4 and oral semaglutide 7 mg tablets once daily from week 5 to week 26.

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

Dosage and administration details:

Semaglutide was administered once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. Semaglutide was required to be taken with up to half a glass of water (approximately 120 mL/4 fluid oz) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could be taken 30 minutes after administration of trial product

Arm title	Oral semaglutide 14 mg

Arm description:

Subjects were to receive oral semaglutide 3 mg tablets once daily from week 0 to week 4, oral semaglutide 7 mg tablets once daily from week 5 to week 8 and oral semaglutide 14 mg tablets once daily from week 9 to week 26.

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

Dosage and administration details:

Semaglutide was administered once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. Semaglutide was required to be taken with up to half a glass of water (approximately 120 mL/4 fluid oz) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could be taken 30 minutes after administration of trial product

Arm title	Placebo

Arm description:

Subjects were to receive placebo tablets once daily from week 0 to week 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:

Placebo was administered once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. Placebo was required to be taken with up to half a glass of water (approximately 120 mL/4 fluid oz) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could be taken 30 minutes after administration of trial product.

Number of subjects in period 1	Oral semaglutide 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg
Started	175	175	175
Exposed	175	175	175
Completed	169	161	163
Not completed	6	14	12
Consent withdrawn by subject	-	5	5
Unclassified	1	2	1
Lost to follow-up	5	7	5
Died	-	-	1

Number of subjects in period 1	Placebo
Started	178
Exposed	178
Completed	170
Not completed	8
Consent withdrawn by subject	4

Unclassified	2
Lost to follow-up	2
Died	-

Baseline characteristics

Reporting groups	
Reporting group title	Oral semaglutide 3 mg
Reporting group description:	
Subjects were to receive oral semaglutide 3 mg tablets once daily from week 0 to week 26.	
Reporting group title	Oral semaglutide 7 mg
Reporting group description:	
Subjects were to receive oral semaglutide 3 mg tablets once daily from week 0 to week 4 and oral semaglutide 7 mg tablets once daily from week 5 to week 26.	
Reporting group title	Oral semaglutide 14 mg
Reporting group description:	
Subjects were to receive oral semaglutide 3 mg tablets once daily from week 0 to week 4, oral semaglutide 7 mg tablets once daily from week 5 to week 8 and oral semaglutide 14 mg tablets once daily from week 9 to week 26.	
Reporting group title	Placebo
Reporting group description:	
Subjects were to receive placebo tablets once daily from week 0 to week 26.	

Reporting group values	Oral semaglutide 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg
Number of subjects	175	175	175
Age Categorical Units: Subjects			
Adults (18-64 years)	136	135	144
From 65-74 years	33	35	29
From 75-84 years	6	5	2
Age Continuous Units: years			
arithmetic mean	55	56	54
standard deviation	± 11	± 11	± 11
Gender Categorical Units: Subjects			
Female	86	82	89
Male	89	93	86
Glycosylated haemoglobin (HbA1c) Units: Percentage of HbA1c			
arithmetic mean	7.9	8.0	8.0
standard deviation	± 0.7	± 0.6	± 0.7
Fasting plasma glucose Units: mmol/L			
arithmetic mean	8.78	8.98	8.77
standard deviation	± 2.35	± 2.34	± 2.17
Body weight Units: kg			
arithmetic mean	86.9	89	88.1
standard deviation	± 21	± 21.8	± 22.1

Reporting group values	Placebo	Total	
Number of subjects	178	703	

Age Categorical Units: Subjects			
Adults (18-64 years)	145	560	
From 65-74 years	29	126	
From 75-84 years	4	17	
Age Continuous Units: years			
arithmetic mean	54		
standard deviation	± 11	-	
Gender Categorical Units: Subjects			
Female	89	346	
Male	89	357	
Glycosylated haemoglobin (HbA1c) Units: Percentage of HbA1c			
arithmetic mean	7.9		
standard deviation	± 0.7	-	
Fasting plasma glucose Units: mmol/L			
arithmetic mean	8.88		
standard deviation	± 2.16	-	
Body weight Units: kg			
arithmetic mean	88.6		
standard deviation	± 23.4	-	

End points

End points reporting groups

Reporting group title	Oral semaglutide 3 mg
Reporting group description:	
Subjects were to receive oral semaglutide 3 mg tablets once daily from week 0 to week 26.	
Reporting group title	Oral semaglutide 7 mg
Reporting group description:	
Subjects were to receive oral semaglutide 3 mg tablets once daily from week 0 to week 4 and oral semaglutide 7 mg tablets once daily from week 5 to week 26.	
Reporting group title	Oral semaglutide 14 mg
Reporting group description:	
Subjects were to receive oral semaglutide 3 mg tablets once daily from week 0 to week 4, oral semaglutide 7 mg tablets once daily from week 5 to week 8 and oral semaglutide 14 mg tablets once daily from week 9 to week 26.	
Reporting group title	Placebo
Reporting group description:	
Subjects were to receive placebo tablets once daily from week 0 to week 26.	

Primary: Change in HbA1c

End point title	Change in HbA1c
End point description:	
Change from baseline (week 0) in HbA1c at week 26. Data from all randomised subjects in the full analysis set (FAS), irrespective of premature trial product discontinuation and initiation of rescue medication (in-trial observation period). 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 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	167	160	160	168
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)	-0.9 (± 1.2)	-1.3 (± 1.0)	-1.5 (± 1.0)	-0.3 (± 1.2)

Statistical analyses

Statistical analysis title	Oral semaglutide 14 mg vs. Placebo
Statistical analysis description:	
The estimated treatment effect includes the effect of any rescue medication and any effect after premature trial product discontinuation (treatment policy estimand). Missing values were imputed by a pattern mixture model using multiple imputation. Patterns were defined by use of trial product and rescue medication. The imputation and the analysis were based on ANCOVA models. Analysis results were combined using Rubin’s rule.	

Comparison groups	Placebo v Oral semaglutide 14 mg
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Pattern mixture model
Parameter estimate	Estimated treatment difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	-0.9

Notes:

[1] - A weighted Bonferroni closed testing strategy was used to control for multiplicity. Subjects in this analysis=number of subjects with available data; all subjects in the FAS (N=353) contributed with data to the analysis.

Statistical analysis title	Oral semaglutide 7 mg vs. Placebo

Statistical analysis description:

The estimated treatment effect includes the effect of any rescue medication and any effect after premature trial product discontinuation (treatment policy estimand). Missing values were imputed by a pattern mixture model using multiple imputation. Patterns were defined by use of trial product and rescue medication. The imputation and the analysis were based on ANCOVA models. Analysis results were combined using Rubin’s rule.

Comparison groups	Oral semaglutide 7 mg v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	Pattern mixture model
Parameter estimate	Estimated treatment difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.6

Notes:

[2] - A weighted Bonferroni closed testing strategy was used to control for multiplicity. Subjects in this analysis=number of subjects with available data; all subjects in the FAS (N=353) contributed with data to the analysis.

Statistical analysis title	Oral semaglutide 3 mg vs. Placebo

Statistical analysis description:

The estimated treatment effect includes the effect of any rescue medication and any effect after premature trial product discontinuation (treatment policy estimand). Missing values were imputed by a pattern mixture model using multiple imputation. Patterns were defined by use of trial product and rescue medication. The imputation and the analysis were based on ANCOVA models. Analysis results were combined using Rubin’s rule.

Comparison groups	Oral semaglutide 3 mg v Placebo

Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001
Method	Pattern mixture model
Parameter estimate	Estimated treatment difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.4

Notes:

[3] - A weighted Bonferroni closed testing strategy was used to control for multiplicity. Subjects in this analysis=number of subjects with available data; all subjects in the FAS (N=353) contributed with data to the analysis.

Secondary: Change in body weight (kg)

End point title	Change in body weight (kg)

End point description:

Change from baseline in body weight at week 26. Data from all randomised subjects in the FAS, irrespective of premature trial product discontinuation and initiation of rescue medication (in-trial observation period). 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 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	168	160	160	168
Units: kg				
arithmetic mean (standard deviation)	-1.5 (± 3.3)	-2.6 (± 4.1)	-4.0 (± 4.2)	-1.4 (± 3.5)

Statistical analyses

Statistical analysis title	Oral semaglutide 14 mg vs Placebo

Statistical analysis description:

The estimated treatment effect includes the effect of any rescue medication and any effect after premature trial product discontinuation (treatment policy estimand). Missing values were imputed by a pattern mixture model using multiple imputation. Patterns were defined by use of trial product and rescue medication. The imputation and the analysis were based on ANCOVA models. Analysis results were combined using Rubin’s rule.

Comparison groups	Oral semaglutide 14 mg v Placebo

Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001
Method	Pattern mixture model
Parameter estimate	Estimated treatment difference
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	-1.5

Notes:

[4] - A weighted Bonferroni closed testing strategy was used to control for multiplicity. Subjects in this analysis=number of subjects with available data; all subjects in the FAS (N=353) contributed with data to the analysis.

Statistical analysis title	Oral semaglutide 7 mg vs. Placebo

Statistical analysis description:

The estimated treatment effect includes the effect of any rescue medication and any effect after premature trial product discontinuation (treatment policy estimand). Missing values were imputed by a pattern mixture model using multiple imputation. Patterns were defined by use of trial product and rescue medication. The imputation and the analysis were based on ANCOVA models. Analysis results were combined using Rubin's rule.

Comparison groups	Oral semaglutide 7 mg v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0866
Method	Pattern mixture model
Parameter estimate	Estimated treatment difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	0.1

Notes:

[5] - A weighted Bonferroni closed testing strategy was used to control for multiplicity. Subjects in this analysis=number of subjects with available data; all subjects in the FAS (N=353) contributed with data to the analysis.

Statistical analysis title	Oral semaglutide 3 mg vs. Placebo

Statistical analysis description:

The estimated treatment effect includes the effect of any rescue medication and any effect after premature trial product discontinuation (treatment policy estimand). Missing values were imputed by a pattern mixture model using multiple imputation. Patterns were defined by use of trial product and rescue medication. The imputation and the analysis were based on ANCOVA models. Analysis results were combined using Rubin's rule.

Comparison groups	Oral semaglutide 3 mg v Placebo

Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.8692
Method	Pattern mixture model
Parameter estimate	Estimated treatment difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.8

Notes:

[6] - A weighted Bonferroni closed testing strategy was used to control for multiplicity. Subjects in this analysis=number of subjects with available data; all subjects in the FAS (N=353) contributed with data to the analysis.

Secondary: Change in fasting plasma glucose

End point title	Change in fasting plasma glucose

End point description:

Change from baseline (week 0) in FPG at week 26. Observed data from all randomised subjects in the FAS, irrespective of premature trial product discontinuation and initiation of rescue medication (in-trial observation period). 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 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	166	160	160	166
Units: mmol/L				
arithmetic mean (standard deviation)	-0.89 (± 2.67)	-1.52 (± 2.28)	-1.92 (± 2.04)	-0.18 (± 2.37)

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:

Percentage of subjects achieving HbA1c <7.0% at week 26. Observed data from all randomised subjects in the FAS, irrespective of premature trial product discontinuation and initiation of rescue medication (in-trial observation period). 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 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	167	160	160	168
Units: Percentage of subjects				
number (not applicable)				
Yes	55.1	68.8	76.9	31.0
No	44.9	31.3	23.1	69.0

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:

An adverse event was defined as being treatment-emergent if the event had onset in the on-treatment observation period. The endpoint was assessed up to approximately 31 weeks, which is the 26-week treatment period plus the 5-week follow-up period. Results are based on the safety analysis set (SAS), which included all randomised subjects who received at least one dose of trial product (oral semaglutide or placebo).

End point type	Secondary

End point timeframe:

Assessed up to approximately 31 weeks

End point values	Oral semaglutide 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	175	175	175	178
Units: Events				
number (not applicable)	290	258	304	263

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:

Severe or blood glucose-confirmed symptomatic hypoglycaemia: an episode that was severe according to the American Diabetes Association (ADA) classification or confirmed by a glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. Results are based on the SAS.

End point type	Secondary

End point timeframe:

Assessed up to approximately 31 weeks

End point values	Oral semaglutide 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	175	175	175	178
Units: hypoglycaemic episodes	5	2	1	1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first trial product dose (Day 1) and up to approximately 31 weeks, which is the 26-week treatment period plus the 5-week follow-up period.	
Adverse event reporting additional description:	
Results are based on safety analysis set.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	Oral semaglutide 3 mg
Reporting group description:	
Subjects were to receive oral semaglutide 3 mg tablets once daily from week 0 to week 26.	
Reporting group title	Oral semaglutide 7 mg
Reporting group description:	
Subjects were to receive oral semaglutide 3 mg tablets once daily from week 0 to week 4 and oral semaglutide 7 mg tablets once daily from week 5 to week 26.	
Reporting group title	Oral semaglutide 14 mg
Reporting group description:	
Subjects were to receive oral semaglutide 3 mg tablets once daily from week 0 to week 4, oral semaglutide 7 mg tablets once daily from week 5 to week 8 and oral semaglutide 14 mg tablets once daily from week 9 to week 26.	
Reporting group title	Placebo
Reporting group description:	
Subjects were to receive placebo tablets once daily from week 0 to week 26.	

Serious adverse events	Oral semaglutide 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 175 (2.86%)	3 / 175 (1.71%)	2 / 175 (1.14%)
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)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 175 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine tumour of the lung			

subjects affected / exposed	0 / 175 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	1 / 175 (0.57%)	0 / 175 (0.00%)	0 / 175 (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 stage II			
subjects affected / exposed	1 / 175 (0.57%)	0 / 175 (0.00%)	0 / 175 (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
Vascular disorders			
Shock			
subjects affected / exposed	0 / 175 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Palatoplasty			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	0 / 175 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	0 / 175 (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
Pulmonary embolism			
subjects affected / exposed	0 / 175 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Hallucination, visual			

subjects affected / exposed	1 / 175 (0.57%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood calcitonin increased			
subjects affected / exposed	0 / 175 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 175 (0.57%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 175 (0.00%)	0 / 175 (0.00%)	1 / 175 (0.57%)
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			
Cerebral infarction			
subjects affected / exposed	0 / 175 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 175 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 175 (0.57%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			

subjects affected / exposed	1 / 175 (0.57%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 175 (0.57%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 175 (0.00%)	0 / 175 (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
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 175 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	0 / 175 (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
Endocrine disorders			
Thyroiditis subacute			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	0 / 175 (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			
Appendicitis perforated			
subjects affected / exposed	0 / 175 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial pyelonephritis			

subjects affected / exposed	0 / 175 (0.00%)	0 / 175 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	0 / 175 (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

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 178 (4.49%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 178 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine tumour of the lung			
subjects affected / exposed	1 / 178 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Papillary thyroid cancer			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate cancer stage II			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Shock			

subjects affected / exposed	1 / 178 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Palatoplasty			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 178 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Hallucination, visual			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood calcitonin increased			
subjects affected / exposed	1 / 178 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			

subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 178 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 178 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			

subjects affected / exposed	1 / 178 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Thyroiditis subacute			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	1 / 178 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial pyelonephritis			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Oral semaglutide 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 175 (27.43%)	37 / 175 (21.14%)	45 / 175 (25.71%)
Nervous system disorders			

Headache			
subjects affected / exposed	6 / 175 (3.43%)	10 / 175 (5.71%)	9 / 175 (5.14%)
occurrences (all)	7	16	31
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 175 (8.57%)	9 / 175 (5.14%)	9 / 175 (5.14%)
occurrences (all)	18	9	10
Nausea			
subjects affected / exposed	14 / 175 (8.00%)	9 / 175 (5.14%)	28 / 175 (16.00%)
occurrences (all)	17	13	43
Vomiting			
subjects affected / exposed	5 / 175 (2.86%)	8 / 175 (4.57%)	12 / 175 (6.86%)
occurrences (all)	5	11	15
Infections and infestations			
Influenza			
subjects affected / exposed	9 / 175 (5.14%)	5 / 175 (2.86%)	4 / 175 (2.29%)
occurrences (all)	9	5	4
Nasopharyngitis			
subjects affected / exposed	10 / 175 (5.71%)	11 / 175 (6.29%)	3 / 175 (1.71%)
occurrences (all)	11	11	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 175 (1.14%)	3 / 175 (1.71%)	9 / 175 (5.14%)
occurrences (all)	2	3	9

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 178 (14.61%)		
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 178 (5.06%)		
occurrences (all)	12		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 178 (2.25%)		
occurrences (all)	4		
Nausea			

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	10 / 178 (5.62%) 12 4 / 178 (2.25%) 4		
Infections and infestations Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 2 / 178 (1.12%) 2 6 / 178 (3.37%) 7		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 1 / 178 (0.56%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2016	Eye examinations and additional data collection for diabetic retinopathy were introduced along with additional minor clarifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported