Clinical trial results:
Efficacy and Safety of Oral Semaglutide versus Liraglutide and versus Placebo in Subjects with Type 2 Diabetes Mellitus. A 52-week randomised, double-blind, active- and placebo-controlled trial.

Summary

EudraCT number	2015-005210-30
Trial protocol	SK LV HU DE CZ HR
Global end of trial date	30 March 2018

Results information

Result version number	v1 (current)
This version publication date	14 April 2019
First version publication date	14 April 2019

Trial information

Trial identification

Sponsor protocol code	NN9924-4224

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02863419
WHO universal trial number (UTN)	U1111-1176-6029
Other trial identifiers	Japanese trial registration: JapicCTI-163358

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	07 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 August 2017
Global end of trial reached?	Yes
Global end of trial date	30 March 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 1.8 mg liraglutide subcutaneous and versus placebo, all in combination with metformin with or without a sodium-glucose co-transporter-2 (SGLT-2) inhibitor, on glycaemic control in subjects with type 2 diabetes mellitus (T2DM).

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:

The subjects continued on their anti-diabetic background medication (metformin alone or in combination with a SGLT-2 inhibitor) throughout the entire trial.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	10 August 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	United Arab Emirates: 24
Country: Number of subjects enrolled	Czech Republic: 30
Country: Number of subjects enrolled	Germany: 59
Country: Number of subjects enrolled	Croatia: 30
Country: Number of subjects enrolled	Hungary: 80
Country: Number of subjects enrolled	Japan: 75
Country: Number of subjects enrolled	Latvia: 30
Country: Number of subjects enrolled	Poland: 73
Country: Number of subjects enrolled	Slovakia: 39
Country: Number of subjects enrolled	Ukraine: 40
Country: Number of subjects enrolled	United States: 179
Country: Number of subjects enrolled	South Africa: 52
Worldwide total number of subjects	711
EEA total number of subjects	341

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)	561
From 65 to 84 years	150
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 101 sites in 12 countries as follows: Croatia (5), Czech Republic (3), Germany (8), Hungary (9), Japan (9), Latvia (4), Poland (9), Slovakia (5), South Africa (5), Ukraine (3), United Arab Emirates (2), United States (39).

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	Investigator, Monitor, Carer, Assessor, Subject

Blinding implementation details:

The trial was double-blinded and the clinical study group and the investigator remained blinded throughout the trial. For both oral semaglutide and liraglutide, the active and corresponding placebo products were visually identical. Furthermore, all semaglutide tablets were visually identical to each other, irrespective of the dose levels.

Arms

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

Arm description:

Subjects were to receive once-daily oral semaglutide tablets for 52 weeks. Subjects started oral semaglutide at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). The subjects also received liraglutide placebo once-daily as subcutaneous injection (under the skin) for 52 weeks where they initiated liraglutide placebo at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.

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

Dosage and administration details:

Oral semaglutide 3 mg was administered from week 0 to week 4, as part of dose escalation regimen. The tablet was taken 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 a 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

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

Dosage and administration details:

Oral semaglutide 3 mg was administered from week 4 to week 8, as part of dose escalation regimen. The tablet was taken 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 a 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

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

Dosage and administration details:

Oral semaglutide 14 mg was administered from week 8 to week 52, 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 a 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	Liraglutide 1.8 mg

Arm description:

Subjects were to receive liraglutide for 52 weeks. Liraglutide was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg. The subjects also received once daily oral semaglutide placebo 14 mg tablets for 52 weeks where they started oral semaglutide placebo at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52).

Arm type	Active comparator
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide 1.8 mg was administered once-daily as sub-cutaneous injection (under the skin) in the abdomen, thigh or upper arm; it was to be taken with or without food, and preferably at the same time each day.

Arm title	Placebo

Arm description:

Subjects were to receive both semaglutide placebo and liraglutide placebo for 52 weeks. Subjects started semaglutide placebo tablets at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). Liraglutide placebo was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide placebo injection at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.

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

Dosage and administration details:

Oral semaglutide placebo was administered 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 a 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.

Investigational medicinal product name	Liraglutide placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide placebo was administered once-daily as sub-cutaneous injection (under the skin) in the abdomen, thigh or upper arm; it was to be taken with or without food, and preferably at the same time each day.

Number of subjects in period 1	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo
Started	285	284	142
Completed	277	274	134
Not completed	8	10	8
Consent withdrawn by subject	5	5	3
Died	3	4	1
Lost to follow-up	-	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Oral semaglutide 14 mg
Reporting group description:	
Subjects were to receive once-daily oral semaglutide tablets for 52 weeks. Subjects started oral semaglutide at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). The subjects also received liraglutide placebo once-daily as subcutaneous injection (under the skin) for 52 weeks where they initiated liraglutide placebo at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.	
Reporting group title	Liraglutide 1.8 mg
Reporting group description:	
Subjects were to receive liraglutide for 52 weeks. Liraglutide was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg. The subjects also received once daily oral semaglutide placebo 14 mg tablets for 52 weeks where they started oral semaglutide placebo at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52).	
Reporting group title	Placebo
Reporting group description:	
Subjects were to receive both semaglutide placebo and liraglutide placebo for 52 weeks. Subjects started semaglutide placebo tablets at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). Liraglutide placebo was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide placebo injection at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.	

Reporting group values	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo
Number of subjects	285	284	142
Age categorical Units: Subjects			
Adults (18-64 years)	232	220	109
From 65 to 74	48	56	27
From 75 to 84	5	8	6
85 and above	0	0	0
Age Continuous Units: Years			
arithmetic mean	56	56	57
standard deviation	± 10	± 10	± 10
Sex: Female, Male Units: Subjects			
Female	138	135	68
Male	147	149	74
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	39	36	19

Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	12	9	8
White	208	212	99
More than one race	3	8	3
Unknown or Not Reported	23	17	12
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	17	18	5
Not Hispanic or Latino	268	266	137
Unknown or Not Reported	0	0	0
HbA1c			
Glycosylate haemoglobin			
Units: %-point			
arithmetic mean	8.0	8.0	7.9
standard deviation	± 0.7	± 0.7	± 0.7
Body weight			
Units: kg			
arithmetic mean	92.9	95.5	93.2
standard deviation	± 20.6	± 21.9	± 20.0

Reporting group values	Total		
Number of subjects	711		
Age categorical			
Units: Subjects			
Adults (18-64 years)	561		
From 65 to 74	131		
From 75 to 84	19		
85 and above	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	341		
Male	370		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	2		
Asian	94		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	29		
White	519		
More than one race	14		
Unknown or Not Reported	52		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	40		
Not Hispanic or Latino	671		
Unknown or Not Reported	0		

HbA1c			
Glycosylate haemoglobin			
Units: %-point arithmetic mean standard deviation	-		
Body weight Units: kg arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Oral semaglutide 14 mg

Reporting group description:

Subjects were to receive once-daily oral semaglutide tablets for 52 weeks. Subjects started oral semaglutide at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). The subjects also received liraglutide placebo once-daily as subcutaneous injection (under the skin) for 52 weeks where they initiated liraglutide placebo at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.

Reporting group title	Liraglutide 1.8 mg

Reporting group description:

Subjects were to receive liraglutide for 52 weeks. Liraglutide was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg. The subjects also received once daily oral semaglutide placebo 14 mg tablets for 52 weeks where they started oral semaglutide placebo at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52).

Reporting group title	Placebo

Reporting group description:

Subjects were to receive both semaglutide placebo and liraglutide placebo for 52 weeks. Subjects started semaglutide placebo tablets at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). Liraglutide placebo was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide placebo injection at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.

Primary: Change in HbA1c (in-trial observation period) (week 26)

End point title	Change in HbA1c (in-trial observation period) (week 26)

End point description:

Observed mean change from baseline (week 0) to week 26 in glycosylated haemoglobin. The endpoint was evaluated based on data from the in-trial observation period. In-trial observation period: the time period from when a subject was randomised until the final scheduled visit, including any period after initiation of rescue medication or premature discontinuation of trial product. Full analysis set comprised of all randomised subjects. "Number analysed"=subjects with available data.

End point type	Primary

End point timeframe:

From baseline to week 26

End point values	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	272	134	
Units: %-point				
arithmetic mean (standard deviation)	-1.2 (± 0.9)	-1.1 (± 0.9)	-0.1 (± 0.7)	

Statistical analyses

Statistical analysis title	Oral semaglutide versus Placebo

Statistical analysis description:

The endpoint was analysed using an ANCOVA model with treatment, stratification factor and region as categorical fixed effects and baseline HbA1c as covariate. The null hypothesis (H0) and the alternate hypothesis (HA) were: H0: μ ≥0.0%-points against HA: μ <0.0%. (μ denotes mean treatment difference). The analysis was based on a pattern mixture model that used multiple imputation to impute missing week-26 data, assuming that such data were missing at random.

Comparison groups	Oral semaglutide 14 mg v Placebo
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.9

Notes:

[1] - The analysis was based on treatment policy estimand. This hypothesis was controlled for multiplicity. "Subjects in this analysis"=number of subjects with available data; all subjects in the FAS (N=427) with data contributed to the analysis.

[2] - Unadjusted two-sided p-value for test of no difference from 0.

Statistical analysis title	Oral semaglutide versus Liraglutide

Statistical analysis description:

Change from baseline was analysed using an ANCOVA model with treatment, strata, and region as categorical fixed effects and baseline value as covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference. The hypothesis tested was: H0: μ ≥0.4%-points against HA: μ <0.4%. A value of 0.4% (the non-inferiority margin) was added to imputed values at week 26 for the oral semaglutide treatment arm only.

Comparison groups	Oral semaglutide 14 mg v Liraglutide 1.8 mg
Number of subjects included in analysis	550
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.0001 [4]
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0

Notes:

[3] - The analysis was based on treatment policy estimand. This hypothesis was controlled for multiplicity. HbA1c non-inferiority was tested using a non-inferiority margin of 0.4%-points. "Subjects in this analysis"=number of subjects with available data; all subjects in the FAS (N=569) contributed with data to the analysis.

[4] - Unadjusted two-sided p-value for test of no difference from the non-inferiority margin.

Statistical analysis title	Oral semaglutide versus Liraglutide

Statistical analysis description:

Change from baseline was analysed using an ANCOVA model with treatment, strata, and region as categorical fixed effects and baseline value as covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference. The null hypothesis (H0) and the alternate hypothesis (HA) were: H0: μ ≥0.0%-points against HA: μ <0.0%. (μ denotes mean treatment difference).

Comparison groups	Oral semaglutide 14 mg v Liraglutide 1.8 mg
Number of subjects included in analysis	550
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0645 [6]
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0

Notes:

[5] - The analysis was based on treatment policy estimand. This hypothesis was controlled for multiplicity. "Subjects in this analysis"=number of subjects with available data; all subjects in the FAS (N=569) contributed with data to the analysis.

[6] - Unadjusted two-sided p-value for test of no difference from 0.

Primary: Change in HbA1c (on-treatment without rescue medication observation period) (week 26)

End point title	Change in HbA1c (on-treatment without rescue medication observation period) (week 26)

End point description:

Observed mean change from baseline (week 0) to week 26 in glycosylated haemoglobin. The primary endpoint was analysed based on data from the on-treatment without rescue medication observation period. On-treatment without rescue medication observation period: the time period when a subject was on treatment with trial product, excluding any period after initiation of rescue medication. Full analysis set comprised of all randomised subjects. "Number analysed"=subjects with available data.

End point type	Primary

End point timeframe:

From baseline to week 26

End point values	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	238	245	112	
Units: %-points				
arithmetic mean (standard deviation)	-1.4 (± 0.9)	-1.2 (± 0.9)	-0.1 (± 0.7)	

Statistical analyses

Statistical analysis title	Oral semaglutide 14 mg vs. Liraglutide

Statistical analysis description:

Changes from baseline were analysed using a mixed model for repeated measurements model with treatment, strata, and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. The hypothesis tested was: H0: μ ≥0.4%-points against HA: μ <0.4%. (μ denotes mean treatment difference).

Comparison groups	Oral semaglutide 14 mg v Liraglutide 1.8 mg
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	< 0.0001 [8]
Method	Mixed model for repeated measurements
Parameter estimate	Treatment difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.1

Notes:

[7] - The analysis was based on hypothetical estimand. This hypothesis was not controlled for multiplicity. HbA1c non-inferiority was tested using a non-inferiority margin of 0.4%-points. "Subjects in this analysis"=number of subjects with available data; all subjects in the FAS (N=569) with data contributed to the analysis.

[8] - Unadjusted two-sided p-value for test of no difference from the non-inferiority margin.

Statistical analysis title	Oral semaglutide 14 mg vs. Liraglutide 1.8 mg

Statistical analysis description:

Changes from baseline were analysed using a mixed model for repeated measurements model with treatment, strata, and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. The null hypothesis (H0) and the alternate hypothesis (HA) were: H0: μ ≥0.0%-points against HA: μ <0.0%. (μ denotes mean treatment difference).

Comparison groups	Oral semaglutide 14 mg v Liraglutide 1.8 mg
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0056 [10]
Method	Mixed model for repeated measurements
Parameter estimate	Treatment difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.1

Notes:

[9] - Analysis was based on hypothetical estimand. This hypothesis was not controlled for multiplicity. "Subjects in this analysis"=number of subjects with available data; all subjects in the FAS (N=569) with data contributed to the analysis.

[10] - Unadjusted two-sided p-value for test of no difference from 0.

Statistical analysis title	Oral semaglutide 14 mg vs. Placebo

Statistical analysis description:

Changes from baseline were analysed using a mixed model for repeated measurements model with treatment, strata, and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. The null hypothesis (H0) and the alternate hypothesis (HA) were: H0: μ ≥0.0%-points against HA: μ <0.0%. (μ denotes mean treatment difference).

Comparison groups	Oral semaglutide 14 mg v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	Mixed model for repeated measurements.
Parameter estimate	Treatment difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-1

Notes:

[11] - The analysis was based on hypothetical estimand. This hypothesis was not controlled for multiplicity. "Subjects in this analysis"=number of subjects with available data; all subjects in the FAS (N=427) with data contributed to the analysis.

[12] - Unadjusted two-sided p-value for test of no difference from 0.

Secondary: Change in body weight (in-trial observation period) (week 26)

End point title	Change in body weight (in-trial observation period) (week 26)

End point description:

Change from baseline (week 0) in body weight to week 26. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.

End point type	Secondary

End point timeframe:

From baseline to week 26

End point values	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	271	134	
Units: kg				
arithmetic mean (standard deviation)	-4.4 (± 4.4)	-3.2 (± 3.7)	-0.6 (± 3.1)	

Statistical analyses

Statistical analysis title	Oral semaglutide versus Placebo

Statistical analysis description:

The endpoint was analysed using an ANCOVA model with treatment, stratification factor and region as categorical fixed effects and the baseline body weight value as the covariate. The null hypothesis (H0) and the alternate hypothesis (HA) were: H0: μ ≥0.0 kg against HA: μ <0.0 kg (μ denotes mean treatment difference). The analysis was based on a pattern mixture model that used multiple imputation to impute missing week-26 data, assuming that such data were missing at random.

Comparison groups	Oral semaglutide 14 mg v Placebo
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001 [14]
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	-3

Notes:

[13] - The analysis was for the treatment policy estimand. This hypothesis was controlled for multiplicity. Subjects in this analysis=number of subjects with available data; all subjects in the FAS (N=427) contributed with data to the analysis.
[14] - Unadjusted two-sided p-value for test of no difference from 0.

Statistical analysis title	Oral semaglutide versus Liraglutide

Statistical analysis description:

The endpoint was analysed using an ANCOVA model with treatment, stratification factor and region as categorical fixed effects and the baseline body weight value as the covariate. The null hypothesis (H0) and the alternate hypothesis (HA) were: H0: μ ≥0.0 kg against HA: μ <0.0 kg (μ denotes mean treatment difference). The analysis was based on a pattern mixture model that used multiple imputation to impute missing week-26 data, assuming that such data were missing at random

Comparison groups	Oral semaglutide 14 mg v Liraglutide 1.8 mg
Number of subjects included in analysis	549
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.0003 [16]
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	-0.6

Notes:

[15] - The analysis was for the treatment policy estimand. This hypothesis was controlled for multiplicity. Subjects in this analysis=number of subjects with available data; all subjects in the FAS (N=569) contributed with data to the analysis
[16] - Unadjusted two-sided p-value for test of no difference from 0.

Secondary: Change in body weight (on-treatment without rescue medication observation period) (week 26)

End point title	Change in body weight (on-treatment without rescue medication observation period) (week 26)

End point description:

Observed mean change from baseline (week 0) to week 26 in body weight. The endpoint was evaluated based on data from the on-treatment without rescue medication observation period. Full analysis set comprised of all randomised subjects. "Number analysed"=subjects with available data.

End point type	Secondary

End point timeframe:

From baseline to week 26

End point values	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223	230	83	
Units: kg				
arithmetic mean (standard deviation)	-5.0 (± 5.2)	-3.3 (± 4.3)	-1.5 (± 3.3)	

Statistical analyses

Statistical analysis title	Oral semagltide 14 mg vs. Liraglutide 1.8 mg

Statistical analysis description:

Changes from baseline were analysed using a mixed model for repeated measurements model with treatment, strata, and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix.

Comparison groups	Oral semaglutide 14 mg v Liraglutide 1.8 mg
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.0001 [18]
Method	Mixed model for repeated measurements
Parameter estimate	Treatment difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	-0.9

Notes:

[17] - The analysis was for hypothetical estimand. This hypothesis was not controlled for multiplicity. "Subjects in this analysis"=number of subjects with available data at week 26; all subjects in the FAS (N=569) contributed to the analysis.

[18] - Unadjusted two sided p-value for test of no difference from 0.

Statistical analysis title	Oral semagltide 14 mg vs. Placebo

Statistical analysis description:

Changes from baseline were analysed using a mixed model for repeated measurements model with treatment, strata, and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix.

Comparison groups	Oral semaglutide 14 mg v Placebo

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.0001
Method	Mixed model for repeated measurements
Parameter estimate	Treatment difference
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	-3.2

Notes:

[19] - Analysis was for the hypothetical estimand. This hypothesis was not controlled for multiplicity. Subjects in this analysis"=number of subjects with available data at week 26; all subjects in the FAS (N=427) contributed to the analysis.

Secondary: Change in HbA1c (week 52)

End point title	Change in HbA1c (week 52)

End point description:

Change from baseline (week 0) in HbA1c to week 52. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.

End point type	Secondary

End point timeframe:

From baseline to week 52

End point values	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	269	133	
Units: %-point				
arithmetic mean (standard deviation)	-1.2 (± 1.0)	-0.9 (± 1.0)	-0.1 (± 0.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight (kg) (week 52)

End point title	Change in body weight (kg) (week 52)

End point description:

Change from baseline (week 0) in body weight to week 52. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.

End point type	Secondary

End point timeframe:

From baseline to week 52

End point values	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	269	133	
Units: kg				
arithmetic mean (standard deviation)	-4.94 (± 6.37)	-3.25 (± 4.33)	-0.99 (± 4.12)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (week 26)

End point title	Change in fasting plasma glucose (week 26)

End point description:

Change from baseline (week 0) in fasting plasma glucose to week 26. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.

End point type	Secondary

End point timeframe:

From baseline to week 26

End point values	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	276	269	133	
Units: mmol/L				
arithmetic mean (standard deviation)	-2.04 (± 2.28)	-1.91 (± 2.05)	-0.33 (± 2.03)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (week 52)

End point title	Change in fasting plasma glucose (week 52)

End point description:

Change from baseline (week 0) in fasting plasma glucose to week 52. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.

End point type	Secondary

End point timeframe:

From baseline to week 52

End point values	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	273	269	132	
Units: mmol/L				
arithmetic mean (standard deviation)	-1.91 (± 2.41)	-1.54 (± 2.41)	-0.66 (± 1.99)	

Statistical analyses

No statistical analyses for this end point

Secondary: Achieved HbA1c < 7.0 % (53 mmol/mol) American Diabetes Association target (yes/no) (week 26)

End point title	Achieved HbA1c < 7.0 % (53 mmol/mol) American Diabetes Association target (yes/no) (week 26)

End point description:

Number of subjects achieving HbA1c < 7.0 % (53 mmol/mol) according to American Diabetes Association (ADA) target, at week 26. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.

End point type	Secondary

End point timeframe:

At week 26

End point values	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	272	134	
Units: percentage				
number (not applicable)				
Yes	67.6	61.8	14.2	
No	32.4	38.2	85.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Achieved HbA1c < 7.0 % (53 mmol/mol) American Diabetes Association target (yes/no) (week 52)

End point title	Achieved HbA1c < 7.0 % (53 mmol/mol) American Diabetes Association target (yes/no) (week 52)

End point description:

Number of subjects achieving HbA1c < 7.0 % (53 mmol/mol) according to American Diabetes Association (ADA) target, at week 52. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.

End point type	Secondary

End point timeframe:

At week 52

End point values	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	269	133	
Units: percentage				
number (not applicable)				
Yes	60.7	55.0	15.0	
No	39.3	45.0	85.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent adverse events

End point title	Number of treatment-emergent adverse events

End point description:

A treatment-emergent adverse event (TEAE) is defined as an adverse event with onset in the on-treatment observation period (the time period where subjects are considered treated with trial product). The safety analysis set (SAS) included all randomised subjects who received at least one dose of trial product. "Number of subjects analysed"=subjects with available data.

End point type	Secondary

End point timeframe:

During exposure to trial product, assessed up to approximately 57 weeks

End point values	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	285	284	142	
Units: Events	973	927	300	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes

End point title	Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes

End point description:

Hypoglycaemic episodes defined as treatment-emergent if the onset of the episode occurs within the on-treatment observation period. Severe or BG-confirmed symptomatic hypoglycaemia is an episode that is severe according to the American Diabetes Association classification or blood glucose-confirmed by a plasma glucose value <3.1 mmol/L (56mg/dL) with symptoms consistent with hypoglycaemia. The safety analysis set (SAS) included all randomised subjects who received at least one dose of trial product. "Number of subjects analysed"=subjects with available data.

End point type	Secondary

End point timeframe:

During exposure to trial product, assessed up to approximately 57 weeks

End point values	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	285	284	142	
Units: Episodes	2	9	3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of first dose of trial product (week 0) to end of treatment (week 52) + 5 weeks of follow-up (until week 57).

Adverse event reporting additional description:

Evaluation of safety was based on safety analysis set (SAS) which comprised of all randomised subjects who received at least one dose of trial product.
AEs with onset during the on-treatment observation period (the period when subjects were exposed to trial product) were considered treatment-emergent.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Oral Semaglutide 14 mg

Reporting group description:

Subjects were to receive once-daily oral semaglutide tablets for 52 weeks. Subjects started oral semaglutide at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). The subjects also received liraglutide placebo once-daily as subcutaneous injection (under the skin) for 52 weeks where they initiated liraglutide placebo at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.

Reporting group title	Liraglutide 1.8 mg

Reporting group description:

Subjects were to receive liraglutide for 52 weeks. Liraglutide was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg. The subjects also received once daily oral semaglutide placebo 14 mg tablets for 52 weeks where they started oral semaglutide placebo at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52).

Reporting group title	Placebo

Reporting group description:

Subjects were to receive both semaglutide placebo and liraglutide placebo for 52 weeks. Subjects started semaglutide placebo tablets at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). Liraglutide placebo was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide placebo injection at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.

Serious adverse events	Oral Semaglutide 14 mg	Liraglutide 1.8 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 285 (10.88%)	22 / 284 (7.75%)	15 / 142 (10.56%)
number of deaths (all causes)	3	4	1
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of thyroid gland			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Colon adenoma			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Lung adenocarcinoma			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Oral fibroma			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Ovarian cancer metastatic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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

Parathyroid tumour benign			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (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
Thyroid cancer metastatic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (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
Vascular disorders			
Diabetic vascular disorder			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (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
Hypertension			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (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
Varicose vein			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
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			
Hospitalisation			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Thyroidectomy			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (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

General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Reproductive system and breast disorders			
Menometrorrhagia			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigation			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Lipase increased			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Weight decreased			

subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ankle fracture			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (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
Meniscus injury			
subjects affected / exposed	1 / 285 (0.35%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle rupture			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Subdural haematoma			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (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
Tibia fracture			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (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
Congenital, familial and genetic disorders			

Respiratory tract malformation			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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			
Acute myocardial infarction			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 285 (0.35%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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 failure chronic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Coronary artery occlusion			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	2 / 285 (0.70%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Cerebellar syndrome			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Cerebrovascular disorder			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic neuropathy			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Dizziness			

subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Facial paresis			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Trigeminal neuralgia			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			

subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Ophthalmic vein thrombosis			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Large intestine polyp			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Nausea			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Vomiting			

subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (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
Cholelithiasis			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (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
Drug-induced liver injury			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Hepatic haematoma			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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 failure			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Endocrine disorders			

Thyroid mass			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 285 (0.00%)	1 / 284 (0.35%)	0 / 142 (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
Bursitis			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Ligamentitis			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Osteoarthritis			
subjects affected / exposed	0 / 285 (0.00%)	2 / 284 (0.70%)	0 / 142 (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
Spinal osteoarthritis			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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

Tendon disorder			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Chronic sinusitis			
subjects affected / exposed	0 / 285 (0.00%)	0 / 284 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Otitis media			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Postoperative wound infection			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 285 (0.35%)	0 / 284 (0.00%)	0 / 142 (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

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

Non-serious adverse events	Oral Semaglutide 14 mg	Liraglutide 1.8 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	148 / 285 (51.93%)	120 / 284 (42.25%)	47 / 142 (33.10%)
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 285 (0.00%)	2 / 284 (0.70%)	9 / 142 (6.34%)
occurrences (all)	0	2	10
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 285 (9.47%)	17 / 284 (5.99%)	8 / 142 (5.63%)
occurrences (all)	33	24	12
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	16 / 285 (5.61%)	6 / 284 (2.11%)	3 / 142 (2.11%)
occurrences (all)	16	6	3
Constipation			
subjects affected / exposed	22 / 285 (7.72%)	11 / 284 (3.87%)	4 / 142 (2.82%)
occurrences (all)	23	12	4
Diarrhoea			
subjects affected / exposed	43 / 285 (15.09%)	31 / 284 (10.92%)	11 / 142 (7.75%)
occurrences (all)	59	42	11
Dyspepsia			
subjects affected / exposed	16 / 285 (5.61%)	12 / 284 (4.23%)	0 / 142 (0.00%)
occurrences (all)	26	13	0
Nausea			

subjects affected / exposed	55 / 285 (19.30%)	51 / 284 (17.96%)	5 / 142 (3.52%)
occurrences (all)	69	67	5
Vomiting			
subjects affected / exposed	24 / 285 (8.42%)	13 / 284 (4.58%)	3 / 142 (2.11%)
occurrences (all)	28	24	3
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 285 (3.86%)	17 / 284 (5.99%)	5 / 142 (3.52%)
occurrences (all)	13	19	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	41 / 285 (14.39%)	37 / 284 (13.03%)	15 / 142 (10.56%)
occurrences (all)	60	59	18
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 285 (5.61%)	20 / 284 (7.04%)	0 / 142 (0.00%)
occurrences (all)	17	23	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2016	Key changes: 1. Introduction of additional eye examinations and additional data collection on diabetic retinopathy 2. Added bicarbonate as a part of the biochemistry laboratory assessment 3. Added text to highlight investigator's responsibility in ensuring evaluation and management of certain risk factors and complications 4. Clarification of the criteria for completion, withdrawal and lost to follow-up 5. Other minor corrections and clarifications

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported