Clinical trial results:
China multi-regional clinical trial: Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only

Summary

EudraCT number	2018-002590-22
Trial protocol	HU
Global end of trial date	27 October 2021

Results information

Result version number	v1 (current)
This version publication date	06 November 2022
First version publication date	06 November 2022

Trial information

Trial identification

Sponsor protocol code	NN9924-4338

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04109547
WHO universal trial number (UTN)	U1111-1188-1173

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Alle, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Office (2834), 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	17 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of three once-daily dose levels of oral semaglutide (3, 7 and 14 mg) versus once-daily placebo on glycaemic control in subjects with T2D treated with diet and exercise only.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, amended by the 64th WMA General Assembly October 2013 and ICH Good Clinical Practice, including archiving of essential documents, E6(R2), Step 4, 09 November 2016 and 21 CFR 312.120.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 October 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 375
Country: Number of subjects enrolled	Hungary: 40
Country: Number of subjects enrolled	Serbia: 42
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	Ukraine: 49
Worldwide total number of subjects	521
EEA total number of subjects	40

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)	448
From 65 to 84 years	73
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 52 sites in 3 countries and Region China (China mainland and Taiwan) as follows: China mainland (37 sites), Taiwan (3 sites); Hungary (4 sites), Serbia (2 sites) and Ukraine (6 sites).

Pre-assignment

Screening details:

Total of 521 subjects with type 2 diabetes mellitus treated with diet and exercise only were randomized 1:1:1:1 to receive once-daily blinded treatment for 26 weeks with oral semaglutide 3, 7 or 14 milligrams (mg), or with placebo. The trial included a 4-week run-in period, a treatment period of 26 weeks and a 5-week follow-up period.

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, Subject

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 the database lock.

Arms

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

Arm description:

Subjects received 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:

Oral semaglutide 3 mg tablets was administered once daily from week 0 to week 26. Semaglutide was administered 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 be swallowed whole and not broken or chewed.

Arm title	Oral semaglutide 7 mg

Arm description:

Subjects received oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 26: 3 mg from week 0 to week 4 and 7 mg from week 4 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:

Oral semaglutide tablets were administered once daily in a dose escalation manner from week 0 to week 26: 3 mg from week 0 to week 4 and 7 mg from week 4 to week 26. Semaglutide was administered 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 be swallowed whole and not broken or chewed.

Arm title	Oral semaglutide 14 mg

Arm description:

Subjects received oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 26: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8 and 14 mg from week 8 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:

Oral semaglutide tablets were administered once daily in a dose escalation manner from week 0 to week 26: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8 and 14 mg from week 8 to week 26. Semaglutide was administered 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 be swallowed whole and not broken or chewed.

Arm title	Placebo

Arm description:

Subjects received oral semaglutide matching 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:

Oral semaglutide matching placebo tablets were administered once daily from week 0 to week 26. Placebo was administered 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 be swallowed whole and not broken or chewed.

Number of subjects in period 1	Oral semaglutide 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg
Started	130	130	130
Treated	130	130	129
Full analysis set	130	130	130
Safety analysis set	130	130	129
Completed	126	126	124
Not completed	4	4	6
Consent withdrawn by subject	3	2	6
Physician decision	1	2	-
Lost to follow-up	-	-	-

Number of subjects in period 1	Placebo
Started	131
Treated	131
Full analysis set	131
Safety analysis set	131
Completed	124
Not completed	7
Consent withdrawn by subject	6
Physician decision	-
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Oral semaglutide 3 mg
Reporting group description:	
Subjects received oral semaglutide 3 mg tablets once daily from week 0 to week 26.	
Reporting group title	Oral semaglutide 7 mg
Reporting group description:	
Subjects received oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 26: 3 mg from week 0 to week 4 and 7 mg from week 4 to week 26.	
Reporting group title	Oral semaglutide 14 mg
Reporting group description:	
Subjects received oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 26: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8 and 14 mg from week 8 to week 26.	
Reporting group title	Placebo
Reporting group description:	
Subjects received oral semaglutide matching 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	130	130	130
Age Categorical Units: Subjects			
Adults (18-64 years)	106	113	112
From 65-84 years	24	17	18
Age Continuous Units: years			
arithmetic mean	54	52	53
standard deviation	± 11	± 11	± 10
Gender Categorical Units: Subjects			
Female	58	41	47
Male	72	89	83

Reporting group values	Placebo	Total	
Number of subjects	131	521	
Age Categorical Units: Subjects			
Adults (18-64 years)	117	448	
From 65-84 years	14	73	
Age Continuous Units: years			
arithmetic mean	51		
standard deviation	± 11	-	
Gender Categorical Units: Subjects			
Female	43	189	
Male	88	332	

End points

End points reporting groups

Reporting group title	Oral semaglutide 3 mg
Reporting group description:	
Subjects received oral semaglutide 3 mg tablets once daily from week 0 to week 26.	
Reporting group title	Oral semaglutide 7 mg
Reporting group description:	
Subjects received oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 26: 3 mg from week 0 to week 4 and 7 mg from week 4 to week 26.	
Reporting group title	Oral semaglutide 14 mg
Reporting group description:	
Subjects received oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 26: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8 and 14 mg from week 8 to week 26.	
Reporting group title	Placebo
Reporting group description:	
Subjects received oral semaglutide matching 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 glycosylated haemoglobin (HbA1c) at week 26 is presented. The endpoint data was evaluated based on the on-treatment without rescue medication observation period: from date of first dose of trial product following randomization up to the end date which was the first date of any of the following: the last dose of trial product plus 3 days or initiation of rescue medication. Full analysis set included all randomized subjects. Number of Subjects Analysed = subjects with available data for this endpoint.	
End point type	Primary
End point timeframe:	
Baseline (Week 0), 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	114	117	116	106
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)	-1.1 (± 0.7)	-1.5 (± 0.8)	-1.6 (± 1.0)	-0.2 (± 0.9)

Statistical analyses

Statistical analysis title	Oral Semaglutide 14 mg, Placebo
Comparison groups	Oral semaglutide 14 mg v Placebo

Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	MMRM
Parameter estimate	Treatment differene
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	-1.3

Notes:

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

Statistical analysis title	Oral Semaglutide 7 mg, Placebo
Comparison groups	Oral semaglutide 7 mg v Placebo
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-1.2

Notes:

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

Statistical analysis title	Oral Semaglutide 3 mg, Placebo
Comparison groups	Oral semaglutide 3 mg v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.8

Notes:

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

Secondary: Change in body weight

End point title	Change in body weight

End point description:

Change from baseline (week 0) in body weight at week 26 is presented. The endpoint data was evaluated based on the on-treatment without rescue medication observation period: from date of first dose of trial product following randomization up to the end date which was the first date of any of the following: the last dose of trial product plus 3 days or initiation of rescue medication. Full analysis set included all randomized subjects. Number of Subjects Analysed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (Week 0), 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	115	119	116	106
Units: Kilograms (kg)				
arithmetic mean (standard deviation)	-1.1 (± 3.3)	-2.2 (± 3.4)	-3.1 (± 3.7)	-1.1 (± 2.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose

End point title	Change in fasting plasma glucose

End point description:

Change from baseline (week 0) in fasting plasma glucose (FPG) at week 26 is presented. The endpoint data was evaluated based on the on-treatment without rescue medication observation period: from date of first dose of trial product following randomization up to the end date which was the first date of any of the following: the last dose of trial product plus 3 days or initiation of rescue medication. Full analysis set included all randomized subjects. Number of Subjects Analysed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (Week 0), 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	114	118	116	104
Units: milligrams per decilitre (mg/dL)				
arithmetic mean (standard deviation)	-19.07 (± 32.44)	-32.28 (± 27.95)	-32.50 (± 24.91)	0.00 (± 27.49)

Statistical analyses

No statistical analyses for this end point

Secondary: If a subject achieves (yes/no) HbA1c below 7.0% (53 mmol/mol) (American Diabetes Association target)

End point title	If a subject achieves (yes/no) HbA1c below 7.0% (53 mmol/mol) (American Diabetes Association target)

End point description:

Number of subjects who achieved HbA1c < 7.0 % (53 millimoles per mole [mmol/mol]) (ADA target) at week 26 is presented. The endpoint data was evaluated based on the on-treatment without rescue medication observation period: from date of first dose of trial product following randomization up to the end date which was the first date of any of the following: the last dose of trial product plus 3 days or initiation of rescue medication. Full analysis set included all randomized subjects. Number of Subjects Analysed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

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	114	117	116	106
Units: Subjects				
Yes	75	100	92	27
No	39	17	24	79

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 (AE) is any untoward medical occurrence in a subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. Treatment-emergent adverse event (TEAE) was defined as an AE with onset in the on-treatment observation period. On-treatment observation period: from date of first dose of trial product following randomisation up to the first date of any of the following: follow-up visit, follow-up prematurely discontinuation visit, last date on trial product plus 38 days or the end-date for the in-trial

observation period. Safety analysis set included all subjects exposed to at least one dose of trial product.

End point type	Secondary

End point timeframe:

Up to 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	130	130	129	131
Units: Events				
number (not applicable)	251	292	231	212

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 (BG) confirmed symptomatic hypoglycaemia was defined as an episode that was severe according to the ADA classification or BG confirmed by a plasma glucose (PG) value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. Severe hypoglycaemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. The endpoint data was evaluated based on the on-treatment observation period: from date of first dose of trial product following randomisation up to the first date of any of the following: follow-up visit, follow-up prematurely discontinuation visit, last date on trial product plus 38 days or the end-date for the in-trial observation period. Safety analysis set included all subjects exposed to at least one dose of trial product.

End point type	Secondary

End point timeframe:

Up to 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	130	130	129	131
Units: Episodes				
number (not applicable)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From week 0 to week 31	
Adverse event reporting additional description:	
All presented adverse events (AEs) are treatment-emergent (i.e., TEAEs). TEAE was defined as an AE with onset in the on-treatment observation period. Results are based on the safety analysis set (SAS) which included all subjects exposed to at least one dose of trial product.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	Oral semaglutide 3 mg
Reporting group description:	
Subjects received oral semaglutide 3 mg tablets once daily from week 0 to week 26.	
Reporting group title	Placebo
Reporting group description:	
Subjects received oral semaglutide matching placebo tablets once daily from week 0 to week 26.	
Reporting group title	Oral semaglutide 14 mg
Reporting group description:	
Subjects received oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 26: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8 and 14 mg from week 8 to week 26.	
Reporting group title	Oral semaglutide 7 mg
Reporting group description:	
Subjects received oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 26: 3 mg from week 0 to week 4 and 7 mg from week 4 to week 26.	

Serious adverse events	Oral semaglutide 3 mg	Placebo	Oral semaglutide 14 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 130 (4.62%)	2 / 131 (1.53%)	5 / 129 (3.88%)
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)			
Papillary thyroid cancer			
subjects affected / exposed	0 / 130 (0.00%)	0 / 131 (0.00%)	0 / 129 (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			
Limb injury			

subjects affected / exposed	0 / 130 (0.00%)	0 / 131 (0.00%)	0 / 129 (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
Nail injury			
subjects affected / exposed	0 / 130 (0.00%)	0 / 131 (0.00%)	0 / 129 (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
Neck injury			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	0 / 129 (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
Pelvic fracture			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	0 / 129 (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
Rib fracture			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	0 / 129 (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 fracture			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	0 / 129 (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
Splenic rupture			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	0 / 129 (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
Ulna fracture			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	0 / 129 (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			
Angina unstable			

subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	0 / 129 (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
Atrial fibrillation			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	0 / 129 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	0 / 129 (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
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 130 (0.00%)	0 / 131 (0.00%)	0 / 129 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 130 (0.00%)	0 / 131 (0.00%)	1 / 129 (0.78%)
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			
Asthma			
subjects affected / exposed	0 / 130 (0.00%)	0 / 131 (0.00%)	1 / 129 (0.78%)
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 failure			
subjects affected / exposed	0 / 130 (0.00%)	0 / 131 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			

subjects affected / exposed	0 / 130 (0.00%)	0 / 131 (0.00%)	0 / 129 (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
Cholelithiasis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 131 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	0 / 130 (0.00%)	0 / 131 (0.00%)	0 / 129 (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	1 / 130 (0.77%)	0 / 131 (0.00%)	0 / 129 (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
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 131 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	0 / 129 (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

Serious adverse events	Oral semaglutide 7 mg		
Total subjects affected by serious adverse events			

subjects affected / exposed	10 / 130 (7.69%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nail injury			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neck injury			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Splenic rupture			

subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 130 (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	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	2 / 130 (1.54%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19 pneumonia			

subjects affected / exposed	3 / 130 (2.31%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Lung abscess			
subjects affected / exposed	0 / 130 (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	Placebo	Oral semaglutide 14 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 130 (23.08%)	16 / 131 (12.21%)	40 / 129 (31.01%)
Investigations			
Lipase increased			
subjects affected / exposed	7 / 130 (5.38%)	0 / 131 (0.00%)	4 / 129 (3.10%)
occurrences (all)	12	0	4
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 130 (0.77%)	1 / 131 (0.76%)	2 / 129 (1.55%)
occurrences (all)	1	1	2
Constipation			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	3 / 129 (2.33%)
occurrences (all)	1	0	3
Diarrhoea			
subjects affected / exposed	4 / 130 (3.08%)	2 / 131 (1.53%)	12 / 129 (9.30%)
occurrences (all)	4	2	18
Nausea			
subjects affected / exposed	6 / 130 (4.62%)	2 / 131 (1.53%)	8 / 129 (6.20%)
occurrences (all)	6	2	8
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	11 / 130 (8.46%)	6 / 131 (4.58%)	9 / 129 (6.98%)
occurrences (all)	12	6	12
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	2 / 130 (1.54%)	0 / 131 (0.00%)	14 / 129 (10.85%)
occurrences (all)	2	0	14
Hyperlipidaemia			
subjects affected / exposed	4 / 130 (3.08%)	7 / 131 (5.34%)	1 / 129 (0.78%)
occurrences (all)	4	7	1

Non-serious adverse events	Oral semaglutide 7 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 130 (36.15%)		
Investigations			
Lipase increased			
subjects affected / exposed	11 / 130 (8.46%)		
occurrences (all)	12		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	10 / 130 (7.69%)		
occurrences (all)	13		
Constipation			
subjects affected / exposed	7 / 130 (5.38%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	12 / 130 (9.23%)		
occurrences (all)	16		
Nausea			
subjects affected / exposed	4 / 130 (3.08%)		
occurrences (all)	4		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	12 / 130 (9.23%)		
occurrences (all)	14		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 130 (4.62%)		
occurrences (all)	7		
Hyperlipidaemia			

subjects affected / exposed occurrences (all)	3 / 130 (2.31%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2019	Changes in trial design and Inclusion/Exclusion criteria. Addition of randomisation criterion. Update to statistical section and reduction of sample size.
18 April 2019	Country specific requirement was added to the inclusion criteria. The randomisation criterion was updated. Pharmacokinetics (PK) and antibody sample collection requirement was removed in all countries except China mainland. Changes to Anti-body analyses were made and Impact of Weight on Quality of Life-Lite (IWQoL-Lite) questionnaire was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported