Clinical trial results:
Efficacy and safety of oral semaglutide 25 mg once daily in adults with overweight or obesity (OASIS 4)

Summary

EudraCT number	2021-006534-40
Trial protocol	PL
Global end of trial date	07 May 2024

Results information

Result version number	v1 (current)
This version publication date	10 May 2025
First version publication date	10 May 2025

Trial information

Trial identification

Sponsor protocol code	NN9932-4954

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05564117
WHO universal trial number (UTN)	U1111-1271-9056

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	18 June 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 May 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm superior efficacy on body weight reduction from baseline (week 0) to end of treatment (week 64) of oral semaglutide 25 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice, including archiving of essential documents. The submitted information, reflecting the data available at the data cut-off date for this report, is confirmed to be accurate.

Background therapy: -

Evidence for comparator:

Not applicable

Actual start date of recruitment	11 October 2022
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	Canada: 32
Country: Number of subjects enrolled	Germany: 81
Country: Number of subjects enrolled	Poland: 80
Country: Number of subjects enrolled	United States: 114
Worldwide total number of subjects	307
EEA total number of subjects	161

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)	278
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 22 sites in 4 countries.

Pre-assignment

Screening details:

Subjects were randomised in 2:1 ratio to receive 25 milligram (mg) oral semaglutide or semaglutide matching placebo once weekly.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Oral semaglutide 25 mg

Arm description:

Subjects received oral semaglutide tablets once daily in a dose escalation manner for 64 weeks: 3 mg (weeks 0 to 4), 7 mg (weeks 5 to 8), 14 mg (weeks 9 to 12), and 25 mg (weeks 13 to 64).

Arm type	Experimental
Investigational medicinal product name	Semaglutide C
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 for 64 weeks.

Arm title	Placebo

Arm description:

Subjects received placebo tablets matched to oral semaglutide once daily for 64 weeks.

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

Dosage and administration details:

Placebo tablets matching oral semaglutide were administered once daily for 64 weeks.

Number of subjects in period 1	Oral semaglutide 25 mg	Placebo
Started	205	102
Full Analysis Set (FAS)	205	102
Safety Analysis Set (SAS)	204	102
Completed	196	94
Not completed	9	8
Physician decision	1	-
Consent withdrawn by subject	1	1
Lost to follow-up	7	7

Baseline characteristics

Reporting groups	
Reporting group title	Oral semaglutide 25 mg
Reporting group description:	
Subjects received oral semaglutide tablets once daily in a dose escalation manner for 64 weeks: 3 mg (weeks 0 to 4), 7 mg (weeks 5 to 8), 14 mg (weeks 9 to 12), and 25 mg (weeks 13 to 64).	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo tablets matched to oral semaglutide once daily for 64 weeks.	

Reporting group values	Oral semaglutide 25 mg	Placebo	Total
Number of subjects	205	102	307
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	184	94	278
From 65-84 years	21	8	29
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	48	47	
standard deviation	± 13	± 13	-
Gender Categorical Units: Subjects			
Female	155	87	242
Male	50	15	65
Race (NIH/OMB) Units: Subjects			
Asian	1	1	2
Black or African American	13	9	22
White	190	91	281
Other	1	1	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	17	7	24
Not Hispanic or Latino	188	95	283

End points

End points reporting groups

Reporting group title	Oral semaglutide 25 mg
Reporting group description:	
Subjects received oral semaglutide tablets once daily in a dose escalation manner for 64 weeks: 3 mg (weeks 0 to 4), 7 mg (weeks 5 to 8), 14 mg (weeks 9 to 12), and 25 mg (weeks 13 to 64).	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo tablets matched to oral semaglutide once daily for 64 weeks.	

Primary: Relative change in body weight

End point title	Relative change in body weight
End point description:	
Relative change in body weight from baseline (week 0) to end of treatment (week 64) is presented. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.	
End point type	Primary
End point timeframe:	
From baseline (week 0) to end of treatment (week 64)	

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	90		
Units: Percentage (%) point of body weight				
arithmetic mean (standard deviation)	-14.4 (± 10.5)	-2.5 (± 7.9)		

Statistical analyses

Statistical analysis title	Hypothetical estimand
Statistical analysis description:	
All responses prior to first discontinuation of treatment (or initiation of other anti-obesity medication or bariatric surgery) were included in a mixed model for repeated measurements with randomised treatment as factor and baseline body weight as covariate, all nested within visit.	
Comparison groups	Oral semaglutide 25 mg v Placebo

Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-13.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.53
upper limit	-11.21

Notes:

[1] - Hypothetical estimand: Total number of subjects included in statistical analysis is 168. The number given here is auto-calculated by the system.

Statistical analysis title	Treatment policy estimand

Statistical analysis description:

Week 64 responses were analysed using an analysis of covariance model with randomised treatment as factor and baseline body weight as covariate.

Comparison groups	Placebo v Oral semaglutide 25 mg
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-11.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.88
upper limit	-8.98

Primary: Achievement of body weight reduction ≥ 5 percentage (%) (Yes/No)

End point title	Achievement of body weight reduction ≥ 5 percentage (%) (Yes/No)

End point description:

Achievement of body weight reduction ≥ 5% (Yes/No) at end of treatment (week 64) is presented. In the reported data, 'Yes' infers the number of participants who have achieved ≥ 5% weight loss, whereas 'No' infers the number of participants who have not achieved ≥ 5% weight loss. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Primary

End point timeframe:

At end-of-treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	90		
Units: Subjects				
Yes	152	28		
No	40	62		

Statistical analyses

Statistical analysis title	Hypothetical estimand

Statistical analysis description:

All responses prior to first discontinuation of treatment (or initiation of other anti-obesity medication or bariatric surgery) were included in a mixed model for repeated measurements with randomised treatment as factor and baseline body weight as covariate, all nested within visit.

Comparison groups	Oral semaglutide 25 mg v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Treatment odds ratio
Point estimate	25.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.24
upper limit	48.07

Notes:

[2] - Hypothetical estimand: Total number of subjects included in statistical analysis is 168. The number given here is auto-calculated by the system.

Statistical analysis title	Treatment policy estimand

Statistical analysis description:

Week 64 responses were analysed using a binary logistic regression model with randomised treatment as factor and baseline body weight as covariate.

Comparison groups	Oral semaglutide 25 mg v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Treatment odds ratio
Point estimate	7.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.22
upper limit	12.76

Secondary: Achievement of body weight reduction ≥ 10% (Yes/No)

End point title	Achievement of body weight reduction ≥ 10% (Yes/No)

End point description:

Achievement of body weight reduction ≥ 10% (Yes/No) at end of treatment (week 64) is presented. In the reported data, 'Yes' infers the number of participants who have achieved ≥ 10% weight loss, whereas 'No' infers the number of participants who have not achieved ≥ 10% weight loss. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

At end-of-treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	90		
Units: Subjects				
Yes	121	13		
No	71	77		

Statistical analyses

No statistical analyses for this end point

Secondary: Achievement of body weight reduction ≥ 15% (Yes/No)

End point title	Achievement of body weight reduction ≥ 15% (Yes/No)

End point description:

Achievement of body weight reduction ≥ 15% (Yes/No) at end of treatment (week 64) is presented. In the reported data, 'Yes' infers the number of participants who have achieved ≥ 15% weight loss, whereas 'No' infers the number of participants who have not achieved ≥ 15% weight loss. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

At end-of-treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	90		
Units: Subjects				
Yes	96	5		
No	96	85		

Statistical analyses

No statistical analyses for this end point

Secondary: Achievement of body weight reduction ≥ 20% (Yes/No)

End point title	Achievement of body weight reduction ≥ 20% (Yes/No)

End point description:

Achievement of body weight reduction ≥ 20% (Yes/No) at end of treatment (week 64) is presented. In the reported data, 'Yes' infers the number of participants who have achieved ≥ 20% weight loss, whereas 'No' infers the number of participants who have not achieved ≥ 20% weight loss. The end point was evaluated based on the data from in-trial period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

At end-of-treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	90		
Units: Subjects				
Yes	57	3		
No	135	87		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Physical function domain (5-items) score (Impact of Weight on Quality of Life-Lite-Clinical Trials version [IWQOL-Lite-CT])

End point title	Change in Physical function domain (5-items) score (Impact of Weight on Quality of Life-Lite-Clinical Trials version [IWQOL-Lite-CT])

End point description:

The Impact of Weight on Quality of Life Clinical Trials Version (IWQOL-Lite-CT) is designed to assess the impact of changes in weight on patient’s quality of life within the context of clinical trials. IWQOL-Lite-CT

is a 20-item questionnaire-based instrument used to assess the impact of body weight changes on subject's overall health-related quality of life (HRQoL). All IWQOL-Lite-CT composite scores range from 0 to 100, with higher scores reflecting better levels of functioning. Results for Physical Function Domain are presented in this presented. The end point was evaluated based on the data from in-trial period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	89		
Units: Score on a scale				
arithmetic mean (standard deviation)	16.8 (± 20.4)	8.3 (± 16.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in systolic blood pressure

End point title	Change in systolic blood pressure

End point description:

Change in systolic blood pressure from baseline (week 0) to end of treatment (week 64) is presented. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	90		
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)	-7 (± 15)	-5 (± 15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in waist circumference

End point title	Change in waist circumference

End point description:

Change in waist circumference from baseline (week 0) to end of treatment (week 64) is presented. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	89		
Units: centimeter (cm)				
arithmetic mean (standard deviation)	-12.9 (± 12.3)	-3.1 (± 11.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body mass index (BMI)

End point title	Change in body mass index (BMI)

End point description:

Change in BMI from baseline (week 0) to end of treatment (week 64) is presented. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	90		
Units: Kilogram per square meter (kg/m^2)				
arithmetic mean (standard deviation)	-5.3 (± 4.0)	-0.9 (± 2.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in diastolic blood pressure

End point title	Change in diastolic blood pressure

End point description:

Change in diastolic blood pressure from randomisation (week 0) to end of treatment (week 64) is presented. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From randomisation (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	90		
Units: mmHg				
arithmetic mean (standard deviation)	-3 (± 9)	-2 (± 10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in glycosylated haemoglobin (HbA1c)

End point title	Change in glycosylated haemoglobin (HbA1c)

End point description:

Change in glycosylated haemoglobin (HbA1c) from baseline (week 0) to end of treatment (week 64) is presented. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	86		
Units: Percentage point of HbA1c				
arithmetic mean (standard deviation)	-0.3 (± 0.3)	-0.0 (± 0.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in high density lipoproteins (HDL) cholesterol

End point title	Change in high density lipoproteins (HDL) cholesterol

End point description:

Change in HDL (mmol/L) from baseline (week 0) to end of treatment (week 64) is presented as ratio to baseline. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	85		
Units: Ratio of high density lipoproteins				
geometric mean (geometric coefficient of variation)	1.04 (± 15.8)	0.99 (± 13.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in total cholesterol

End point title	Change in total cholesterol

End point description:

Change in total cholesterol measured in millimoles per liter (mmol/L) from baseline (week 0) to end of treatment (week 64) is presented as ratio to baseline. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	87		
Units: Ratio of total cholesterol				
geometric mean (geometric coefficient of variation)	0.96 (± 15.3)	0.98 (± 16.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in low density lipoprotein (LDL) cholesterol

End point title	Change in low density lipoprotein (LDL) cholesterol

End point description:

Change in LDL (mmol/L) from baseline (week 0) to end of treatment (week 64) is presented as ratio to baseline. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	85		
Units: Ratio of low density lipoproteins				
geometric mean (geometric coefficient of variation)	0.96 (± 24.0)	0.99 (± 25.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in very low density lipoprotein (VLDL)

End point title	Change in very low density lipoprotein (VLDL)

End point description:

Change in VLDL (mmol/L) from baseline (week 0) to end of treatment (week 64) is presented as ratio to baseline. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	87		
Units: Ratio of very low density lipoproteins				
geometric mean (geometric coefficient of variation)	0.80 (± 38.9)	0.92 (± 36.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in triglycerides

End point title	Change in triglycerides

End point description:

Change in triglycerides (mmol/L) from baseline (week 0) to end of treatment (week 64) is presented as ratio to baseline. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	87		
Units: Ratio of triglycerides				
geometric mean (geometric coefficient of variation)	0.80 (± 39.2)	0.93 (± 36.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in free fatty acids

End point title	Change in free fatty acids

End point description:

Change in free fatty acids (mmol/L) from baseline (week 0) to end of treatment (week 64) is presented as ratio to baseline. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	84		
Units: Ratio of free fatty acids				
geometric mean (geometric coefficient of variation)	0.86 (± 64.2)	0.95 (± 76.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in high sensitivity C-Reactive Protein

End point title	Change in high sensitivity C-Reactive Protein

End point description:

Change in high sensitivity C-Reactive Protein (hsCRP) measured in milligram per litre (mg/L) from baseline (week 0) to end of treatment (week 64) is presented as ratio to baseline. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	87		
Units: Ratio of hsCRP				
geometric mean (geometric coefficient of variation)	0.50 (± 111.9)	0.91 (± 122.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting serum insulin

End point title	Change in fasting serum insulin

End point description:

Change in fasting serum insulin measured in picomoles per liter (pmol/L) from baseline (week 0) to end of treatment (week 64) is presented as ratio to baseline. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	84		
Units: Ratio of fasting serum insulin				
geometric mean (geometric coefficient of variation)	0.74 (± 57.9)	1.03 (± 62.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (FPG)

End point title	Change in fasting plasma glucose (FPG)

End point description:

Change in FPG measured in mg/dL from baseline (week 0) to end of treatment (week 64) is presented. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from the start of randomisation to last trial-related subject-site contact. Full analysis set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 64)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	87		
Units: mg/dL				
arithmetic mean (standard deviation)	-7.3 (± 10.8)	0.1 (± 12.0)		

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:

An adverse event (AE) was defined as any untoward medical occurrence in a clinical study participant that is temporally associated with the use of IMP, whether or not considered related to the IMP. All AEs mentioned here are treatment emergent adverse events (TEAE) defined as an event with onset during the on-treatment observation period. On-treatment observation period: from the date of first IMP administration to date of last IMP administration excluding potential off-treatment time intervals of more than 3 consecutive days. Safety analysis set (SAS) included all participants randomly assigned to study treatment and who took at least 1 dose of trial product. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of study (week 71)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	102		
Units: Events				
number (not applicable)	1239	432		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent serious adverse events

End point title	Number of treatment emergent serious adverse events

End point description:

Number of treatment emergent serious adverse events from baseline (week 0) to end of study (week 71) is presented. A serious adverse event (SAE) is any untoward medical occurrence that fulfils at least one of following criteria: results in death; is life-threatening; requires inpatient or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is congenital anomaly/birth defect; important medical event. The end point was evaluated based on data from on-treatment observation period. On-treatment observation period: from date of first investigational medicinal product (IMP) administration to date of last IMP administration excluding potential off-treatment time intervals of more than 3 consecutive days. Safety analysis set (SAS) included all participants randomly assigned to study treatment and who took at least 1 dose of trial product. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of study (week 71)

End point values	Oral semaglutide 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	102		
Units: Events				
number (not applicable)	17	13		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline (week 0) to end of study (week 71)

Adverse event reporting additional description:

All presented adverse events (AEs) are treatment emergent adverse events (TEAEs). Treatment emergent adverse events: defined as an event with onset during on-treatment observation period. Safety analysis set (SAS) included all participants randomly assigned to study treatment and who took at least 1 dose of trial product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo tablets matched to oral semaglutide once daily for 64 weeks.

Reporting group title	Oral semaglutide 25 mg

Reporting group description:

Subjects received oral semaglutide tablets once daily in a dose escalation manner for 64 weeks: 3 mg (weeks 0 to 4), 7 mg (weeks 5 to 8), 14 mg (weeks 9 to 12), and 25 mg (weeks 13 to 64).

Serious adverse events	Placebo	Oral semaglutide 25 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 102 (8.82%)	8 / 204 (3.92%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal neoplasm			
subjects affected / exposed	1 / 102 (0.98%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign salivary gland neoplasm			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 102 (0.98%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Sleeve gastrectomy			
subjects affected / exposed	1 / 102 (0.98%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical polyp			
subjects affected / exposed	1 / 102 (0.98%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian mass			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 102 (0.98%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 102 (0.98%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture displacement			

subjects affected / exposed	1 / 102 (0.98%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac aneurysm			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dysarthria			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Microcytic anaemia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 102 (0.98%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 102 (0.98%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Furuncle			
subjects affected / exposed	1 / 102 (0.98%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			

subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitamin D deficiency			
subjects affected / exposed	0 / 102 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Oral semaglutide 25 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 102 (77.45%)	172 / 204 (84.31%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 102 (0.98%)	11 / 204 (5.39%)	
occurrences (all)	1	14	
Headache			
subjects affected / exposed	9 / 102 (8.82%)	24 / 204 (11.76%)	
occurrences (all)	10	34	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 102 (0.98%)	15 / 204 (7.35%)	
occurrences (all)	1	15	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 102 (3.92%)	15 / 204 (7.35%)	
occurrences (all)	5	16	
Abdominal pain upper			
subjects affected / exposed	2 / 102 (1.96%)	18 / 204 (8.82%)	
occurrences (all)	2	23	
Dyspepsia			
subjects affected / exposed	9 / 102 (8.82%)	37 / 204 (18.14%)	
occurrences (all)	11	50	
Diarrhoea			
subjects affected / exposed	9 / 102 (8.82%)	36 / 204 (17.65%)	
occurrences (all)	10	61	
Constipation			
subjects affected / exposed	10 / 102 (9.80%)	41 / 204 (20.10%)	
occurrences (all)	11	59	
Eructation			
subjects affected / exposed	2 / 102 (1.96%)	21 / 204 (10.29%)	
occurrences (all)	2	23	
Vomiting			
subjects affected / exposed	6 / 102 (5.88%)	63 / 204 (30.88%)	
occurrences (all)	6	105	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 102 (4.90%)	16 / 204 (7.84%)	
occurrences (all)	5	17	
Nausea			
subjects affected / exposed	19 / 102 (18.63%)	95 / 204 (46.57%)	
occurrences (all)	27	157	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 102 (1.96%)	13 / 204 (6.37%)	
occurrences (all)	2	14	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	6 / 102 (5.88%)	6 / 204 (2.94%)	
occurrences (all)	6	6	
Arthralgia			
subjects affected / exposed	6 / 102 (5.88%)	6 / 204 (2.94%)	
occurrences (all)	9	6	
Infections and infestations			
COVID-19			
subjects affected / exposed	18 / 102 (17.65%)	41 / 204 (20.10%)	
occurrences (all)	19	45	
Bronchitis			
subjects affected / exposed	7 / 102 (6.86%)	9 / 204 (4.41%)	
occurrences (all)	8	10	
Urinary tract infection			
subjects affected / exposed	3 / 102 (2.94%)	13 / 204 (6.37%)	
occurrences (all)	4	16	
Upper respiratory tract infection			
subjects affected / exposed	9 / 102 (8.82%)	11 / 204 (5.39%)	
occurrences (all)	13	11	
Tonsillitis			
subjects affected / exposed	6 / 102 (5.88%)	5 / 204 (2.45%)	
occurrences (all)	7	5	
Sinusitis			
subjects affected / exposed	7 / 102 (6.86%)	7 / 204 (3.43%)	
occurrences (all)	8	8	
Nasopharyngitis			
subjects affected / exposed	27 / 102 (26.47%)	43 / 204 (21.08%)	
occurrences (all)	40	59	
Influenza			
subjects affected / exposed	10 / 102 (9.80%)	15 / 204 (7.35%)	
occurrences (all)	10	21	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 102 (0.98%)	14 / 204 (6.86%)	
occurrences (all)	1	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported