Clinical trial results:
Effect of Semaglutide 2.4 mg once weekly on function and symptoms in subjects with obesity-related heart failure with preserved ejection fraction

Summary

EudraCT number	2019-004452-11
Trial protocol	CZ HU NL DE DK
Global end of trial date	18 April 2023

Results information

Result version number	v1 (current)
This version publication date	04 May 2024
First version publication date	04 May 2024

Trial information

Trial identification

Sponsor protocol code	EX9536-4665

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04788511
WHO universal trial number (UTN)	U1111-1243-4358

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, 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	10 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effects of semaglutide subcutaneous 2.4 mg once-weekly on physical function, symptoms and body weight compared with placebo, both added to standard of care, in subjects with obesity-related heart failure with preserved ejection fraction (HFpEF).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Oct 2013) and ICH Good Clinical Practice, including archiving of essential documents (May 1996) and EN ISO 14155 Part 1 and 2 and FDA 21 CFR 312.120.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 March 2021
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	Argentina: 30
Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Czechia: 38
Country: Number of subjects enrolled	Germany: 47
Country: Number of subjects enrolled	Denmark: 24
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	United Kingdom: 47
Country: Number of subjects enrolled	Hungary: 60
Country: Number of subjects enrolled	Israel: 39
Country: Number of subjects enrolled	Netherlands: 28
Country: Number of subjects enrolled	Poland: 62
Country: Number of subjects enrolled	United States: 86
Worldwide total number of subjects	529
EEA total number of subjects	291

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)	175
From 65 to 84 years	344
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 83 sites in 13 countries, as follows: Argentina (6), Australia (5), Hungary (8), Czech Republic (5), Poland (6), Spain (3), Netherlands (6), Denmark (3), United States (16), Canada (4), Israel (5), Germany (7) and United Kingdom (9).

Pre-assignment

Screening details:

A total of 817 subjects were screened for this trial, out of which 281 subjects were screening failures and seven subjects were withdrawn before randomisation. Overall, 529 eligible subjects were randomised (1:1) to treatment with semaglutide (263) and placebo (266).

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	Semaglutide 2.4 mg

Arm description:

Subjects with obesity (body mass index [BMI] greater than or equal to (≥) 30.0 kilogram per square meter (kg/m^2) related heart failure with preserved ejection fraction received semaglutide 2.4 milligrams (mg) once weekly by subcutaneous injection (in the abdomen, thigh or upper arm). Subjects initially received 0.25 mg of semaglutide. The dose was then escalated every fourth week with increments of 0.25 mg for 16 weeks until the target dose of 2.4 mg was reached. The treatment period was 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Semaglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects with obesity (BMI ≥30.0 kg/m^2) related heart failure with preserved ejection fraction received semaglutide 2.4 mg once weekly by subcutaneous injection (in the abdomen, thigh or upper arm).

Arm title	Placebo

Arm description:

Subjects with obesity (BMI ≥30.0 kg/m^2) related heart failure with preserved ejection fraction received placebo once weekly by subcutaneous injection (in the abdomen, thigh or upper arm) for 52 weeks. The dose escalation and maintenance of placebo matched that of semaglutide.

Arm type	Placebo
Investigational medicinal product name	Placebo matched to semaglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects with obesity (BMI ≥30.0) kg/m^2) related heart failure with preserved ejection fraction received placebo matched to semaglutide once weekly by subcutaneous injection (in the abdomen, thigh or upper arm).

Number of subjects in period 1	Semaglutide 2.4 mg	Placebo
Started	263	266
Full Analysis Set (FAS)	263	266
Safety Analysis Set (SAS)	263	266
Completed	256	254
Not completed	7	12
Adverse event, serious fatal	3	4
Consent withdrawn by subject	2	1
Lost to follow-up	2	7

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide 2.4 mg
Reporting group description:	
Subjects with obesity (body mass index [BMI] greater than or equal to (≥) 30.0 kilogram per square meter (kg/m^2) related heart failure with preserved ejection fraction received semaglutide 2.4 milligrams (mg) once weekly by subcutaneous injection (in the abdomen, thigh or upper arm). Subjects initially received 0.25 mg of semaglutide. The dose was then escalated every fourth week with increments of 0.25 mg for 16 weeks until the target dose of 2.4 mg was reached. The treatment period was 52 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects with obesity (BMI ≥30.0 kg/m^2) related heart failure with preserved ejection fraction received placebo once weekly by subcutaneous injection (in the abdomen, thigh or upper arm) for 52 weeks. The dose escalation and maintenance of placebo matched that of semaglutide.	

Reporting group values	Semaglutide 2.4 mg	Placebo	Total
Number of subjects	263	266	529
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 (18-65 years)	84	91	175
From 65-75 years	113	104	217
75-85 years	60	67	127
85 years and over	6	4	10
Age Continuous Units: years			
arithmetic mean	69	68	
standard deviation	± 9	± 10	-
Sex: Female, Male Units: subjects			
Female	149	148	297
Male	114	118	232
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	8	13	21
White	255	252	507
More than one race	0	0	0
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB)			

Units: Subjects			
Hispanic or Latino	15	21	36
Not Hispanic or Latino	248	245	493
Unknown or Not Reported	0	0	0
Age Continuous			
Units: years			
arithmetic mean	69	68	
standard deviation	± 9	± 10	-

End points

End points reporting groups

Reporting group title	Semaglutide 2.4 mg

Reporting group description:

Subjects with obesity (body mass index [BMI] greater than or equal to (≥) 30.0 kilogram per square meter (kg/m^2) related heart failure with preserved ejection fraction received semaglutide 2.4 milligrams (mg) once weekly by subcutaneous injection (in the abdomen, thigh or upper arm). Subjects initially received 0.25 mg of semaglutide. The dose was then escalated every fourth week with increments of 0.25 mg for 16 weeks until the target dose of 2.4 mg was reached. The treatment period was 52 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects with obesity (BMI ≥30.0 kg/m^2) related heart failure with preserved ejection fraction received placebo once weekly by subcutaneous injection (in the abdomen, thigh or upper arm) for 52 weeks. The dose escalation and maintenance of placebo matched that of semaglutide.

Primary: Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score

End point title	Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score

End point description:

The KCCQ is standardised 23-item, self-administered instrument that quantifies heart failure symptoms (frequency, severity, and recent change), physical limitation, quality of life, and social limitation. The overall summary score (OSS) and all domains have been independently demonstrated to be valid, reliable, and responsive to clinical change. KCCQ-CSS includes symptom and physical limitation domains of the KCCQ. Scores are transformed to a range of 0-100, in which higher scores reflect better health status. The endpoint was evaluated based on data from in-trial period. In-trial period was defined as uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS included all randomised subjects for this trial. Here, "Number of Subjects Analysed (N)" signifies those subjects who had an observed value at week 52.

End point type	Primary

End point timeframe:

From baseline (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	237		
Units: Score on a scale				
arithmetic mean (standard deviation)	16.8 (± 17.9)	10.3 (± 17.3)		

Statistical analyses

Statistical analysis title	Semaglutide 2.4 mg vs Placebo

Statistical analysis description:

The responses at week 52 were analysed using an analysis of covariance model with randomised treatment and stratification (BMI<35.0 kg/m^2, BMI>=35.0 kg/m^2) as factors and baseline KCCQ-CSS as covariate.

Comparison groups	Semaglutide 2.4 mg v Placebo
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Estimated Treatment Difference
Point estimate	7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.8
upper limit	10.9

Notes:

[1] - The analysis was based on the in-trial period using the FAS population. Missing observations at week 52 were multiple (x1000) imputed from retrieved subjects of the same randomised treatment arm.

Primary: Change in Body Weight

End point title	Change in Body Weight

End point description:

Change in body weight from baseline (week 0) to end of treatment (week 52) is presented. The endpoint was evaluated based on the data from in-trial period. In-trial period was defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS included all the randomised subjects for this trial. Here, "N" signifies those subjects who had an observed value at week 52.

End point type	Primary

End point timeframe:

From baseline (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	242		
Units: Percentage of body weight				
arithmetic mean (standard deviation)	-13.9 (± 8.1)	-2.5 (± 5.6)		

Statistical analyses

Statistical analysis title	Semaglutide 2.4 mg vs Placebo

Statistical analysis description:

The responses at week 52 were analysed using an analysis of covariance model with randomised treatment and stratification (BMI<35.0 kg/m^2, BMI>=35.0 kg/m^2) as factors and baseline body weight (kg) as covariate.

Comparison groups	Semaglutide 2.4 mg v Placebo

Number of subjects included in analysis	488
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Estimated Treatment Difference
Point estimate	-10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	-9.4

Notes:

[2] - The analysis was based on the in-trial period using the FAS population. Missing observations at week 52 were multiple (x1000) imputed from retrieved subjects of the same randomised treatment arm.

Secondary: Change in Six-minute Walking Distance (6MWD)

End point title	Change in Six-minute Walking Distance (6MWD)

End point description:

Observed mean change from baseline (week 0) in 6 minutes walking distance (6MWD) test to end of treatment (week 52) is presented. The 6MWD is a common test of functional exercise capacity that assesses the distance a subject can walk in 6 minutes. The endpoint was evaluated based on the data from in-trial period. In-trial period was defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS included all the randomised subjects for this trial. Here, "N" signifies those subjects who had an observed value at week 52.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	225		
Units: Meters				
arithmetic mean (standard deviation)	23.5 (± 59.2)	5.8 (± 62.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Hierarchical Composite Endpoint: Percentage of Wins of Subjects Pairs

End point title	The Hierarchical Composite Endpoint: Percentage of Wins of Subjects Pairs

End point description:

Hierarchical composite endpoint from baseline (week 0) to end of study (week 57) consists of the components: time to all-cause death, number of heart failure events requiring hospitalisation or urgent heart failure visit, time to first heart failure event requiring hospitalisation or urgent heart failure visit, difference at least 15 in KCCQ CSS change from baseline to 52 weeks, difference at least 10 in KCCQ CSS change from baseline to 52 weeks, difference at least 5 in KCCQ CSS change from baseline to 52

weeks and difference at least 30 meters in 6MWD change from baseline to 52 weeks. It was analysed by the win-ratio approach using all subjects pairs across treatment groups. Overall summary of wins in each treatment group will be presented. The endpoint was evaluated based on data from in-trial period. In-trial period was defined as uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS included all randomised subjects for this trial.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of study (week 57)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	266		
Units: Percentage of wins of subjects pairs				
number (not applicable)	60.1	34.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in C-Reactive Protein (CRP): Ratio to baseline

End point title	Change in C-Reactive Protein (CRP): Ratio to baseline

End point description:

Change in high sensitivity C-reactive protein measured in ratio of C-reactive protein to baseline (week -2) at end of treatment (week 52) is presented. The endpoint was evaluated based on the data from in-trial period. In-trial period was defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS included all the randomised subjects for this trial. Here, "N" signifies those subjects who had an observed value at week 52.

End point type	Secondary

End point timeframe:

From baseline (week -2) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	243		
Units: Ratio of C-reactive protein				
geometric mean (geometric coefficient of variation)	0.55 (± 121.5)	0.92 (± 105.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving 10 Percent (%) Weight Loss (Yes/No)

End point title	Percentage of Subjects Achieving 10 Percent (%) Weight Loss (Yes/No)

End point description:

Percentage of subjects who achieved 10% weight loss (yes/no) from baseline (week 0) to end of treatment (week 52) is presented. In the reported data, 'Yes' infers percentage of subjects who have achieved 10% weight loss whereas 'No' infers percentage of subjects who have not achieved 10% weight loss. The endpoint was evaluated based on the data from in-trial period. In-trial period was defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS included all the randomised subjects for this trial. Here, "N" signifies those subjects who had an observed value at week 52.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	242		
Units: Percentage of subjects				
number (not applicable)				
No	34.1	90.5		
Yes	65.9	9.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving 15% Weight Loss (Yes/No)

End point title	Percentage of Subjects Achieving 15% Weight Loss (Yes/No)

End point description:

Percentage of subjects who achieved 15% weight loss (yes/no) from baseline (week 0) to end of treatment (week 52) is presented. In the reported data, 'Yes' infers percentage of subjects who have achieved 15% weight loss whereas 'No' infers percentage of subjects who have not achieved 15% weight loss. The endpoint was evaluated based on the data from in-trial period. In-trial period was defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS included all the randomised subjects for this trial. Here, "N" signifies those subjects who had an observed value at week 52.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	242		
Units: Percentage of subjects				
number (not applicable)				
No	56.1	97.9		
Yes	43.9	2.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving 20% Weight Loss (Yes/No)

End point title	Percentage of Subjects Achieving 20% Weight Loss (Yes/No)

End point description:

Percentage of subjects who achieved 20% weight loss (yes/no) from baseline (week 0) to end of treatment (week 52) is presented. In the reported data, 'Yes' infers percentage of subjects who have achieved 20% weight loss whereas 'No' infers percentage of subjects who have not achieved 20% weight loss The endpoint was evaluated based on the data from in-trial period. In-trial period was defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS included all the randomised subjects for this trial. Here, "N" signifies those subjects who had an observed value at week 52.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	242		
Units: Percentage of Subjects				
number (not applicable)				
No	76.4	99.6		
Yes	23.6	0.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Improving 10 Points or more in KCCQ Clinical Summary Score (Yes/No)

End point title	Percentage of Subjects Improving 10 Points or more in KCCQ Clinical Summary Score (Yes/No)

End point description:

Percentage of subjects improving 10 points or more in KCCQ-CSS from baseline to end of treatment is presented. The KCCQ is standardised 23-item, self-administered instrument that quantifies heart failure

symptoms(frequency, severity, and recent change), physical limitation, quality of life, and social limitation. KCCQ-CSS includes the symptom and physical limitation domains of the KCCQ. Scores are transformed to range of 0-100, in which higher scores reflect better health status. In reported data, 'Yes' infers percentage of subjects who have improved 5 points or more in score whereas 'No' infers percentage of subjects who have not improved 10 points or more in score. The endpoint was evaluated based on the data from in-trial period. In-trial period was defined as uninterrupted time interval from date of randomization to date of last contact with trial site. FAS included all randomised subjects for this trial. Here, "N" signifies those subjects who had an observed value at week 52.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	237		
Units: Percentage of subjects				
number (not applicable)				
No	36.6	51.5		
Yes	63.4	48.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Improving 5 Points or more in KCCQ Clinical Summary Score (Yes/No)

End point title	Percentage of Subjects Improving 5 Points or more in KCCQ Clinical Summary Score (Yes/No)

End point description:

Percentage of subjects improving 5 points or more in KCCQ-CSS from baseline to end of treatment is presented. The KCCQ is standardised 23-item, self-administered instrument that quantifies heart failure symptoms(frequency, severity, and recent change), physical limitation, quality of life, and social limitation. KCCQ-CSS includes symptom and physical limitation domains of KCCQ. Scores are transformed to range of 0-100, in which higher scores reflect better health status. The reported data, 'Yes' infers percentage of subjects who have improved 5 points or more in score whereas 'No' infers percentage of subjects who have not improved 5 points or more in score. The endpoint was evaluated based on the data from in-trial period. In-trial period was defined as the uninterrupted time interval from date of randomization to date of last contact with trial site. FAS included all randomised subjects for this trial. Here, "N" signifies those subjects who had an observed value at week 52.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	237		
Units: Percentage of subjects				
number (not applicable)				
No	24.7	36.3		
Yes	75.3	63.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in KCCQ Overall Summary Score (KCCQ-OSS)

End point title	Change in KCCQ Overall Summary Score (KCCQ-OSS)

End point description:

The KCCQ is a standardised 23-item, self-administered instrument that quantifies heart failure symptoms (frequency, severity, and recent change), physical limitation, quality of life, and social limitation. The overall summary score and all domains have been independently demonstrated to be valid, reliable, and responsive to clinical change. KCCQ-CSS includes the symptom and physical limitation domains of the KCCQ while KCCQ-OSS includes the symptom, physical limitation, quality of life, and social limitation domains. Scores are transformed to a range of 0-100, in which higher scores reflect better health status. The endpoint was evaluated based on the data from in-trial period. In-trial period was defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS included all the randomised subjects for this trial. Here, "N" signifies those subjects who had an observed value at week 52.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	237		
Units: Score on a scale				
arithmetic mean (standard deviation)	16.8 (± 18.3)	10.9 (± 17.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Threshold for Clinically Meaningful within-subjects Change in KCCQ-CSS (PGI-S)

End point title	Percentage of Subjects Achieving Threshold for Clinically Meaningful within-subjects Change in KCCQ-CSS (PGI-S)

End point description:

The patient global impression of status (PGI-S) for KCCQ was used to rate subjects' symptoms of heart failure using a 4-category ordinal scale (no symptoms, mild, moderate, severe). The KCCQ is a

standardised 23-item, self-administered instrument that quantifies heart failure symptoms (frequency, severity, and recent change), physical limitation, quality of life, and social limitation. OSS and all domains have been independently demonstrated to be valid, reliable, and responsive to clinical change. KCCQ-CSS includes the symptom and physical limitation domains of the KCCQ. Scores are transformed to a range of 0-100, in which higher scores reflect better health status. The threshold was defined as the mean change in KCCQ-CSS in those subjects with an one-category improvement in PGI-S from baseline to week 52. FAS included all the randomised subjects for this trial. Here, "N" signifies those subjects who had an observed value at week 52.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	237		
Units: Percentage of subjects				
number (not applicable)	43.2	32.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Threshold for Clinically Meaningful within-subjects Change in 6MWD (PGI-S)

End point title	Percentage of Subjects Achieving Threshold for Clinically Meaningful within-subjects Change in 6MWD (PGI-S)

End point description:

Observed mean change from baseline in 6 minutes walking distance (6MWD) test using PGI-S is evaluated for this endpoint. The 6MWD is a common test of functional exercise capacity that assesses the distance a subject can walk in 6 minutes. The endpoint was evaluated based on the data from in-trial period. In-trial period was defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. The threshold was defined as the mean change in 6MWD in those subjects with an one-category improvement in PGI-S from baseline to week 52. FAS included all the randomised subjects for this trial. Here, "N" signifies those subjects who had an observed value at week 52.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	225		
Units: Percentage of subjects				
number (not applicable)	42.5	28.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Systolic blood pressure (SBP)

End point title	Change in Systolic blood pressure (SBP)

End point description:

Observed mean change in systolic blood pressure from baseline (week -2) to end of treatment (week 52) is presented. The endpoint was evaluated based on the data from in-trial period. In-trial period was defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS included all the randomised subjects for this trial. Here, "N" signifies those subjects who had an observed value at week 52.

End point type	Secondary

End point timeframe:

From baseline (week -2) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	243		
Units: millimetre of mercury (mmHg)				
arithmetic mean (standard deviation)	-6.4 (± 19.0)	-1.1 (± 17.5)		

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 from baseline (week 0) to week 52 in waist circumference is evaluated. Waist circumference is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest. Measurement must be obtained in standing position with a non-stretchable measuring tape and to the nearest cm or inch. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally. The same measuring tape should be used throughout the trial. The endpoint was evaluated based on the data from in-trial period. In-trial period was defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS included all the randomised subjects for this trial. Here, "N" signifies those subjects who had an observed value at week 52.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (visit 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	240		
Units: Centimeter				
arithmetic mean (standard deviation)	-12.0 (± 8.5)	-2.8 (± 7.4)		

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 trial (week 57)

Adverse event reporting additional description:

All presented adverse events (AEs) are treatment-emergent AEs. It was defined as event that had onset during on-treatment period (date of first trial product administration to date of last trial product administration excluding potential off-treatment time intervals triggered by at least 5 consecutive missed doses).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Semaglutide 2.4 mg

Reporting group description:

Subjects with obesity (BMI ≥30.0 kg/m^2) related heart failure with preserved ejection fraction received semaglutide 2.4 mg once weekly by subcutaneous injection (in the abdomen, thigh or upper arm). Subjects initially received 0.25 mg of semaglutide. The dose was then escalated every fourth week with increments of 0.25 mg for 16 weeks until the target dose of 2.4 mg was reached. The treatment period was 52 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects with obesity (BMI ≥30.0 kg/m^2) related heart failure with preserved ejection fraction received placebo once weekly by subcutaneous injection (in the abdomen, thigh or upper arm) for 52 weeks. The dose escalation and maintenance of placebo matched that of semaglutide.

Serious adverse events	Semaglutide 2.4 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 263 (13.31%)	71 / 266 (26.69%)	
number of deaths (all causes)	3	4	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			

subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Haematoma evacuation			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			

subjects affected / exposed	1 / 263 (0.38%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Amyloidosis			
subjects affected / exposed	1 / 263 (0.38%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 263 (0.00%)	3 / 266 (1.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			

subjects affected / exposed	0 / 263 (0.00%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiration abnormal			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical observation			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arterial injury			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			

Hydrocele			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Aortic valve stenosis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 263 (1.14%)	9 / 266 (3.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 263 (0.00%)	3 / 266 (1.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 263 (0.00%)	3 / 266 (1.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	0 / 263 (0.00%)	12 / 266 (4.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 263 (0.38%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tricuspid valve incompetence			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 263 (0.38%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	0 / 263 (0.00%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 263 (0.38%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic unconsciousness			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	2 / 263 (0.76%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 263 (0.38%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 263 (0.00%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 263 (0.38%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal wall haematoma			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal discomfort			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 263 (1.14%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 263 (0.38%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 263 (0.38%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 263 (0.38%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 263 (0.76%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 263 (1.90%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	3 / 6	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nephrolithiasis			
subjects affected / exposed	1 / 263 (0.38%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 263 (0.38%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint stiffness			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteolysis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 263 (0.38%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 263 (0.76%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 263 (0.00%)	3 / 266 (1.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	1 / 263 (0.38%)	3 / 266 (1.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
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 / 263 (0.38%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 263 (0.38%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 263 (0.76%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 263 (0.38%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Semaglutide 2.4 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 263 (35.36%)	57 / 266 (21.43%)	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	17 / 263 (6.46%)	7 / 266 (2.63%)	
occurrences (all)	18	8	
Vomiting			

subjects affected / exposed	17 / 263 (6.46%)	3 / 266 (1.13%)	
occurrences (all)	22	3	
Nausea			
subjects affected / exposed	45 / 263 (17.11%)	7 / 266 (2.63%)	
occurrences (all)	51	8	
Diarrhoea			
subjects affected / exposed	24 / 263 (9.13%)	10 / 266 (3.76%)	
occurrences (all)	28	16	
Infections and infestations			
COVID-19			
subjects affected / exposed	36 / 263 (13.69%)	41 / 266 (15.41%)	
occurrences (all)	36	43	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2021	The overall rationale for the changes implemented in the amended protocol was to account for collection of vital status and to include additional blood sampling for pharmacokinetic assessment following comments received from the Food and Drug administration (FDA). Plasma semaglutide concentrations were to be used to describe the exposure-response analysis. In addition, information regarding the COVID-19 pandemic was included.
18 September 2022	The overall rationale for the changes implemented in the amended protocol was to anticipate an increasing interest in reporting results in a manner that reflects the clinical relevance across different domains including subject-reported endpoint combined with objective measures and events. To account for this, a hierarchical composite endpoint was added to confirmatory secondary endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported