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, and type 2 diabetes

Summary

EudraCT number	2020-004170-22
Trial protocol	NL DE HU SE PL AT IT ES CZ
Global end of trial date	11 October 2023

Results information

Result version number	v1 (current)
This version publication date	26 October 2024
First version publication date	26 October 2024

Trial information

Trial identification

Sponsor protocol code	EX9536-4773

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04916470
WHO universal trial number (UTN)	U1111-1257-5069

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	02 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to investigate the effects of semaglutide subcutaneous (s.c.) 2.4 milligrams (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) and type 2 diabetes (T2D).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki last amended by the 64th World Medical Association General Assembly, October 2013 and International Council for Harmonisation (ICH) Good Clinical Practice, including archiving of essential documents, and 21 U.S. Code of Federal Regulations (CFR) 312.120, 312.50 and 312.56.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	15 June 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: 57
Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	Canada: 24
Country: Number of subjects enrolled	Czechia: 34
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	Hungary: 71
Country: Number of subjects enrolled	India: 55
Country: Number of subjects enrolled	Israel: 35
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Japan: 17
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Poland: 82
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United States: 69

Worldwide total number of subjects	616
EEA total number of subjects	331

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)	193
From 65 to 84 years	409
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 108 sites in 16 countries. Number of sites that randomised subjects are as follows: Argentina (6), Austria (4), Canada (6), Czech Republic (4) Germany (7), Hungary (10), India (9), Israel (5), Italy (6), Japan (6), Netherlands (5), Poland (6), Spain (3), Sweden (2), United Kingdom (7) and United States (22).

Pre-assignment

Screening details:

The trial included a 16-week dose escalation period with a dose increase every 4th week, a maintenance period and a 5-week follow-up period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Semaglutide 2.4 mg

Arm description:

Subjects received semaglutide 2.4 milligrams (mg) once weekly by subcutaneous injection (in the abdomen, thigh or upper arm) as an add-on to standard of care. Subjects initially received 0.25 mg of semaglutide. The dose was then escalated every fourth week for a period of 16 weeks until the target dose of 2.4 mg was reached as an add-on to standard of care. The treatment period was 52 weeks. Subjects were followed up for 5 weeks after end of treatment till week 57.

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

Dosage and administration details:

Subjects received semaglutide 2.4 mg once weekly by subcutaneous injection (in the abdomen, thigh or upper arm).

Arm title	Placebo

Arm description:

Subjects received placebo once weekly by subcutaneous injection (in the abdomen, thigh or upper arm) for 52 weeks as an add-on to standard of care. The dose escalation and maintenance of placebo matched that of semaglutide. Subjects were followed up for 5 weeks after end of treatment till week 57.

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

Dosage and administration details:

Subjects 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	310	306
Exposed	310	306
Full analysis set (FAS)	310	306
Safety analysis set (SAS)	310	306
Completed	292	291
Not completed	18	15
Consent withdrawn by subject	5	3
Death	6	10
Lost to follow-up	7	2

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide 2.4 mg

Reporting group description:

Subjects received semaglutide 2.4 milligrams (mg) once weekly by subcutaneous injection (in the abdomen, thigh or upper arm) as an add-on to standard of care. Subjects initially received 0.25 mg of semaglutide. The dose was then escalated every fourth week for a period of 16 weeks until the target dose of 2.4 mg was reached as an add-on to standard of care. The treatment period was 52 weeks. Subjects were followed up for 5 weeks after end of treatment till week 57.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo once weekly by subcutaneous injection (in the abdomen, thigh or upper arm) for 52 weeks as an add-on to standard of care. The dose escalation and maintenance of placebo matched that of semaglutide. Subjects were followed up for 5 weeks after end of treatment till week 57.

Reporting group values	Semaglutide 2.4 mg	Placebo	Total
Number of subjects	310	306	616
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)	98	95	193
From 65-84 years	206	203	409
85 years and over	6	8	14
Age Continuous Units: years			
arithmetic mean	68	69	
standard deviation	± 9	± 9	-
Gender Categorical Units: Subjects			
Female	128	145	273
Male	182	161	343
Race Units: Subjects			
Asian	45	31	76
Black or African American	13	5	18
Other	1	2	3
White	251	268	519
Ethnicity Units: Subjects			
Hispanic or Latino	38	38	76
Not Hispanic or Latino	272	268	540

Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS)			
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 (QOL), and social limitation. Scores are transformed to a range of 0 to 100 in which higher scores reflect better health status. KCCQ-CSS includes the symptom and physical limitation domains of the KCCQ. Full analysis set included all randomised subjects.			
Units: Score on a scale			
arithmetic mean	58.8	56.4	
standard deviation	± 20.3	± 19.7	-
High Sensitive C-Reactive Protein			
Full analysis set included all randomised subjects			
Units: Milligrams per liter (mg/L)			
arithmetic mean	6.7	7.2	
standard deviation	± 9.0	± 14.1	-
Six minute walking test			
The six minute walk test is a direct and timed measure of walk distance. The goal is for the participant to walk as far as possible in six minutes without running. Full analysis set included all randomised subjects			
Units: Meters (m)			
arithmetic mean	279.7	276.7	
standard deviation	± 96.6	± 93.5	-
Body weight			
Full analysis set included all randomised subjects.			
Units: kilograms (kg)			
arithmetic mean	106.4	105.2	
standard deviation	± 20.9	± 21.4	-

End points

End points reporting groups

Reporting group title	Semaglutide 2.4 mg

Reporting group description:

Subjects received semaglutide 2.4 milligrams (mg) once weekly by subcutaneous injection (in the abdomen, thigh or upper arm) as an add-on to standard of care. Subjects initially received 0.25 mg of semaglutide. The dose was then escalated every fourth week for a period of 16 weeks until the target dose of 2.4 mg was reached as an add-on to standard of care. The treatment period was 52 weeks. Subjects were followed up for 5 weeks after end of treatment till week 57.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo once weekly by subcutaneous injection (in the abdomen, thigh or upper arm) for 52 weeks as an add-on to standard of care. The dose escalation and maintenance of placebo matched that of semaglutide. Subjects were followed up for 5 weeks after end of treatment till week 57.

Primary: Change in KCCQ (Kansas City Cardiomyopathy Questionnaire)-CSS (clinical summary score)

End point title	Change in KCCQ (Kansas City Cardiomyopathy Questionnaire)-CSS (clinical summary score)

End point description:

Change in KCCQ-CSS from baseline (week 0) to end of treatment (week 52) is presented. 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 (QOL), and social limitation. Scores were transformed to a range of 0 to 100 in which higher scores reflected better health status. KCCQ-Clinical Summary Score (CSS) included the symptom and physical limitation domains of the KCCQ. The outcome data was evaluated based on the in-trial observation period and the full analysis set (FAS). The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). Full analysis set included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	281	272		
Units: Score on a scale				
arithmetic mean (standard deviation)	14.4 (± 18.3)	7.6 (± 18.8)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Missing observations at week 52 were multiple (x1000) imputed using available measurements at week 52 from subjects of the same randomized treatment arm (using a missing at random (MAR) assumption). Missing observations due to cardiovascular (CV) death or previous heart failure (HF) event were single imputed using change from baseline to the overall lowest KCCQ-CSS value across treatment

arms and time points. Results were combined using Rubin's rule.

Comparison groups	Semaglutide 2.4 mg v Placebo
Number of subjects included in analysis	553
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.1
upper limit	10.4

Notes:

[1] - The responses at week 52 were analysed using an an analysis of covariance (ANCOVA) with randomised treatment & stratification (body mass index [BMI] less than 35.0 kilogram per meter square [kg/m^2], BMI more than equal to 35.0 kg/m^2) as factors and baseline KCCQ-CSS as covariate for each of the 1000 complete data sets. Results were combined using Rubin's rule.

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 outcome data was evaluated based on the in-trial observation period and FAS. The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). FAS included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	286	278		
Units: Percentage (%) change in body weight				
arithmetic mean (standard deviation)	-10.2 (± 6.8)	-3.2 (± 5.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Missing observations at week 52 were multiple (x1000) imputed using available measurements at week 52 from subjects of the same randomized treatment arm (using a missing at random (MAR) assumption). Results were combined using Rubin's rule.

Comparison groups	Semaglutide 2.4 mg v Placebo

Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	-5.2

Notes:

[2] - The responses at week 52 were analysed using an an analysis of covariance (ANCOVA) with randomised treatment & stratification (body mass index [BMI] less than 35.0 kilogram per meter square [kg/m^2], BMI more than equal to 35.0 kg/m^2) as factors and baseline KCCQ-CSS as covariate for each of the 1000 complete data sets. Results were combined using Rubin's rule.

Secondary: Change in six-minute walking distance

End point title	Change in six-minute walking distance

End point description:

Change in six-minute walking distance (6MWD) from baseline (week 0) to end of treatment (week 52) is presented. The 6 Minute Walk Test is a direct and timed measure of walk distance. The goal is for the subject to walk as far as possible in six minutes without running. The outcome data was evaluated based on the in-trial observation period and FAS. The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). FAS included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	281	265		
Units: Metres				
arithmetic mean (standard deviation)	16.9 (± 54.3)	3.8 (± 49.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hierarchical composite endpoint

End point title	Hierarchical composite endpoint

End point description:

The hierarchical composite endpoint is presented. Analysis (win-ratio) of the hierarchical composite endpoint was based on direct comparisons of each participant randomised to semaglutide 2.4 mg and placebo within each stratum. A ‘treatment winner’ (1000 imputations) based on similar observation time was declared based on endpoint hierarchy. Outcome data was evaluated based on in-trial observation

period which was defined as time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death) and FAS. Missing observations at week 52 for KCCQ-CSS and body weight were multiple (x1000) imputed (by MAR assumption) using available measurements at week 52 from participants of same randomized treatment arm. Missing KCCG-CSS observations due to CV death or previous HF event were single imputed to overall lowest KCCQ-CSS value across treatment arms and time points. FAS included all randomised subjects.

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	310	306		
Units: Number of wins				
number (not applicable)				
Time to all-cause death	2796	1814		
Number of heart failure events	4434	1171		
Time to first heart failure event	34	26		
Change in KCCQ-CSS >= 15 point difference	30618	17303		
Change in KCCQ-CSS >=10 point difference	6250	4763		
Change in KCCQ-CSS >=5 point difference	6925	5912		
Change in 6MWD >=30 metre difference	4607	3920		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in C-Reactive Protein

End point title	Change in C-Reactive Protein

End point description:

Change in C-Reactive Protein from baseline (week -2) to end of treatment (week 52) is presented. The outcome data was evaluated based on the in-trial observation period and FAS. The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). FAS included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	286	277		
Units: Ratio to baseline of C-Reactive Protein				
geometric mean (geometric coefficient of variation)	0.58 (± 146.6)	0.91 (± 128.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects achieving 15% weight loss or more (Yes/No)

End point title	Subjects achieving 15% weight loss or more (Yes/No)

End point description:

Subjects achieving 15% weight loss or more (Yes/No) from baseline (week 0) to end of treatment (week 52) is presented. In the reported data, 'Yes' infers number of subjects who have achieved 15% weight loss or more whereas 'No' infers number of subjects who have not achieved 15% weight loss or more. The outcome data was evaluated based on the in-trial observation period and FAS. The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). FAS included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	286	278		
Units: Subjects				
Yes	64	11		
No	222	267		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects achieving 10% weight loss or more (Yes/No)

End point title	Subjects achieving 10% weight loss or more (Yes/No)

End point description:

Subjects achieving 10% weight loss or more (Yes/No) from baseline (week 0) to end of treatment (week 52) is presented. In the reported data, 'Yes' infers number of subjects who have achieved 10% weight loss or more whereas 'No' infers number of subjects who have not achieved 10% weight loss or more. The outcome data was evaluated based on the in-trial observation period and FAS. The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). FAS included all randomised subjects. Number of subjects

analysed = Subjects with available data for this endpoint 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	286	278		
Units: Subjects				
Yes	147	29		
No	139	249		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects improving 5 points or more in KCCQ clinical summary score (Yes/No)

End point title	Subjects improving 5 points or more in KCCQ clinical summary score (Yes/No)

End point description:

Subjects improving 5 points or more in KCCQ clinical summary score (Yes/No) from baseline (week 0) to end of treatment (week 52) is presented. 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 (QOL), and social limitation. Scores are transformed to a range of 0 to 100 in which higher scores reflect better health status. KCCQ-clinical summary score (CSS) includes the symptom and physical limitation domains of the KCCQ. The outcome data was evaluated based on the in-trial observation period and FAS. The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). FAS included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	281	272		
Units: Subjects				
Yes	205	149		
No	76	123		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects achieving 20% weight loss or more (Yes/No)

End point title	Subjects achieving 20% weight loss or more (Yes/No)

End point description:

Subjects achieving 20% weight loss or more (Yes/No) from baseline (week 0) to end of treatment (week 52) is presented. In the reported data, 'Yes' infers number of subjects who have achieved 20% weight loss or more whereas 'No' infers number of subjects who have not achieved 20% weight loss or more. The outcome data was evaluated based on the in-trial observation period and FAS. The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). FAS included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	286	278		
Units: Subjects				
Yes	21	5		
No	265	273		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in KCCQ overall summary score (OSS)

End point title	Change in KCCQ overall summary score (OSS)

End point description:

Change in KCCQ-OSS from baseline (week 0) to end of treatment (week 52) is presented. The KCCQ is a standardised 23-item, self-administered instrument that quantifies heart failure symptoms (frequency, severity, and recent change), physical limitation, QOL, and social limitation. Scores are transformed to a range of 0 to 100 in which higher scores reflect better health status. KCCQ-OSS included the symptom, physical limitation, quality of life, and social limitation domains. The outcome data was evaluated based on the in-trial observation period and FAS. The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). FAS included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	281	272		
Units: Score on a scale				
arithmetic mean (standard deviation)	14.4 (± 18.1)	7.6 (± 18.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects achieving threshold for clinically meaningful within-subject change in KCCQ-CSS

End point title	Subjects achieving threshold for clinically meaningful within-subject change in KCCQ-CSS

End point description:

Subjects achieving threshold for clinically meaningful within-subject change in KCCQ-CSS (PGI-S) from week 0 to week 52 is presented. KCCQ is standardised 23-item instrument that quantifies heart failure symptoms (frequency, severity, and recent change), physical limitation, QOL, and social limitation. Scores are transformed to range of 0 to 100 in which higher scores reflect better health status. KCCQ-CSS includes the symptom and physical limitation domains of KCCQ. PGI-S for KCCQ was used to rate participants' symptoms of heart failure in last two weeks using a 4-category ordinal scale (no symptoms, mild, moderate, severe). Outcome data was evaluated based on in-trial observation period which was defined as time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death) and FAS. FAS included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	281	272		
Units: Subjects	120	83		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects achieving threshold for clinically meaningful within-subject change in six minute walking distance (6MWD)

End point title	Subjects achieving threshold for clinically meaningful within-subject change in six minute walking distance (6MWD)

End point description:

Subjects achieving threshold for clinically meaningful within-subject change in 6MWD (PGI-S) from baseline (week 0) to end of treatment (week 52) is presented. The six minute walk test (6MWT) is a direct and timed measure of walk distance. The goal is for the subject to walk as far as possible in six minutes without running. The PGI-S for six minute walk test (6MWT) was used to rate any difficulty that

participants were experiencing in walking quickly using a 5-category ordinal scale (not at all difficult, a little difficult, moderately difficult, very difficult, or unable to walk quickly). The outcome data was evaluated based on the in-trial observation period and FAS. The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). FAS included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	281	265		
Units: Subjects	148	104		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects improving 10 points or more in KCCQ clinical summary score (Yes/No)

End point title	Subjects improving 10 points or more in KCCQ clinical summary score (Yes/No)

End point description:

Subjects improving 10 points or more in KCCQ clinical summary score (Yes/No) from baseline (week 0) to end of treatment (week 52) is presented. The KCCQ is a standardised 23-item, self-administered instrument that quantifies heart failure symptoms (frequency, severity, and recent change), physical limitation, QOL, and social limitation. Scores are transformed to a range of 0 to 100 in which higher scores reflect better health status. KCCQ-CSS includes the symptom and physical limitation domains of the KCCQ. The outcome data was evaluated based on the in-trial observation period and FAS. The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). FAS included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	281	272		
Units: Subjects				
Yes	163	116		
No	118	156		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent severe or clinically significant hypoglycaemia episodes

End point title	Number of treatment emergent severe or clinically significant hypoglycaemia episodes

End point description:

Number of treatment emergent severe or clinically significant hypoglycaemia episodes from baseline (week 0) to end of trial (week 57) is presented. Clinically significant hypoglycemic episode is defined as blood glucose concentration of less than 54 milligrams per deciliter (mg/dL) which is sufficiently low to indicate serious, clinically important hypoglycaemia. Severe hypoglycemic episode is defined as hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. The outcome data was evaluated based on on-treatment period. A time-point was considered as 'on-treatment' if any dose of trial product had been administered within the prior 5 weeks (35 days). Safety analysis set (SAS) included all subjects randomly assigned to trial treatment and who took at least one dose of trial product.

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	310	306		
Units: Episodes				
number (not applicable)	20	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in glycated haemoglobin (HbA1c)

End point title	Change in glycated haemoglobin (HbA1c)

End point description:

Change in HbA1c from baseline (week 0) to end of treatment (week 52) in percentage-point is presented. The outcome data was evaluated based on the in-trial observation period and FAS. The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). FAS included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	284	270		
Units: Percentage-point of HbA1c				
arithmetic mean (standard deviation)	-0.8 (± 1.1)	0.1 (± 0.9)		

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 52) is presented. The outcome data was evaluated based on the in-trial observation period and FAS. The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). FAS included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	284	277		
Units: Centimetre (cm)				
arithmetic mean (standard deviation)	-8.9 (± 7.9)	-2.4 (± 7.2)		

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 -2) to end of treatment (week 52) is presented. The outcome data was evaluated based on the in-trial observation period and FAS. The in-trial period was defined as the time interval from date of randomisation to date of last contact with trial site (or date of withdrawal of informed consent or death). FAS included all randomised subjects. Number of subjects analysed = Subjects with available data for this endpoint 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	286	278		
Units: Millimetres of mercury (mmHg)				
arithmetic mean (standard deviation)	-4.0 (± 16.9)	-2.9 (± 16.8)		

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:

Results were based on safety analysis set, subjects randomly assigned to trial treatment & took at least 1 dose of trial product. Presented AE were treatment emergent, that initiated/worsened while being on treatment. AE were reported from on-treatment period & in-trial period (deaths, cardiovascular disorders, neoplasms, retinal disorders).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo once weekly by subcutaneous injection (in the abdomen, thigh or upper arm) for 52 weeks as an add-on to standard of care. The dose escalation and maintenance of placebo matched that of semaglutide. Subjects were followed up for 5 weeks after end of treatment till week 57.

Reporting group title	Semaglutide 2.4 mg

Reporting group description:

Subjects received semaglutide 2.4 milligrams (mg) once weekly by subcutaneous injection (in the abdomen, thigh or upper arm) as an add-on to standard of care. Subjects initially received 0.25 mg of semaglutide. The dose was then escalated every fourth week for a period of 16 weeks until the target dose of 2.4 mg was reached as an add-on to standard of care. The treatment period was 52 weeks. Subjects were followed up for 5 weeks after end of treatment till week 57.

Serious adverse events	Placebo	Semaglutide 2.4 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	88 / 306 (28.76%)	55 / 310 (17.74%)	
number of deaths (all causes)	10	6	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of adrenal gland			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			

subjects affected / exposed	1 / 306 (0.33%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ductal adenocarcinoma of pancreas			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung carcinoma cell type unspecified stage IV			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer metastatic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer metastatic			

subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer metastatic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic arteriosclerosis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 306 (0.65%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 306 (0.33%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 306 (0.33%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Gastric bypass			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sudden cardiac death			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Allergy to vaccine			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (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			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 306 (0.00%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 306 (0.65%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 306 (0.33%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal turbinate hypertrophy			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septum perforation			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
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	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (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			
Acetabulum fracture			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
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	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
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 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 306 (0.00%)	3 / 310 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural hypotension			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 306 (0.00%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic arthritis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	5 / 306 (1.63%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 306 (0.33%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	6 / 306 (1.96%)	5 / 310 (1.61%)	
occurrences causally related to treatment / all	1 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmic storm			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	1 / 306 (0.33%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	22 / 306 (7.19%)	4 / 310 (1.29%)	
occurrences causally related to treatment / all	2 / 30	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure acute			
subjects affected / exposed	3 / 306 (0.98%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	3 / 306 (0.98%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 306 (0.33%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetic cardiomyopathy			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	2 / 306 (0.65%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			

subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 306 (0.65%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Coma			

subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 306 (0.33%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical radiculopathy			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic neuropathy			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal nerve palsy			

subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 306 (0.33%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 306 (0.00%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normocytic anaemia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	2 / 306 (0.65%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal adhesions			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastritis			
subjects affected / exposed	1 / 306 (0.33%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic cyst			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (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 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholangitis acute			

subjects affected / exposed	2 / 306 (0.65%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 306 (1.31%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	3 / 306 (0.98%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (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			
Bursal haematoma			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma muscle			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Facet joint syndrome			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nose deformity			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oligoarthritis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteoarthritis			
subjects affected / exposed	3 / 306 (0.98%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (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			
Bacterial sepsis			
subjects affected / exposed	2 / 306 (0.65%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	3 / 306 (0.98%)	3 / 310 (0.97%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 306 (0.65%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus infection			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 306 (0.65%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 306 (0.00%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Keratitis fungal			

subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	9 / 306 (2.94%)	3 / 310 (0.97%)	
occurrences causally related to treatment / all	0 / 11	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			

subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 306 (0.65%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 306 (0.33%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 306 (0.65%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperkalaemia			

subjects affected / exposed	2 / 306 (0.65%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 310 (0.32%)	
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	Placebo	Semaglutide 2.4 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 306 (19.61%)	104 / 310 (33.55%)	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	30 / 306 (9.80%)	13 / 310 (4.19%)	
occurrences (all)	40	17	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	18 / 306 (5.88%)	55 / 310 (17.74%)	
occurrences (all)	22	77	
Vomiting			
subjects affected / exposed	7 / 306 (2.29%)	26 / 310 (8.39%)	
occurrences (all)	8	32	
Diarrhoea			
subjects affected / exposed	20 / 306 (6.54%)	42 / 310 (13.55%)	
occurrences (all)	23	61	
Infections and infestations			
COVID-19			
subjects affected / exposed	31 / 306 (10.13%)	26 / 310 (8.39%)	
occurrences (all)	32	26	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	10 / 306 (3.27%) 11	16 / 310 (5.16%) 19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2021	The overall rationale for the changes implemented in the amended protocol was to account for collection of vital status for subjects lost to follow-up to align internally with other Novo Nordisk trials, following health authority feedback.
23 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 patient-reported outcomes combined with objective measures and events. To account for this, a hierarchical composite endpoint was added to confirmatory secondary endpoints, and additional endpoints related to weight loss, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) and 6-minute walk distance (6MWD) were added to supportive secondary endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported