Clinical trial results:
Effect of subcutaneous semaglutide 2.4 mg once-weekly compared to placebo in subjects with obesity and knee osteoarthritis

Summary

EudraCT number	2020-000204-11
Trial protocol	FR DK SE NO
Global end of trial date	08 September 2023

Results information

Result version number	v1 (current)
This version publication date	21 September 2024
First version publication date	21 September 2024

Trial information

Trial identification

Sponsor protocol code	NN9536-4578

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05064735
WHO universal trial number (UTN)	U1111-1246-5824

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

Global end of trial reached?	Yes
Global end of trial date	08 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm superiority of semaglutide subcutaneous (s.c.; under the skin) 2.4 mg once-weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with obesity and knee osteoarthritis (OA) in change from baseline to week 68 in body weight and knee OA-related pain.

Protection of trial subjects:

This study was conducted in accordance with the principles of the Declaration of Helsinki, and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice including the archiving of essential documents and US Food and Drug Administration (FDA) 21 US Code of Federal Regulations (CFR) 312.120 and FDA 21 CFR 312.120, 50, and 56.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 October 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	Canada: 22
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Sweden: 30
Country: Number of subjects enrolled	Russian Federation: 77
Country: Number of subjects enrolled	United States: 68
Country: Number of subjects enrolled	South Africa: 51
Country: Number of subjects enrolled	Colombia: 47
Country: Number of subjects enrolled	Saudi Arabia: 25
Country: Number of subjects enrolled	Norway: 16
Country: Number of subjects enrolled	Denmark: 19
Worldwide total number of subjects	407
EEA total number of subjects	117

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)	330
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 61 sites in 11 countries as follows (number of sites that screened subjects/ number of sites that randomised subjects): Canada (5/ 5); Colombia (3/ 3); Denmark (2/ 2); France (5/ 5); Norway (3/ 3); Russia (10/ 10); Saudi Arabia (4/ 4); South Africa (5/ 5); Spain (3/ 3); Sweden (4/ 4) and United States (17/ 17).

Pre-assignment

Screening details:

The study included a screening visit followed by visits every 4th week during dose escalation period and every 8th week until end-of-treatment (week 68). Follow-up period was 7 weeks after end-of-treatment (week 75).

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 initiated at a once-weekly dose of 0.24 milligrams (mg) semaglutide subcutaneously (s.c.) as a adjunct to a reduced calorie diet and increased physical activity and followed a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), until the target dose was reached after 16 weeks. Subjects continued 2.4 mg semaglutide s.c. once- weekly from week 16 to week 68 as a adjunct to a reduced calorie diet and increased physical activity. Subjects were followed up for 7 weeks after end of treatment till week 75.

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

Arm title	Placebo

Arm description:

Subjects received semaglutide matching placebo subcutaneously once weekly as a adjunct to a reduced calorie diet and increased physical activity from week 0 to week 68. Subjects were followed up for 7 weeks after end of treatment till week 75.

Arm type	Placebo
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	271	136
Full Analysis Set (FAS)	271	136
Safety Analysis Set (SAS)	269	135
Completed	246	122
Not completed	25	14
Site Closure	7	2
Consent withdrawn by subject	7	8
Physician decision	2	1
Failing to Meet Randomisation Requirements	2	1
Lost to follow-up	7	2

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide 2.4 mg
Reporting group description:	
Subjects initiated at a once-weekly dose of 0.24 milligrams (mg) semaglutide subcutaneously (s.c.) as a adjunct to a reduced calorie diet and increased physical activity and followed a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), until the target dose was reached after 16 weeks. Subjects continued 2.4 mg semaglutide s.c. once- weekly from week 16 to week 68 as a adjunct to a reduced calorie diet and increased physical activity. Subjects were followed up for 7 weeks after end of treatment till week 75.	
Reporting group title	Placebo
Reporting group description:	
Subjects received semaglutide matching placebo subcutaneously once weekly as a adjunct to a reduced calorie diet and increased physical activity from week 0 to week 68. Subjects were followed up for 7 weeks after end of treatment till week 75.	

Reporting group values	Semaglutide 2.4 mg	Placebo	Total
Number of subjects	271	136	407
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)	222	108	330
From 65-84 years	49	28	77
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	56	56	
standard deviation	± 10	± 10	-
Gender Categorical Units: Subjects			
Female	228	104	332
Male	43	32	75
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	37	11	48
Asian	16	6	22
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	18	13	31
White	168	80	248
More than one race	0	0	0
Unknown or Not Reported	32	26	58
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	43	13	56
Not Hispanic or Latino	216	112	328
Unknown or Not Reported	12	11	23

End points

End points reporting groups

Reporting group title	Semaglutide 2.4 mg

Reporting group description:

Subjects initiated at a once-weekly dose of 0.24 milligrams (mg) semaglutide subcutaneously (s.c.) as a adjunct to a reduced calorie diet and increased physical activity and followed a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), until the target dose was reached after 16 weeks. Subjects continued 2.4 mg semaglutide s.c. once- weekly from week 16 to week 68 as a adjunct to a reduced calorie diet and increased physical activity. Subjects were followed up for 7 weeks after end of treatment till week 75.

Reporting group title	Placebo

Reporting group description:

Subjects received semaglutide matching placebo subcutaneously once weekly as a adjunct to a reduced calorie diet and increased physical activity from week 0 to week 68. Subjects were followed up for 7 weeks after end of treatment till week 75.

Primary: Change in Body Weight

End point title	Change in Body Weight

End point description:

Percentage change in body weight from baseline (week 0) to end of treatment (week 68) 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 randomised subjects according to the intention-to-treat principle. Here, Number of subjects Analysed (N) = subjects with available data for this endpoint.

End point type	Primary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	120		
Units: Percentage change in body weight				
arithmetic mean (standard deviation)	-14.2 (± 8.6)	-2.5 (± 5.6)		

Statistical analyses

Statistical analysis title	Semaglutide 2.4 mg Vs Placebo

Statistical analysis description:

The responses at week 68 were analysed using an analysis of covariance model with randomised treatment as factor and baseline body weight as covariate.

Comparison groups	Semaglutide 2.4 mg v Placebo

Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Estimated Treatment Difference
Point estimate	-10.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.34
upper limit	-8.63

Primary: Change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Score

End point title	Change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Score

End point description:

WOMAC: disease-specific subject-reported endpoint designed to assess changes in symptoms and lower extremity functioning associated with treatment in subjects with osteoarthritis (OA) of hip and/or knee. It's a 24-item questionnaire to assesses clinically important, subject-relevant symptoms in area of pain, stiffness, and physical function in subject with OA. It consists of 3 subscales: pain, stiffness and physical function. WOMAC raw pain score is derived as sum of 5 item scores in pain domain. It will be normalised and expressed on 0-100 scale. This is done by dividing raw score by highest possible value of raw score for pain domain (i.e. 50) and multiplying by 100. Higher scores indicate worse outcome. Endpoint was reported for in-trial period, defined as uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS:all randomised subjects according to intention-to-treat principle. Here, N =subjects with available data for this endpoint.

End point type	Primary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	117		
Units: Score on a scale				
arithmetic mean (standard deviation)	-43.7 (± 25.3)	-26.2 (± 25.0)		

Statistical analyses

Statistical analysis title	Semaglutide 2.4 mg vs Placebo

Statistical analysis description:

The responses at week 68 were analysed using an analysis of covariance model with randomised treatment as factor and baseline WOMAC pain score as covariate.

Comparison groups	Semaglutide 2.4 mg v Placebo

Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Estimated Treatment Difference
Point estimate	-14.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.98
upper limit	-8.3

Secondary: Achieving Body Weight Reduction Greater than or Equal to (≥) 5 Percent (%) (Yes/No)

End point title	Achieving Body Weight Reduction Greater than or Equal to (≥) 5 Percent (%) (Yes/No)

End point description:

Percentage of subjects who achieved ≥ 5% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 68) is presented. In the reported data, 'Yes' infers percentage of subjects who have achieved ≥5% weight reduction whereas 'No' infers percentage of subjects who have not achieved ≥5% weight reduction. 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 randomised subjects according to the intention-to-treat principle. Here, N= subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	120		
Units: Percentage of subjects				
number (not applicable)				
Yes	87.0	29.2		
No	13.0	70.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Achieving Body Weight Reduction ≥ 10% (Yes/No)

End point title	Achieving Body Weight Reduction ≥ 10% (Yes/No)

End point description:

Percentage of subjects who achieved ≥10% body weight reduction (yes/no) from baseline (week 0) to

end of treatment (week 68) is presented. In the reported data, 'Yes' infers percentage of subjects who have achieved ≥10% weight reduction whereas 'No' infers percentage of subjects who have not achieved ≥10% weight reduction. 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 randomised subjects according to the intention-to-treat principle. Here, N= subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	120		
Units: Percentage of subjects				
number (not applicable)				
Yes	70.4	9.2		
No	29.6	90.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in WOMAC Physical Function Score

End point title	Change in WOMAC Physical Function Score

End point description:

WOMAC is 24 item questionnaire which assesses clinically important, subject -relevant symptoms in area of pain, stiffness, and physical function in subjects with osteoarthritis (OA). It consists of 3 subscales: pain, stiffness and physical function. WOMAC physical function is 17-item questionnaire used to assess degree of difficulty experienced due to OA in knee. It is calculated as sum of 17 item scores in physical function domain. It is normalized and expressed on a 0-100 scale. This is done by dividing raw score by highest possible value of raw score for physical function domain (i.e. 170) and multiplying by 100. Higher scores indicate worse outcome. 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 according to intention-to-treat principle. Here, N= subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	117		
Units: Score on a scale				
arithmetic mean (standard deviation)	-43.4 (± 25.5)	-25.8 (± 25.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Short Form 36 (SF-36) Physical Functioning Score

End point title	Change in Short Form 36 (SF-36) Physical Functioning Score

End point description:

SF-36: self-administered questionnaire that measures each of following 8 health domains: physical functioning, role limitations due to physical problems, social functioning, bodily pain, mental health, role limitations due to emotional problems, vitality, and general health perception. There are also 2 component scores derived from 8 subscale scores: physical component summary (physical functioning, role-physical, bodily pain and general health) and mental component summary (vitality, social functioning, role-emotional and mental health). Each SF-36 domain and component summary score ranges from 0-100, higher scores reflect better subject health status. Positive change score=improvement since baseline. Endpoint was reported for in-trial period, defined as uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS: all randomised subjects according to intention-to-treat principle. Here, N=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	115		
Units: Score on a scale				
arithmetic mean (standard deviation)	12.7 (± 9.9)	6.4 (± 9.8)		

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 the treatment (visit 68) 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 randomised subjects according to intention-to-treat principle. Here, N= subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	120		
Units: Centimeter				
arithmetic mean (standard deviation)	-13.3 (± 9.3)	-5.9 (± 10.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in WOMAC Stiffness Score

End point title	Change in WOMAC Stiffness Score

End point description:

WOMAC: disease-specific subject-reported endpoint designed to assess changes in symptoms and lower extremity functioning associated with treatment in patients with OA of hip and/or knee. It's a 24 item questionnaire which assesses clinically important, subject-relevant symptoms in area of pain, stiffness, and physical function in subjects with OA. It consists of 3 subscales: pain, stiffness and physical function. WOMAC raw stiffness score is derived as sum of 2 item scores in stiffness domain. It will be normalized and expressed on 0-100 scale. This is done by dividing raw score by highest possible value of raw score for stiffness domain (i.e. 20) and multiplying by 100. Higher scores=worse outcome. Endpoint was reported for in-trial period, defined as uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS: all randomised subjects according to intention-to-treat principle. Here, N= subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	117		
Units: Score on a scale				
arithmetic mean (standard deviation)	-45.4 (± 27.7)	-27.6 (± 29.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 Bodily Pain Score

End point title	Change in SF-36 Bodily Pain Score

End point description:

Change in SF-36 bodily pain score from baseline (week 0) to end of treatment (week 68) is presented.

SF-36 is self-administered questionnaire that measures each of following 8 health domains: physical functioning, role limitations due to physical problems (role-physical), social functioning, bodily pain, mental health, role limitations due to emotional problems (role-emotional), vitality, and general health perception. Also 2 component scores derived from 8 subscale scores: physical component summary and mental component summary. Each SF-36 domain and component summary score ranges from 0 to 100, higher scores reflect better health status. A positive change score indicates an improvement since baseline. Endpoint was reported for in-trial period, defined as uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS: all randomised subjects according to intention-to-treat principle. Here, N =subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	115		
Units: Score on a scale				
arithmetic mean (standard deviation)	12.8 (± 9.4)	7.7 (± 10.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in WOMAC Total Score

End point title	Change in WOMAC Total Score

End point description:

WOMAC is a disease-specific patient-reported endpoint designed to assess changes in symptoms and lower extremity functioning associated with treatment in patients with osteoarthritis of hip and/or knee. WOMAC is a 24 item questionnaire which assesses clinically important, subject-relevant symptoms in area of pain, stiffness, and physical function in subjects with OA. WOMAC raw total score is derived as sum of 24 item scores respectively on pain, stiffness and physical function domain. It will be normalized and expressed on a 0-100 scale. This is done by dividing raw score by highest possible value of raw score for total domain (i.e. 240) and multiplying by 100. Higher scores indicate worse outcome. Endpoint was reported for in-trial period, defined as uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS:all randomised subjects according to intention-to-treat principle. Here, N =subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	117		
Units: Score on a scale				
arithmetic mean (standard deviation)	-43.8 (± 24.9)	-26.0 (± 24.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 Physical Component Summary

End point title	Change in SF-36 Physical Component Summary

End point description:

Change in SF-36 physical component summary is presented. It is self-administered questionnaire that measures each of following 8 health domains: physical functioning, role limitations due to physical problems, social functioning, bodily pain, mental health, role limitations due to emotional problems, vitality, and general health perception. Also 2 component scores derived from 8 subscale scores: physical component summary and mental component summary. Physical component summary: physical functioning, role-physical, bodily pain and general health. Each SF-36 domain and component summary score ranges from 0 to 100, higher scores=better subject health status. Positive change score=improvement since baseline. Endpoint was reported for in-trial period, defined as uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS: all randomised subjects according to intention-to-treat principle. Here, N=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	115		
Units: Score on a scale				
arithmetic mean (standard deviation)	13.2 (± 9.1)	6.9 (± 9.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 Mental Component Summary

End point title	Change in SF-36 Mental Component Summary

End point description:

Change in SF-36 mental component summary is presented. SF-36 is self-administered questionnaire that measures each of following 8 health domains: physical functioning, role limitations due to physical problems, social functioning, bodily pain, mental health, role limitations due to emotional problems, vitality, and general health perception. Also 2 component scores derived from 8 subscale scores: mental component summary and physical component summary. Mental component summary contain vitality, social functioning, role-emotional and mental health. Each SF-36 domain and component summary score ranges from 0-100, higher scores= better subject health status. Positive change score= improvement since baseline. Endpoint was reported for in-trial period, defined as uninterrupted time interval from date of randomisation to date of last contact with trial site. FAS: all randomised subjects according to intention-to-treat principle. Here, N= subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	115		
Units: Score on a scale				
arithmetic mean (standard deviation)	1.9 (± 11.3)	1.1 (± 11.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Use of Allowed Rescue Analgesics During Wash out

End point title	Use of Allowed Rescue Analgesics During Wash out

End point description:

Percentage of subjects using allowed rescue analgesics during wash out at end of treatment (week 68) is presented. In the reported data, 'Yes' infers percentage of subjects who have used allowed rescue analgesics during wash out whereas 'No' infers percentage of subjects who have not used allowed rescue analgesics during wash out. Use of allowed rescue analgesics is evaluated based on use of acetaminophen reported in the pain medication diary from one up to 3 days prior to WOMAC assessment. 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 randomised subjects according to the intention-to-treat principle. Here, N= subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	117		
Units: Percentage of subjects				
number (not applicable)				
Yes	4.9	5.1		
No	95.1	94.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Amount of Allowed Rescue Analgesics Used During Wash out

End point title	Amount of Allowed Rescue Analgesics Used During Wash out

End point description:

Amount of allowed rescue analgesics used during wash out at end of treatment (week 68) is presented. Allowed rescue analgesic during washout is defined as acetaminophen taken 24-72 hour before the visit. The endpoint is approximated by a total dose of acetaminophen reported in the pain medication diary from one and up to 3 days prior to WOMAC assessment. 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 randomised subjects according to the intention-to-treat principle. Here, N= subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	117		
Units: Milligram				
arithmetic mean (standard deviation)	224.2 (± 1756.4)	170.1 (± 1100.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Use of Pain Medication

End point title	Percentage of Subjects With Use of Pain Medication

End point description:

Percentage of subjects with use of pain medication from baseline (week 0) to end of treatment (week 68) 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 randomised subjects according to the intention-to-treat principle.

End point type	Secondary

End point timeframe:

From baseline (week 0) to end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	136		
Units: Percentage of subjects				
number (not applicable)				
Opioids	8.5	9.6		
NSAID	55.7	59.6		
Acetaminophen	57.2	58.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Pain Intensity (Numerical rating scale [NRS])

End point title	Change in Pain Intensity (Numerical rating scale [NRS])

End point description:

Pain intensity was assessed on an 11-point NRS over the past 24 hours (before each specified visit), where a score of 0 indicated "no pain" and a score of 10 indicated "worst possible pain", where higher the score, greater the pain intensity. Response at visit was derived from the pain diary data as an average score over 4 days interval leading up to visit-related washout period for pain medication. 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 randomised subjects according to the intention-to-treat principle. Here, N= subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (week 0), end of treatment (week 68)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	82		
Units: Score on a scale				
arithmetic mean (standard deviation)	-2.9 (± 2.7)	-1.4 (± 2.4)		

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 75)

Adverse event reporting additional description:

Treatment-emergent adverse events defined as event with onset during on-treatment period (date of 1st trial product use to date of last trial product use excluding potential off-treatment time intervals triggered by at least 2 consecutive missed doses) presented. SAS: all randomised subjects exposed to at least 1 dose of randomised treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received semaglutide matching placebo subcutaneously once weekly as a adjunct to a reduced calorie diet and increased physical activity from week 0 to week 68. Subjects were followed up for 7 weeks after end of treatment till week 75.

Reporting group title	Sema 2.4 mg

Reporting group description:

Subjects initiated at a once-weekly dose of 0.24 mg semaglutide s.c. as a adjunct to a reduced calorie diet and increased physical activity and followed a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), until the target dose was reached after 16 weeks. Subjects continued 2.4 mg semaglutide s.c. once- weekly from week 16 to week 68 as a adjunct to a reduced calorie diet and increased physical activity. Subjects were followed up for 7 weeks after end of treatment till week 75.

Serious adverse events	Placebo	Sema 2.4 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 135 (8.15%)	27 / 269 (10.04%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 135 (0.74%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer metastatic			
subjects affected / exposed	0 / 135 (0.00%)	2 / 269 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer stage I			

subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma stage III			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung squamous cell carcinoma stage II			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 135 (0.74%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 135 (0.74%)	2 / 269 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Teratoma benign			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Abdominoplasty			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mammoplasty			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleeve gastrectomy			
subjects affected / exposed	2 / 135 (1.48%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervix disorder			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heavy menstrual bleeding			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse			

subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
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 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 135 (0.74%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Gastric pH decreased			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	1 / 135 (0.74%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal tunnel syndrome			

subjects affected / exposed	1 / 135 (0.74%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 135 (0.74%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholecystitis acute			
subjects affected / exposed	0 / 135 (0.00%)	2 / 269 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 135 (0.74%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 135 (0.74%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism primary			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
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			
Osteoarthritis			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 135 (0.74%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			

subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 135 (0.74%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmodium malariae infection			
subjects affected / exposed	1 / 135 (0.74%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 135 (0.00%)	1 / 269 (0.37%)	
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	Sema 2.4 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 135 (37.78%)	128 / 269 (47.58%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 135 (3.70%)	16 / 269 (5.95%)	
occurrences (all)	5	18	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 135 (5.19%)	32 / 269 (11.90%)	
occurrences (all)	7	35	
Vomiting			

subjects affected / exposed	1 / 135 (0.74%)	21 / 269 (7.81%)	
occurrences (all)	1	30	
Nausea			
subjects affected / exposed	12 / 135 (8.89%)	59 / 269 (21.93%)	
occurrences (all)	16	109	
Diarrhoea			
subjects affected / exposed	7 / 135 (5.19%)	21 / 269 (7.81%)	
occurrences (all)	8	32	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 135 (9.63%)	8 / 269 (2.97%)	
occurrences (all)	13	11	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 135 (5.19%)	12 / 269 (4.46%)	
occurrences (all)	8	12	
COVID-19			
subjects affected / exposed	30 / 135 (22.22%)	50 / 269 (18.59%)	
occurrences (all)	31	54	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2021	To specify that other anti-obesity treatment (e.g. medication or bariatric surgery), which is not part of the study procedures, was not recommended in the study 4578. This specification was crucial to control the number of subjects on or starting other anti-obesity therapies at start or during the study. This was also done to ensure alignment with the other clinical studies in the development of semaglutide for weight management and to ensure interpretability of treatment effect.
24 November 2021	To include a pain and pain medication diary, to update supportive secondary endpoints and adjust WOMAC assessments with respect to frequency and recall period. This was to ensure interpretability of treatment effect and to ensure subjects safety and data integrity during coronavirus disease 2019 (COVID-19) and allows for co-participation in COVID-19 related studies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported