



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

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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| 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 (\geq) 5 Percent (%) (Yes/No)

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

End point description:

Percentage of subjects who achieved $\geq 5\%$ 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 $\geq 5\%$ weight reduction whereas 'No' infers percentage of subjects who have not achieved $\geq 5\%$ 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 $\geq 10\%$ (Yes/No)

| | |
|-----------------|------------------------------------------------------|
| End point title | Achieving Body Weight Reduction $\geq 10\%$ (Yes/No) |
|-----------------|------------------------------------------------------|

End point description:

Percentage of subjects who achieved $\geq 10\%$ 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 $\geq 10\%$ weight reduction whereas 'No' infers percentage of subjects who have not achieved $\geq 10\%$ 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

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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| End point title | Change in WOMAC Physical Function Score |
| End point description: | |
| <p>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.</p> | |
| 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 (\pm 25.5) | -25.8 (\pm 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

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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title | Change in WOMAC Stiffness Score |
| End point description: | |
| <p>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.</p> | |
| 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 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 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 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 occurrences (all) | 1 / 135 (0.74%) 1 | 21 / 269 (7.81%) 30 | |
| Nausea subjects affected / exposed occurrences (all) | 12 / 135 (8.89%) 16 | 59 / 269 (21.93%) 109 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 7 / 135 (5.19%) 8 | 21 / 269 (7.81%) 32 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 13 / 135 (9.63%) 13 | 8 / 269 (2.97%) 11 | |
| Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) | 7 / 135 (5.19%) 8 | 12 / 269 (4.46%) 12 | |
| COVID-19 subjects affected / exposed occurrences (all) | 30 / 135 (22.22%) 31 | 50 / 269 (18.59%) 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