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Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis

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ABSTRACT

BACKGROUND

Weight reduction has been shown to alleviate symptoms of osteoarthritis of the knee, including pain. The effect of glucagon-like peptide-1 receptor agonists on outcomes in knee osteoarthritis among persons with obesity has not been well studied.

METHODS

We conducted a 68-week, double-blind, randomized, placebo-controlled trial at 61 sites in 11 countries. Participants with obesity (a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30) and a clinical and radiologic diagnosis of moderate knee osteoarthritis with at least moderate pain were randomly assigned, in a 2:1 ratio, to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo, in addition to counseling on physical activity and a reduced-calorie diet. The primary end points were the percentage change in body weight and the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (on a scale of 0 to 100, with higher scores reflecting worse outcomes) from baseline to week 68. A key confirmatory secondary end point was the physical-function score on the 36-Item Short Form Health Survey (SF-36), version 2 (on a scale of 0 to 100, with higher scores indicating greater well-being).

RESULTS

A total of 407 participants were enrolled. The mean age was 56 years, the mean BMI 40.3, and the mean WOMAC pain score 70.9. A total of 81.6% of the participants were women. The mean change in body weight from baseline to week 68 was −13.7% with semaglutide and −3.2% with placebo (P<0.001). The mean change in the WOMAC pain score at week 68 was −41.7 points with semaglutide and −27.5 points with placebo (P<0.001). Participants in the semaglutide group had a greater improvement in SF-36 physical-function score than those in the placebo group (mean change, 12.0 points vs. 6.5 points; P<0.001). The incidence of serious adverse events was similar in the two groups. Adverse events that led to permanent discontinuation of the trial regimen occurred in 6.7% of the participants in the semaglutide group and in 3.0% in the placebo group, with gastrointestinal disorders being the most common reason for discontinuation.

CONCLUSIONS

Among participants with obesity and knee osteoarthritis with moderate-to-severe pain, treatment with once-weekly injectable semaglutide resulted in significantly greater reductions in body weight and pain related to knee osteoarthritis than placebo. (Funded by Novo Nordisk; STEP 9 ClinicalTrials.gov number, NCT05064735.)

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CME

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Osteoarthritis of the knee represents the most prevalent form of osteoarthritis[1] and leads to chronic pain, reduced mobility, disability, and impaired quality of life.[2-5] Obesity is a major risk factor for the development and progression of osteoarthritis of the knee.[6-8] Obesity-related knee osteoarthritis arises from a combination of increased mechanical stress on weight-bearing joints, metabolic dysfunction, and obesity-induced inflammation.[7,8] Weight reduction alleviates symptoms — with a 2% improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, function, and stiffness scores with every 1% reduction in body weight[9] — and may reduce the risk of structural progression.[10]

Treatment guidelines recommend weight reduction and physical activity as first-line management for obesity-related knee osteoarthritis.[11-13] Clinically important weight reduction requires a combination of a reduced-calorie diet and patient-centered physical-activity interventions, which may be challenging to adhere to[14] but have been shown to improve patient-reported outcomes related to pain.[15-17] Bariatric surgery may reduce knee pain in persons with obesity, although data from randomized, controlled trials are lacking.[18] There remains an unmet need for weight-management medications that can facilitate nonsurgical, sustained weight reduction and reduce pain in persons with obesity-related knee osteoarthritis. The effect of glucagon-like peptide-1 (GLP-1) receptor agonists in persons with obesity and knee osteoarthritis in this population has not been well established.[16,19]

Semaglutide, administered subcutaneously once weekly, is a GLP-1 receptor agonist that is approved in several countries for weight management in persons with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or greater, or 27 or greater for those with at least one weight-related coexisting condition. In the United States, this antiobesity medication is approved for reducing the risk of major adverse cardiovascular events in adults with established cardiovascular disease and overweight or obesity. The Semaglutide Treatment Effect in People with Obesity (STEP) 9 trial assessed whether a 2.4-mg dose of semaglutide would be superior to placebo as an adjunct to lifestyle modifications in reducing body weight and pain related to knee osteoarthritis in participants with obesity, clinical and radiologic diagnosis of moderate knee osteoarthritis, and pain that is at least moderately severe.

Methods

Trial Design and Oversight

The STEP 9 trial was a multicenter, double-blind, randomized, placebo-controlled trial conducted at 61 sites across 11 countries, in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.[20,21] The protocol (available with the full text of this article at NEJM.org) was approved by independent ethics committees or institutional review boards at the participating institutions.

The sponsor (Novo Nordisk) designed the trial, prepared the protocol and statistical analysis plan, and performed the statistical analyses. The investigators were responsible for trial-related medical decisions and data collection. The authors interpreted the aggregated data, participated in writing the first and subsequent drafts of the manuscript (with assistance from a medical writer funded by the sponsor, who wrote the first draft under the direction of the authors in accordance with Good Publication Practice guidelines), and made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Participants

Participants were 18 years of age or older and had obesity (BMI ≥30), a clinical diagnosis of knee osteoarthritis according to American College of Rheumatology criteria (knee pain with three or more of the following factors: an age of >50 years, stiffness for <30 minutes in the morning, crepitus, bony tenderness, bony enlargement, and no palpable warmth),[22] with moderate radiographic changes (Kellgren–Lawrence grade 2 or 3)[23] in the target knee. Eligible participants also had pain related to knee osteoarthritis, with a WOMAC pain score at randomization of at least 40 (on a scale of 0 to 100, with higher scores reflecting worse outcomes). For eligibility and efficacy assessments, the trial used the WOMAC numerical rating scale, version 3.1, with a 24-hour recall period; scores were normalized and expressed on a scale of 0 to 100, with higher scores reflecting worse outcomes (additional information is provided in the

Supplementary Appendix, available at NEJM.org). Participants who were receiving analgesic agents had to complete a 72-hour washout period before randomization. Full eligibility criteria are provided in the Supplementary Appendix. All the participants provided written informed consent.

PROCEDURES

Participants were randomly assigned in a 2:1 ratio, with the use of an interactive Web-response system, to receive once-weekly subcutaneous semaglutide or visually identical placebo for 68 weeks, followed by a 7-week follow-up period during which the participants did not receive semaglutide or placebo. Block randomization was used (with a block size of six), with no stratification factors. Throughout the trial, participants in both groups received counseling on a reduced-calorie diet and physical activity (additional details are provided in the Supplementary Appendix). Semaglutide was initiated at a dose of 0.24 mg, with dose escalation intended to reach the 2.4-mg target at week 16. Participants who had unacceptable side effects with a 2.4-mg dose could continue to receive a lower dose (1.7 mg), provided that the investigator considered the treatment to be safe. The protocol recommended that participants make at least one additional attempt to escalate to the target dose of 2.4 mg, at the investigator's discretion.

Treatment with other antiobesity medications was not permitted; the use of other interventions for knee osteoarthritis was permitted. Although pain medication could be used throughout the trial, opioid use was an exclusion criterion at baseline, and use was discouraged during the trial. During the washout periods (24 to 72 hours before visits), acetaminophen could be used for pain management at a maximum of 4 g per day; no pain medication could be used within the 24 hours before a visit. Participants kept an electronic diary to record pain and pain-medication use. The worst daily knee pain was recorded in the electronic diary with the use of a numerical rating scale ranging from 0 to 10, with higher scores indicating worse pain. Additional details are provided in the Supplementary Appendix.

END POINTS AND ASSESSMENTS

All the end points were assessed from baseline to week 68. The primary end points were the percentage change in body weight and the change in WOMAC pain score. Confirmatory secondary end points were the percentage of participants with a body-weight reduction of at least 5% or at least 10%, the change in the WOMAC physical-function score, and the change in physical-function score on the 36-Item Short Form Health Survey (SF-36), version 2.0. The supportive secondary end points included changes in waist circumference, WOMAC stiffness score, WOMAC total score, pain intensity (as reported in the pain diary with the numerical rating scale), and pain-medication use. Exploratory end points included the change in the 6-minute walk distance. The SF-36 (acute version with a 7-day recall period) used norm-based scoring, on a scale of 0 to 100, with higher scores reflecting better outcomes.

Because the incidence of mild and moderate adverse events with a 2.4-mg dose of semaglutide has been characterized in previous trials,[24-31] a targeted approach to collection of safety data was used. Investigators recorded only serious adverse events, adverse events leading to discontinuation of semaglutide or placebo, adverse events warranting invasive knee procedures, medication error (i.e., an unintended failure with the investigational product, including administration of the wrong drug, incorrect route of administration, missed doses, or drug misuse or abuse by the participant [e.g., drug overdose to maximize the effect or with the intention to cause harm]), acute pancreatitis, coronavirus disease 2019, and pregnancy or pregnancy-related adverse events. Blood pressure was measured as part of the safety assessments.

STATISTICAL ANALYSIS

The two primary end points were tested at a significance level of 5%, with the alpha split between the two end points (1% for the percentage change in body weight and 4% for the change in WOMAC pain score). If superiority was confirmed for both primary end points, the confirmatory secondary end points could be tested at a 5% significance level in a prespecified hierarchical manner, as described in the Supplementary Appendix. Supportive secondary and exploratory end-point analyses were not controlled for multiplicity and should not be used to infer definitive treatment effects.

The full analysis population included all the participants who underwent randomization (according to the intention-to-treat principle). The safety analysis population included all the participants who underwent randomization and re-

ceived at least one dose of semaglutide or placebo. Observation periods included the in-trial period (the interval between the date a participant had undergone randomization and that participant's last date of contact with the trial site, regardless of treatment discontinuation or rescue intervention) and the on-treatment period (any period during which a participant had received semaglutide or placebo within the previous 2 weeks, excluding any period of temporary interruption of the assigned regimen).

The efficacy end points were analyzed with the use of two estimands.[32] A treatment policy estimand, which is consistent with an intention-to-treat analysis, is a precise description of the treatment effect in a "real world" setting, regardless of adherence, unacceptable adverse events, or additional interventions. The treatment policy estimand was used to assess efficacy in the full analysis population regardless of adherence to the assigned regimen, use of other interventions, or adherence to pain-medication washout and was used for statistical inference, including confirmatory testing. Multiple imputation was performed to account for missing data at week 68, with the use of the available data from the participants in each group. The primary end points were also analyzed with the use of the trial product estimand, which assessed efficacy if the trial regimen was followed as intended (i.e., without discontinuations or the use of other interventions). Additional details regarding estimands and analysis methods are provided in the Supplementary Appendix. Pain medication use was assessed with descriptive statistics. The change in the 6-minute walk distance was assessed post hoc according to the treatment policy estimand. In addition, a post hoc analysis was conducted of the change in the WOMAC pain score, stratified according to BMI at baseline (<35, 35 to <40, or ≥40). The analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

TRIAL PARTICIPANTS

From October 2021 through March 2022, a total of 407 participants underwent randomization; 271 were assigned to receive semaglutide, and 136 to receive placebo. Most of the participants completed the treatment period (86.7% in the semaglutide group and 77.9% in the placebo group) and the trial (90.8% and 89.7%, respectively) (Fig. S1 in the Supplementary Appendix). Among the 235 participants in the semaglutide group who completed the treatment period, at the last treatment visit, 211 (89.8%) were receiving the full 2.4-mg dose, 9 (3.8%) were receiving 1.7 mg to less than 2.4 mg, and 11 (4.7%) were receiving less than 1.7 mg; 4 participants (1.7%) did not report the dose.

Most participants were women (81.6%) and White (60.9%), and the mean age was 56 years (Table 1 and Table S1). At baseline, the mean body weight was 108.6 kg, the BMI 40.3, the waist circumference 118.7 cm, and the WOMAC pain score 70.9. A higher percentage of participants (41.0%) had severe obesity (BMI ≥40) than other weight categories (the BMI was 35 to <40 in 34.4% of the participants, 30 to <35 in 24.3%, and <30 in 0.2%). Overall, the characteristics of the participants at baseline were balanced between the two groups. The representativeness of the trial population is shown in Table S2.

PRIMARY END POINTS

The mean change from baseline in body weight at week 68 was −13.7% in the semaglutide group and −3.2% in the placebo group (estimated difference, −10.5 percentage points; 95% confidence interval [CI], −12.3 to −8.6; P<0.001) (Fig. 1). The results for the trial product estimand were similar (estimated difference, −12.1 percentage points; 95% CI, −13.8 to −10.5) (Fig. S2).

The mean change from baseline in the WOMAC pain score at week 68 was −41.7 points in the semaglutide group and −27.5 points in the placebo group (estimated difference, −14.1 points; 95% CI, −20.0 to −8.3; P<0.001) (Fig. 1). The results of the trial product estimand were similar (estimated difference, −14.8 points; 95% CI, −20.1 to −9.4) (Fig. S3).

CONFIRMATORY SECONDARY END POINTS

At week 68, the percentages of participants who had body-weight reductions from baseline of at least 5% and at least 10% were significantly higher in the semaglutide group (87.0% and 70.4%, respectively) than in the placebo group (29.2% and 9.2%, respectively) (Fig. 2A and Table S3). Over a period of 68 weeks, participants in the semaglutide group had a greater decrease (improvement) from baseline in WOMAC physical-function score than participants in the placebo group (mean change,

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Semaglutide (N=271)	Placebo (N=136)	Total (N=407)
Age — yr	56±10	56±10	56±10
Female sex — no. (%)	228 (84.1)	104 (76.5)	332 (81.6)
Race or ethnic group — no. (%)†			
White	168 (62.0)	80 (58.8)	248 (60.9)
Asian	16 (5.9)	6 (4.4)	22 (5.4)
Black	18 (6.6)	13 (9.6)	31 (7.6)
American Indian or Alaska Native	37 (13.7)	11 (8.1)	48 (11.8)
Other	32 (11.8)	26 (19.1)	58 (14.3)
Body weight — kg	108.7±24.1	108.5±24.5	108.6±24.2
Body-mass index			
Mean	40.5±7.3	40.0±7.1	40.3±7.2
Distribution — no. (%)			
<30	0	1 (0.7)	1 (0.2)
30 to <35	67 (24.7)	32 (23.5)	99 (24.3)
35 to <40	84 (31.0)	56 (41.2)	140 (34.4)
≥40	120 (44.3)	47 (34.6)	167 (41.0)
Waist circumference — cm‡	118.3±15.8	119.7±15.9	118.7±15.8
WOMAC pain score§	72.8±15.6	67.2±16.0	70.9±16.0
Systolic blood pressure — mm Hg¶	132±14	131±15	132±15
Diastolic blood pressure — mm Hg¶	82±10	82±10	82±10
Coexisting conditions — no. (%)‖			
Hypertension	128 (47.2)	68 (50.0)	196 (48.2)
Dyslipidemia	80 (29.5)	44 (32.4)	124 (30.5)
Gastroesophageal reflux disease	31 (11.4)	15 (11.0)	46 (11.3)
Asthma	19 (7.0)	19 (14.0)	38 (9.3)
Cardiovascular disease	13 (4.8)	8 (5.9)	21 (5.2)

* Plus–minus values are means ±SD. Data are shown for the full analysis population, which consisted of all the participants who had undergone randomization. Additional information about baseline characteristics is provided in Table S1 in the Supplementary Appendix. Percentages may not total 100 because of rounding.
† Race or ethnic group was reported by the participants. The "Other" category includes participants for whom race or ethnic group was not reported.
‡ Data on waist circumference were available for 405 participants (270 in the semaglutide group and 135 in the placebo group).
§ The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores were normalized and expressed on a scale of 0 to 100, with higher scores reflecting worse outcomes.
¶ Data on blood pressure were available for 404 participants (269 in the semaglutide group and 135 in the placebo group).
‖ Included are the coexisting conditions reported in more than 5% of the participants in the total trial population; additional information is provided in Table S1.

–41.5 points vs. –26.7 points; estimated difference, –14.9 points; 95% CI, –20.4 to –9.3; P<0.001) (Fig. S4A). At week 68, participants in the semaglutide group also had a greater increase (improvement) in SF-36 physical-function score from baseline than those in the placebo group (mean change, 12.0 points vs. 6.5 points; estimated difference, 5.6 points; 95% CI, 3.1 to 8.0; P<0.001) (Fig. S4C).

SUPPORTIVE SECONDARY AND EXPLORATORY END POINTS

A greater percentage of participants in the semaglutide group than in the placebo group had a body-weight reduction of at least 15% (47.8% vs. 2.5%) and at least 20% (23.3% vs. 0%) (Fig. 2A). A greater percentage of participants in the semaglutide group also had a reduction in the WOMAC

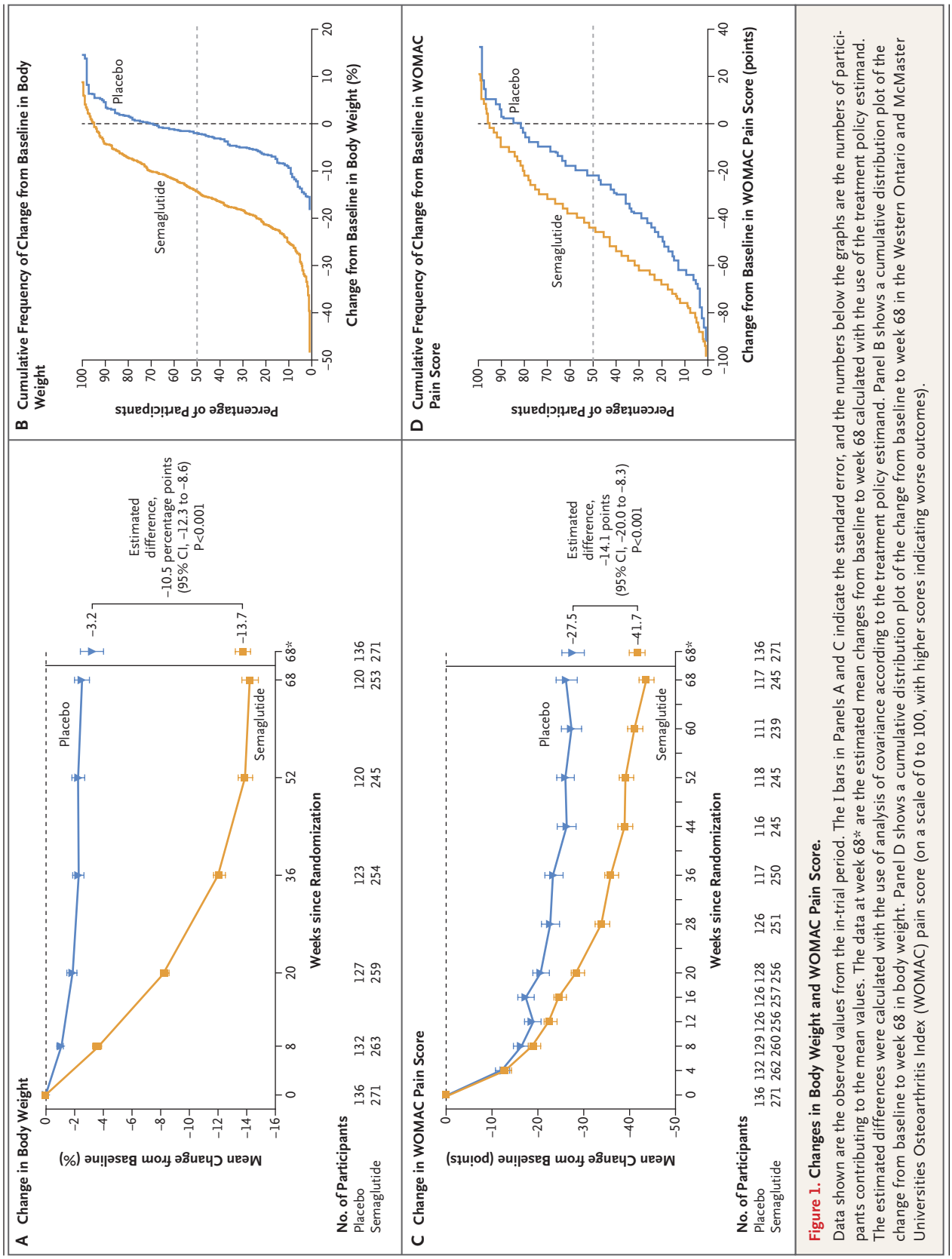

Figure 1. Changes in Body Weight and WOMAC Pain Score.

Data shown are the observed values from the in-trial period. The I bars in Panels A and C indicate the standard error, and the numbers below the graphs are the numbers of participants contributing to the mean values. The data at week 68* are the estimated mean changes from baseline to week 68 calculated with the use of the treatment policy estimand. The estimated differences were calculated with the use of analysis of covariance according to the treatment policy estimand. Panel B shows a cumulative distribution plot of the change from baseline to week 68 in body weight. Panel D shows a cumulative distribution plot of the change from baseline to week 68 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (on a scale of 0 to 100, with higher scores indicating worse outcomes).

pain score of at least 30% and at least 50% (Fig. 2B). In addition, treatment with semaglutide resulted in a greater reduction in waist circumference over a period of 68 weeks than placebo (difference, −6.9 cm; 95% CI, −9.1 to −4.7) (Fig. S5).

The results of subgroup analyses indicated greater improvements in WOMAC pain scores with semaglutide than with placebo in all subgroups defined according to BMI at baseline (Table S4). Semaglutide resulted in greater reductions over a 68-week period than placebo in pain intensity according to the score on the numerical rating scale for daily knee pain (difference, −1.0 point; 95% CI, −1.6 to −0.5) (Fig. S6).

Semaglutide resulted in greater reductions over a period of 68 weeks than placebo in the WOMAC stiffness score (estimated difference, −15.9 points; 95% CI, −23.2 to −8.6) and WOMAC total score (estimated difference, −14.9 points; 95% CI, −20.5 to −9.3) (Figs. S7 and S8). Greater improvements from baseline to week 68 in the 6-minute walk distance were reported in the semaglutide group than in the placebo group (mean change, 56.8 m and 14.2 m, respectively; estimated difference, 42.6 m; 95% CI, 25.6 to 59.7).

The percentage of participants who were using nonsteroidal antiinflammatory drugs (NSAIDs) or acetaminophen decreased during the trial in both groups, although to a greater extent in the semaglutide group (Fig. 3). Acetaminophen use was more prevalent at baseline in the semaglutide group but reached a level similar to that in the placebo group by approximately week 36. NSAID use was similarly prevalent at baseline in the two groups but was lower in the semaglutide group by approximately week 16. Only 23 participants (8.5%) in the semaglutide group and 13 (9.6%) in the placebo group reported taking opioids at any time during the trial; of these participants, 12 in the semaglutide group and 7 in the placebo group reported codeine use.

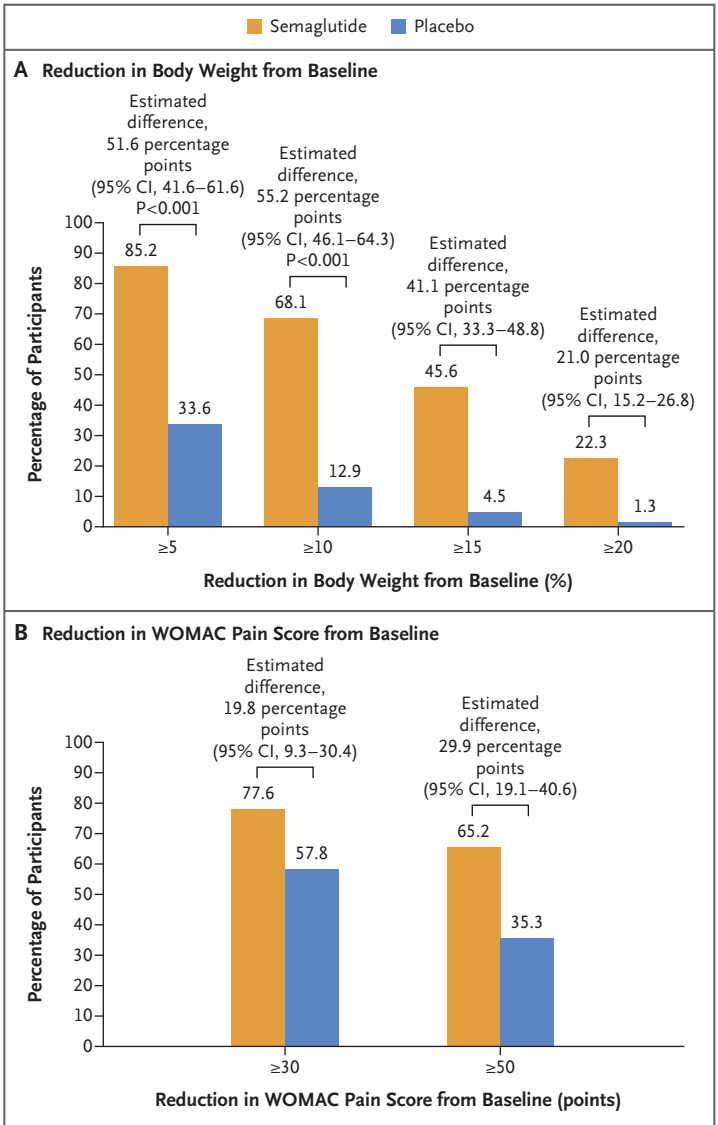

Figure 2. Reduction in Body Weight and WOMAC Pain Score at Week 68.
The estimated percentages and differences were derived from a logistic-regression model according to the treatment policy estimand. The confidence intervals for the differences were obtained with the use of the delta method. P values are reported for confirmatory secondary end-point analyses only, on the basis of odds ratios estimated from the same logistic-regression model. The odds ratios for these end points are provided in Table S3 in the Supplementary Appendix.

SAFETY

Safety was assessed in 269 participants in the semaglutide group and in 135 participants in the placebo group. The incidence of serious adverse events was similar in the two groups (10.0% in the semaglutide group and 8.1% in the placebo group) (Table 2). The most frequently reported serious adverse events were neoplasms (benign, malignant, or unspecified; nine events reported among 9 participants [3.3%] in the semaglutide group and three events reported among 3 participants [2.2%] in the placebo group) and gastrointestinal disorders (five events reported among 4 participants [1.5%] in the semaglutide group and one event reported in 1 participant [0.7%] in the placebo group) (Table S5). Adverse events leading to permanent discontinuation of

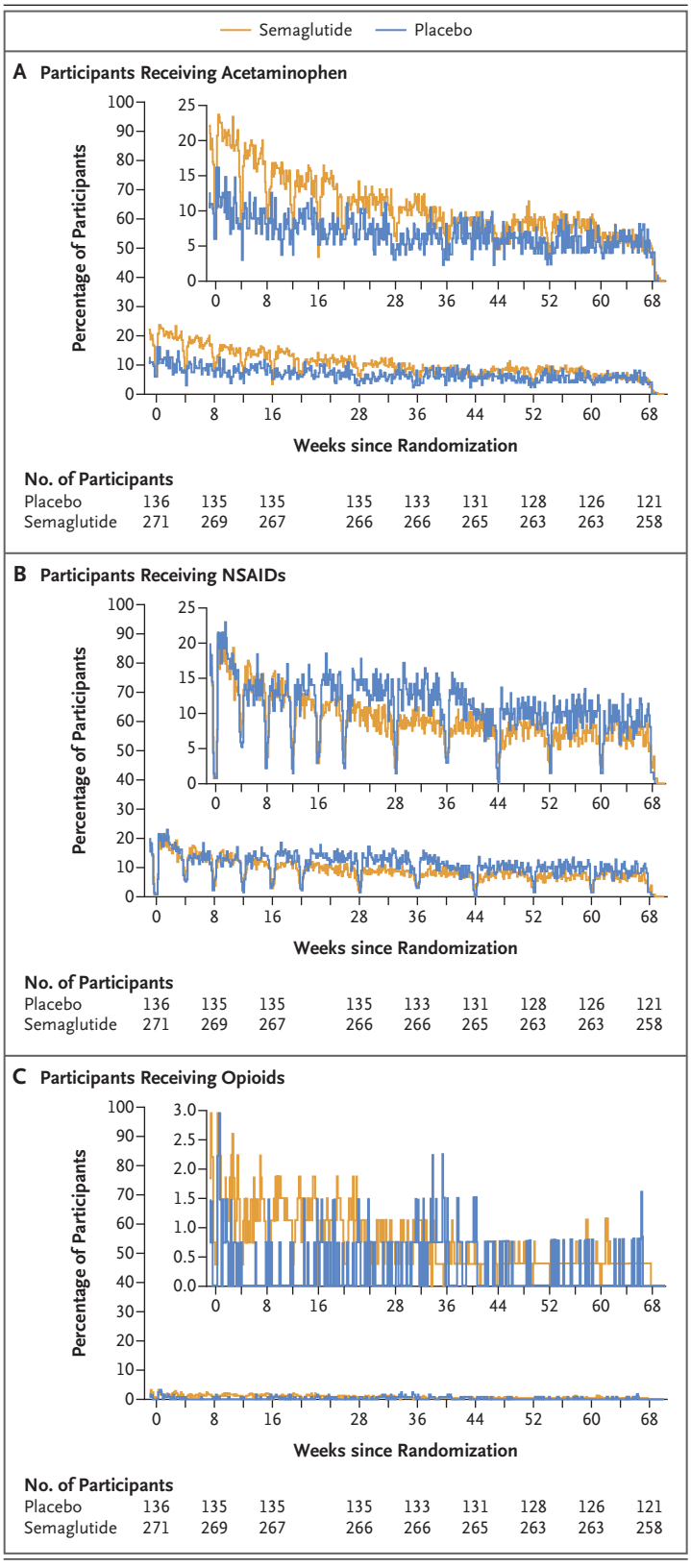

Figure 3. Use of Pain Medication According to Type.

Data shown are the observed data from the in-trial period, including a 7-day prerandomization period. The numbers below the graphs are the numbers of participants contributing to the analysis at each time point. Current opioid use was an exclusion criterion at randomization, and initiation or use of opioids was discouraged during the trial; three cases of ongoing use of opioids at randomization (which represented protocol deviations) were identified. The inset in each panel shows the same data on an enlarged y axis. NSAID denotes nonsteroidal antiinflammatory drug.

the trial regimen were reported in 6.7% of the participants in the semaglutide group and in 3.0% of those in the placebo group. Gastrointestinal disorders (in 2.2% in the semaglutide group and in 0% in the placebo group) and neoplasms (benign, malignant, or unspecified; in 1.9% and 1.5%, respectively) were the most common event types that led to discontinuation of the trial regimen (Table S6). There were no unexpected findings with respect to the safety focus areas (Table 2). Among the participants who were receiving semaglutide or placebo at week 68, the systolic and diastolic blood pressure were reduced from baseline by a mean (±SD) of 8±15 mm Hg and 3±9 mm Hg, respectively, in the semaglutide group and 0±13 mm Hg and 1±9 mm Hg, respectively, in the placebo group.

DISCUSSION

The STEP 9 trial, which involved persons with obesity and moderate-to-severe pain due to knee osteoarthritis, showed that semaglutide was superior to placebo in reducing pain related to knee osteoarthritis as well as body weight and was associated with improved physical function. Although previous studies have indicated a benefit of weight reduction with respect to symptoms,[9] this randomized trial used full blinding of the participants to the trial-group assignment and also showed larger effects. Weight reductions and safety outcomes with semaglutide were consistent with those reported in previous STEP trials.[24-31]

Treatment with semaglutide resulted in greater improvements than placebo across all pain-related end points, a finding that is in line with those from an observational study involving adults

Table 2. Adverse Events.*

Adverse Event	Semaglutide (N=269)	Placebo (N=135)	Relative Risk (95% CI)	Risk Difference (95% CI)†
	no. of participants (%)			
Any serious adverse event	27 (10.0)	11 (8.1)	1.23 (0.64 to 2.40)	1.9 (–4.7 to 7.3)
Adverse event leading to permanent discontinuation of semaglutide or placebo				
Any event	18 (6.7)	4 (3.0)	2.26 (0.82 to 6.30)	3.7 (–1.3 to 7.7)
Gastrointestinal disorder	6 (2.2)	0	—	2.2 (–0.8 to 4.8)
Fatal event	0	0	—	—
Safety focus areas				
Coronavirus disease 2019	51 (19.0)	32 (23.7)	0.80 (0.54 to 1.19)	–4.7 (–13.7 to 3.4)
Serious neoplasm‡	10 (3.7)	6 (4.4)	0.84 (0.32 to 2.18)	–0.7 (–5.9 to 3.1)
Serious malignant neoplasm‡	8 (3.0)	2 (1.5)	2.01 (0.49 to 8.31)	1.5 (–2.5 to 4.5)
Serious gastrointestinal event‡	4 (1.5)	1 (0.7)	2.01 (0.31 to 13.33)	0.7 (–2.7 to 3.1)
Serious acute gallbladder disease‡	3 (1.1)	1 (0.7)	1.51 (0.22 to 10.49)	0.4 (–3.0 to 2.6)
Serious cardiovascular disorder‡	3 (1.1)	2 (1.5)	0.75 (0.15 to 3.75)	–0.4 (–4.2 to 2.0)
Medication error§	2 (0.7)	4 (3.0)	0.25 (0.05 to 1.16)	–2.2 (–6.7 to 0.4)
Serious acute renal failure‡	0	1 (0.7)	0.00 (0.00 to 1.93)	–0.7 (–4.1 to 0.8)
Serious psychiatric disorder‡	0	1 (0.7)	0.00 (0.00 to 1.93)	–0.7 (–4.1 to 0.8)
Acute pancreatitis	0	0	—	—
Pregnancy or pregnancy-related adverse event‡	0	0	—	—
Joint replacement	2 (0.7)	0	—	—

* Shown are adverse events that occurred during the on-treatment period with any dose of semaglutide or placebo that was administered within the previous 49 days, unless indicated otherwise (the on-treatment period was any period during which a participant had received semaglutide or placebo within the previous 2 weeks, excluding any period of temporary interruption of the assigned regimen). Adverse events are shown for the safety analysis population, which included all the participants who had undergone randomization and received at least one dose of semaglutide or placebo. Additional information on serious adverse event types, adverse event types leading to discontinuation of semaglutide or placebo, and malignant neoplasms according to type is provided in Tables S5, S6, and S7, respectively.

† The risk differences are expressed in percentage points.

‡ Shown are the number of events that were reported during the in-trial period (the interval between the date a participant had undergone randomization and that participant's last date of contact with the trial site, regardless of treatment discontinuation or rescue intervention).

§ Medication error was defined as an unintended failure with the investigational product, including administration of the wrong drug, incorrect route of administration, missed doses, or drug misuse or abuse by the participant (e.g., drug overdose to maximize the effect or with the intention to cause harm).

with knee osteoarthritis and type 2 diabetes, in which greater reductions in WOMAC total and pain scores were seen among participants who received GLP-1 receptor agonists than among those who did not receive these agents (mean BMI at baseline, 25).[19] In contrast, a trial of the GLP-1 receptor agonist liraglutide (administered subcutaneously once daily at a dose of 3.0 mg) that involved participants with overweight or obesity and knee osteoarthritis showed no significant differences in pain as compared with placebo (according to the Knee Injury and Osteoarthritis Outcome Score).[16] However, in the liraglutide trial, weight reduction was modest (mean change, –2.8 kg in the liraglutide group and 1.2 kg in the placebo group), which may have contributed to the lack of improvement in pain scores.

The use of analgesic agents decreased during the trial, with a greater reduction observed in the semaglutide group than in the placebo group, a finding that confirms that pain reduction with semaglutide was not due to increased

use of analgesic agents. These results suggest an NSAID-sparing effect of semaglutide, potentially limiting the adverse effects of NSAIDs[33] and reducing polypharmacy. Opioid use was discouraged and was low throughout the trial in both groups.

The trial was not designed to investigate the mechanism of action of semaglutide on knee osteoarthritis, so mechanistic conclusions cannot be drawn. Weight reduction is most likely a major contributor, as a result of reduced mechanical stress on the knee joints; previous studies have shown that weight reduction through various strategies can lead to considerable alleviation of knee pain and joint stiffness.[9] However, preclinical studies have shown that GLP-1 receptor agonists have antiinflammatory and antidegradative effects.[34,35]

The severity of obesity varied among the enrolled participants, and subgroup analyses indicated a benefit of semaglutide with respect to pain regardless of BMI values at baseline. However, overall mean BMI and pain scores at baseline were higher than in previous studies involving persons with knee osteoarthritis,[15,16,19] and a high percentage of participants (41%) had severe obesity (BMI ≥40) at baseline. Future studies could further explore the applicability of these findings to wider populations.

The limitations of this trial include a lack of imaging at follow-up and a lack of assessment of metabolic and inflammatory markers; therefore, the effect of semaglutide on the pathophysiology of knee osteoarthritis could not be determined. In addition, adherence to dietary and physical-activity recommendations was not assessed. Although most participants were women, knee osteoarthritis is known to be more prevalent among women than among men.[1] The prevalence of coexisting conditions at baseline, such as nonalcoholic fatty liver disease and obstructive sleep apnea, was lower than expected on the basis of previous epidemiologic data,[36] most likely because coexisting conditions were reported by the investigator and not objectively assessed. In addition, changes in outcomes were not assessed after the end of the treatment period; however, previous studies have shown weight regain after discontinuation of semaglutide,[28,37] a finding that suggests that longer-term treatment strategies may be needed to maintain benefits. Perceived trial-group assignment and the effect of such perception were not assessed; however, the magnitude and consistency of treatment benefit with semaglutide across outcomes suggests that perceived assignment was unlikely to account for the improvements observed.[38]

This randomized, double-blind, placebo-controlled trial showed that treatment with semaglutide alleviated pain related to osteoarthritis of the knee among persons with obesity and knee osteoarthritis. The findings support the use of once-weekly subcutaneous semaglutide at a dose of 2.4 mg for weight management and treatment of pain in persons with obesity and moderate-to-severe pain due to knee osteoarthritis.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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Semaglutide in Obesity and Knee Osteoarthritis

A PLAIN LANGUAGE SUMMARY

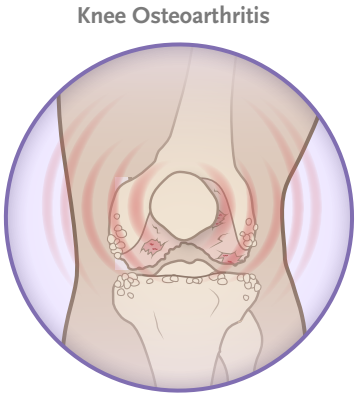
Based on the NEJM publication: Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis by H. Bliddal et al. (published October 31, 2024)

In this trial, researchers evaluated whether the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide is superior to placebo in reducing body weight and pain related to knee osteoarthritis in persons with obesity and knee osteoarthritis.

Osteoarthritis of the knee is the most prevalent form of osteoarthritis and leads to chronic pain and impaired quality of life.

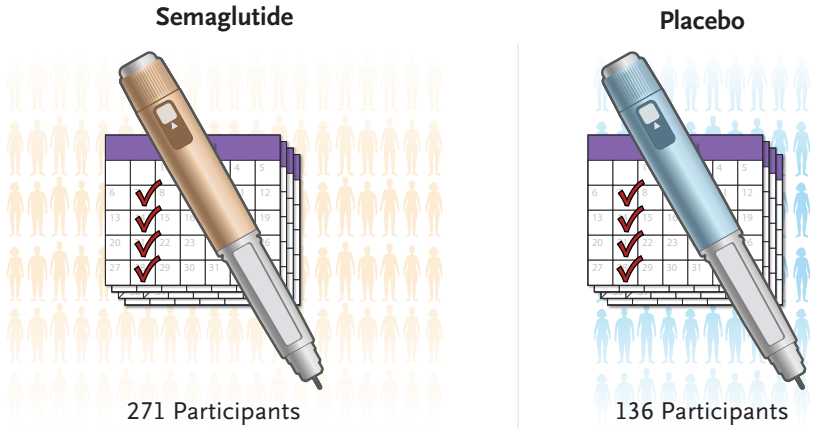
WHY WAS THE TRIAL DONE?

Obesity is a major risk factor for development of knee osteoarthritis and disease progression. Whether GLP-1 receptor agonists can reduce pain due to knee osteoarthritis in persons with obesity is unclear.



HOW WAS THE TRIAL CONDUCTED?

Adults with obesity and moderate-to-severe pain due to knee osteoarthritis were randomly assigned to receive weekly subcutaneous semaglutide (2.4 mg) or placebo, in addition to counseling on physical activity and a reduced-calorie diet. The primary end points were the percentage change in body weight and the change in WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) pain score (scale, 0 to 100, with higher scores reflecting worse outcomes). Both end points were assessed from baseline to week 68.



PARTICIPANTS

WHO	407 adults
	Mean age: 56 years
	Women: 82%; Men: 18%
CLINICAL STATUS	Clinical and radiologic diagnosis of moderate knee osteoarthritis
	Body-mass index of 30 or greater
	Moderate-to-severe pain due to knee osteoarthritis

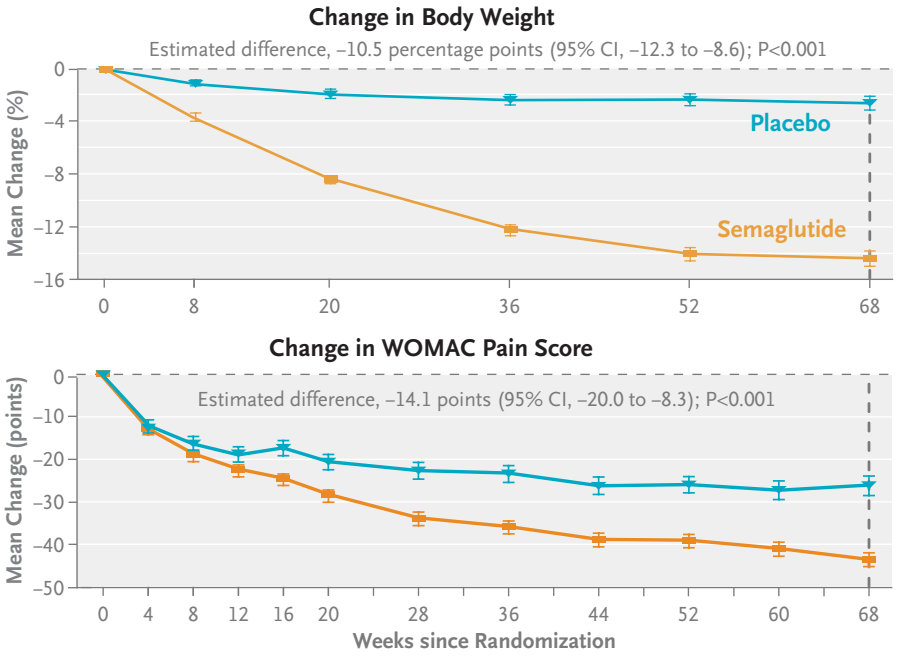
TRIAL DESIGN

- RANDOMIZED
- DOUBLE-BLIND
- PLACEBO-CONTROLLED
- LOCATION: 61 SITES IN 11 COUNTRIES

RESULTS

At week 68, treatment with semaglutide resulted in a significantly greater reduction in body weight than placebo. Participants in the semaglutide group also had a greater decrease (improvement) in WOMAC pain score.

The incidence of serious adverse events was similar in the two groups.



COMPLETION OF TREATMENT PERIOD AND TRIAL

Most of the participants completed the treatment period (86.7% in the semaglutide group and 77.9% in the placebo group) and the trial (90.8% and 89.7%, respectively).

LIMITATIONS AND REMAINING QUESTIONS

- The trial did not include imaging at follow-up or assessment of metabolic and inflammatory markers; therefore, the effect of semaglutide on the pathophysiology of knee osteoarthritis could not be determined.
- Participants' adherence to dietary and physical-activity recommendations was not assessed.
- Changes in outcomes were not assessed after the end of the treatment period; however, previous studies have reported weight regain after discontinuation of semaglutide, a finding that suggests that longer-term treatment strategies may be needed to maintain benefits.

CONCLUSIONS

In persons with obesity and knee osteoarthritis, once-weekly semaglutide significantly reduced body weight and knee osteoarthritis pain, as compared with placebo.

LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT05064735

Trial funding: Novo Nordisk

Full citation: Bliddal H, Bays H, Czernichow S, et al. Once-weekly semaglutide in persons with obesity and knee osteoarthritis. N Engl J Med 2024;391:1573-83. DOI: 10.1056/NEJMoa2403664

Supplementary Appendix

Supplement to: Bliddal H, Bays H, Czernichow S, et al. Once-weekly Semaglutide in persons with obesity and knee osteoarthritis. N Engl J Med 2024;391:1573-83. DOI: 10.1056/NEJMoa2403664

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis

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Supplementary Methods

Information on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The WOMAC is a tri-dimensional, patient-reported outcome measure consisting of 24 questions on pain, stiffness, and physical function in patients with hip and/or knee osteoarthritis. Of the 24 questions, 5 refer to pain, 2 to stiffness, and 17 to physical function. The version used in this trial was the WOMAC Numeric Rating Scale (NRS) 3.1, an 11-point NRS with responses ranging from no symptoms/difficulty (0) to extreme symptoms/difficulty (10). This version has a 24-hour recall period. Subscores for pain, stiffness, and physical function scores, as well as a total score, were calculated according to guidelines in the WOMAC user manual.

Information on the Worst Daily Knee Pain Numeric Rating Scale

Participants kept an electronic pain and pain medication diary, which included recording their worst daily knee pain using an NRS. This was a single item measure of knee pain at its worst in the last 24 hours. The response scale included an 11-point numeric rating scale from 0 (no knee pain) to 10 (worst possible knee pain). The NRS item related to the target knee joint that was defined as the most symptomatic knee at screening. If pain in the knees was equal, the target knee joint was in the most dominant leg.

Information on Diet and Exercise Counselling

All participants in both treatment arms received counselling with regards to reduced calorie diet and physical activity taking participants' knee osteoarthritis into consideration. Counselling was done by a dietician or a similarly qualified healthcare professional. Counselling included the optional provision of a booklet providing guidance on use of a healthy diet and physical activity, combined with counselling by study site staff every 4 weeks until week 20, and every 8 weeks thereafter, until week 68.

Full Participant Inclusion and Exclusion Criteria

Inclusion Criteria

Subjects are eligible to be included in the trial only if all of the following criteria apply:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male or female, aged ≥18 years at the time of signing informed consent
3. Body mass index ≥30.0 kg/m^2
4. Clinical diagnosis of knee osteoarthritis (American College of Rheumatology criteria) with moderate radiographic changes (Kellgren–Lawrence grade 2 or 3 as per central reading [Calyx]) in target knee. Target knee joint is defined as most symptomatic knee at screening. If pain is equal in both knees, target knee joint will be in the most dominant leg
5. Pain due to knee osteoarthritis
6. Willingness to complete 72-hour washout period of analgesics before all visits involving WOMAC questionnaire (acetaminophen is allowed as rescue medication)

Exclusion Criteria

Subjects are excluded from the trial if any of the following criteria apply:

Knee osteoarthritis-related:

1. Joint replacement in target knee
2. Arthroscopy or injections in target knee in the 3 months before enrollment
3. Elective surgery scheduled during the trial period, except for minor surgical procedures
4. Any other joint disease in target knee
5. Current use of medical marijuana or opioids
6. Symptomatic hip osteoarthritis unless treated with hip replacement
7. Primary localization of pain not in target knee
8. Chronic widespread pain, including neuropathic pain

Obesity-related:

9. Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device, except for: (1) liposuction and/or abdominoplasty, if performed >1 year before screening, (2) lap banding, if the band has been removed >1 year before screening, (3) intragastric balloon, if the balloon has been removed >1 year before screening, or (4) duodenal–jejunal bypass sleeve, if the sleeve has been removed >1 year before screening
10. A transient ischemic at irrespective of medical records
11. Uncontrolled thyroid disease
12. Treatment with any medication for the indication of obesity in the 90 days before screening

Glycemia-related:

13. Glycated hemoglobin ≥48 mmol/mol (6.5%) as measured by local laboratory at screening

14. History or presence of type 1 or type 2 diabetes (history of gestational diabetes is allowed)
15. Treatment with any glucagon-like peptide-1 receptor agonist in the 90 days before screening

General health and safety-related:

16. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
17. Presence of acute pancreatitis in the 180 days before screening
18. History or presence of chronic pancreatitis
19. End-stage renal disease or chronic or intermittent hemodialysis or peritoneal dialysis
20. Presence or history of malignant neoplasm in the 5 years before screening (basal and squamous cell cancer and any carcinoma in-situ are allowed)
21. Any of the following in the 60 days before screening: myocardial infarction, stroke, hospitalization for unstable angina, or transient ischemic attack
22. Subjects presently classified with heart failure New York Heart Association Class IV
23. Known or suspected hypersensitivity to trial product(s) or related products
24. Previous participation in this trial. Participation is defined as signed informed consent
25. Participation in another clinical trial in the 90 days before screening
26. Other subject(s) from the same household participating in any semaglutide trial
27. Female subject who is pregnant, breast-feeding, or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method (highly effective contraceptive measures as required by local regulation or practice)
28. History of major depressive disorder in the 2 years before screening
29. Diagnosis of severe psychiatric disorder (eg, schizophrenia, bipolar disorder)
30. History of a suicide attempt
31. Suicidal behavior in the 30 days before screening
32. Known or suspected abuse of alcohol or recreational drugs
33. Any disorder, unwillingness, or inability, not covered by any of the other exclusion criteria, that in the investigator’s opinion might jeopardize the subject’s safety or compliance with the protocol

Statistical Analysis

Predefined Hierarchical Testing Strategy

Efficacy endpoints were tested for superiority of semaglutide versus placebo using a predefined fixed-sequence statistical strategy and a weighted Holm-Bonferroni procedure (with weights one). This strategy tests the endpoints using a predefined hierarchical order; first. First the two primary endpoints (percentage change in body weight and change in WOMAC pain score) were tested at the significance level of 5%, with the alpha split between the two endpoints (using 1% for percentage change in body weight and 4% for change in WOMAC pain score). A sample size of 375 participants would have provided a marginal power of >99% to detect a between-group difference of 9.5%-points in body weight and 90% power to detect a between-group difference of 7.7 score-points in WOMAC pain score, at a two-sided significance level of 1% and 4% respectively. If superiority was confirmed for both primary endpoints, confirmatory secondary endpoints were tested at a 5% significance level in the following prespecified order:

1. Achievement of a body weight reduction ≥5%
2. Achievement of a body weight reduction ≥10%
3. Change in WOMAC physical function score
4. Change in 36-Item Short Form survey (SF-36v2) physical function score

Testing for superiority of each confirmatory secondary endpoint could proceed only after a statistically significant result (p-value <5%) for the previous endpoint.

Analysis Methodology for Treatment Policy Estimand and Trial Product Estimand

Most efficacy endpoints were analyzed according to the treatment policy estimand, which aims to capture the average effect of treatment exposure, adherence, tolerability, and safety. The treatment policy estimand included all observations from the in-trial period (time from date of randomization to last contact with the trial site), regardless of treatment adherence, use of other anti-obesity therapies or knee osteoarthritis interventions, or compliance with the pain medication washout period. Continuous endpoints were analyzed by analysis of covariance using randomized treatment as a factor and baseline value of the endpoint as a covariate; categorical endpoints were analyzed by logistic regression using randomized treatment as a factor and baseline value of the endpoint as a covariate.

Missing data at week 68 were imputed using multiple imputation based on available data from participants in each treatment group; the imputation approach assumed missing at random (MAR) conditional on factors and covariates in the imputation model. Except for analyses of the NRS pain intensity endpoint, imputation was performed using a linear regression model, with sex (male/female), baseline BMI (in categories of <35, 35–<40, ≥40 kg/m^2), baseline value for the outcome, timing of last available observation during the on-treatment period (LAO-OT), and LAO-OT value for the outcome as covariates. One thousand complete data sets were generated, analyzed using the analysis models (analysis of covariance or logistic regression), and pooled using Rubin's formula to generate the final

result. For the change in NRS pain intensity endpoint, imputation was performed using a jump-to-reference multiple imputation approach, using the assumption that participants instantly after discontinuation lose any effect of randomized treatment beyond what can be expected from semaglutide placebo treatment as adjunct to reduced-calorie diet and increased physical activity. Missing values for both the semaglutide and placebo group were imputed by sampling among all available assessments at week 68 in the semaglutide placebo group. In this analysis, imputation was performed using a linear regression model, with sex (male/female), baseline BMI (in categories of <35, 35–<40, ≥40 kg/m^2), and baseline value for the outcome as covariates. The remaining steps in the imputation approach were similar to that described previously for other endpoints.

Pain medication use was analyzed by descriptive statistics. 6WMD data were analyzed descriptively, as per the statistical analysis protocol; a *post-hoc* analysis of change in 6MWD was assessed as per the treatment policy estimand,

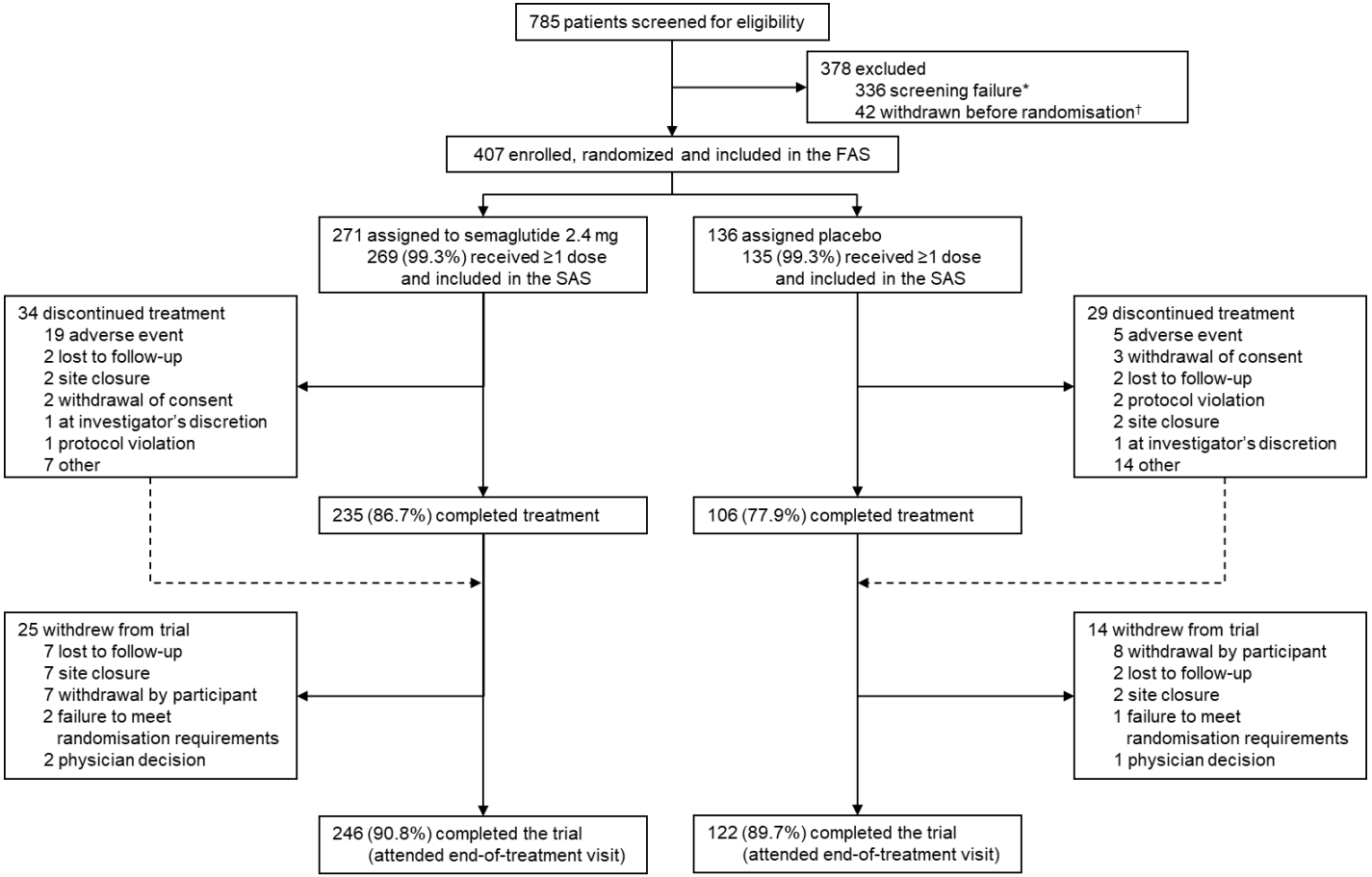
For the primary endpoints, results were also analyzed according to the trial product estimand, which aims to capture the average effect of treatment exposure when taken as intended. The trial product estimand used all observations from the on-treatment period (any timepoint when treatment had been administered within the previous 2 weeks) had participants continued receiving their randomized treatment, not initiated other anti-obesity medication or other knee osteoarthritis-related intervention, and complied with the pain medication washout period (the latter was required only for the endpoint assessing change in WOMAC pain score). Endpoints were analyzed by a mixed model for repeated measurement. Randomized treatment was used as a factor and baseline value of the endpoint as a covariate.

Methodology for Defining Clinically Relevant Improvements in Pain and Physical Function

The clinical relevance of the treatment effect on pain and physical function was evaluated based on the proportions of participants in each group who experienced clinically relevant improvements. The thresholds for such improvements (reflecting the participants' perspective of meaningful change) were established in line with U.S. Food and Drug Administration guidance for patient-reported outcome measures,[1] and defined as a decrease of ≥37.3 points in WOMAC pain score and ≥41.2 points for WOMAC physical function score, and an increase of ≥11.4 points for SF-36v2 physical functioning score. The thresholds were computed by the mean change from baseline to week 68 in the WOMAC pain and physical function scores and SF-36v2 physical functioning score among patients with a 1-category improvement on the corresponding Patient Global Impression of Status scale. In addition to the anchor-based threshold, the proportions of responders with ≥30% and ≥50% reduction in WOMAC pain score were computed to support the interpretation.

Supplementary Figures

Figure S1. Participant Disposition.

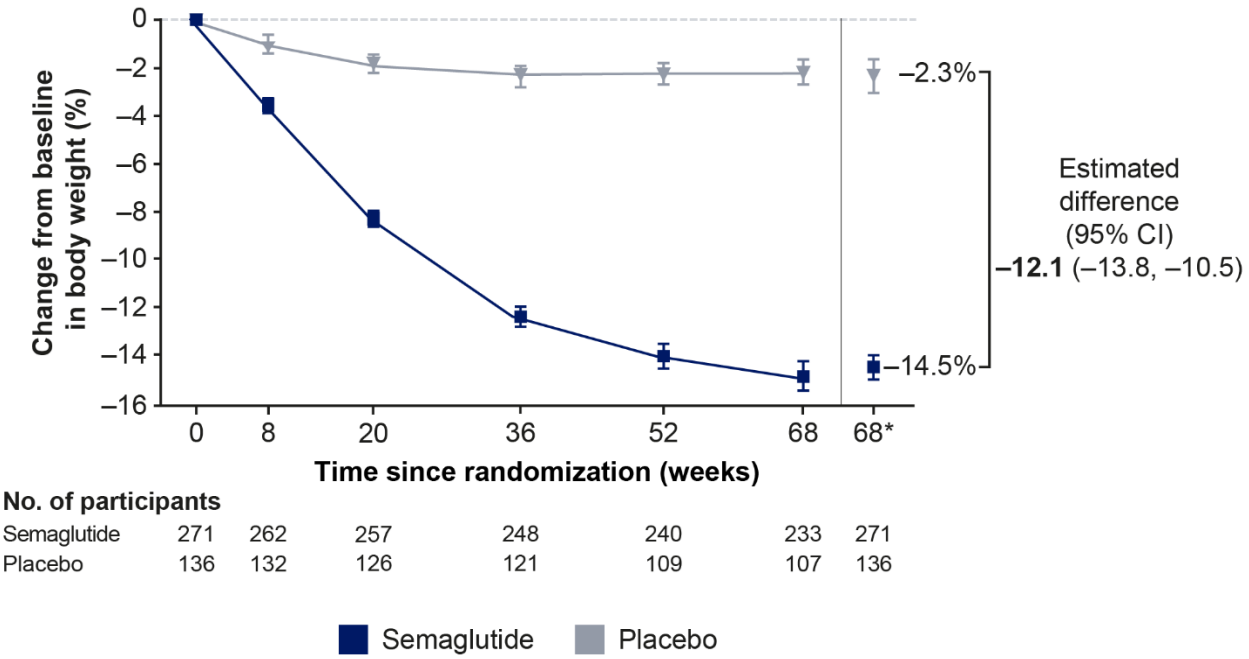


Percentages represent the proportion of participants in the FAS. Among the 235 participants completing treatment in the semaglutide group, at the last treatment visit 211 (89.8%) were receiving the full 2.4 mg dose, 9 (3.8%) were receiving 1.7 mg – <2.4 mg, and 11 (4.7%) were receiving less than 1.7 mg; 4 (1.7%) did not report the dose.

N, number of participants; FAS, full analysis set; SAS, safety analysis set. *Most screening failures (276/336 [82.1%]) were due to participants not meeting the inclusion criterion that required a clinical diagnosis of knee osteoarthritis (American College of Rheumatology criteria) with moderate radiographic changes (Kellgren–Lawrence grade 2 or 3 as per central reading) in the target knee. Failure to meet the inclusion criterion related to pain due to knee osteoarthritis led to screening failure for 4 patients (1.2%). †Of 42 participants who passed screening but were withdrawn prior to randomization, 37 did not meet the randomization criteria for WOMAC pain score (≥40) or were non-compliant with pain medication washout at baseline.

SAS denotes safety analysis set.

Figure S2. Change in Body weight – Trial Product Estimand.

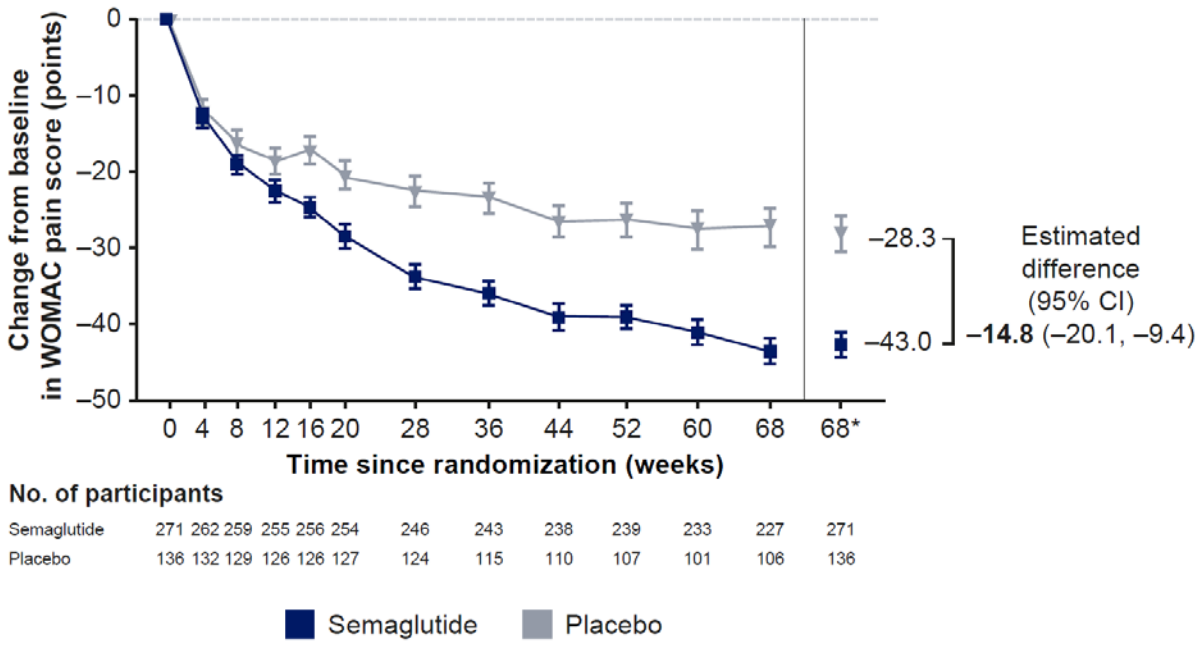


Data are observed values from the on-treatment period. Error bars are ± standard error of the mean. Numbers below the graph show the number of participants contributing to each mean.

*Estimated mean change at week 68 using the trial product estimand. Estimated difference was calculated using a mixed model for repeated measurement according to the trial product estimand.

CI denotes confidence interval.

Figure S3. Change in WOMAC Pain Score – Trial Product Estimand.

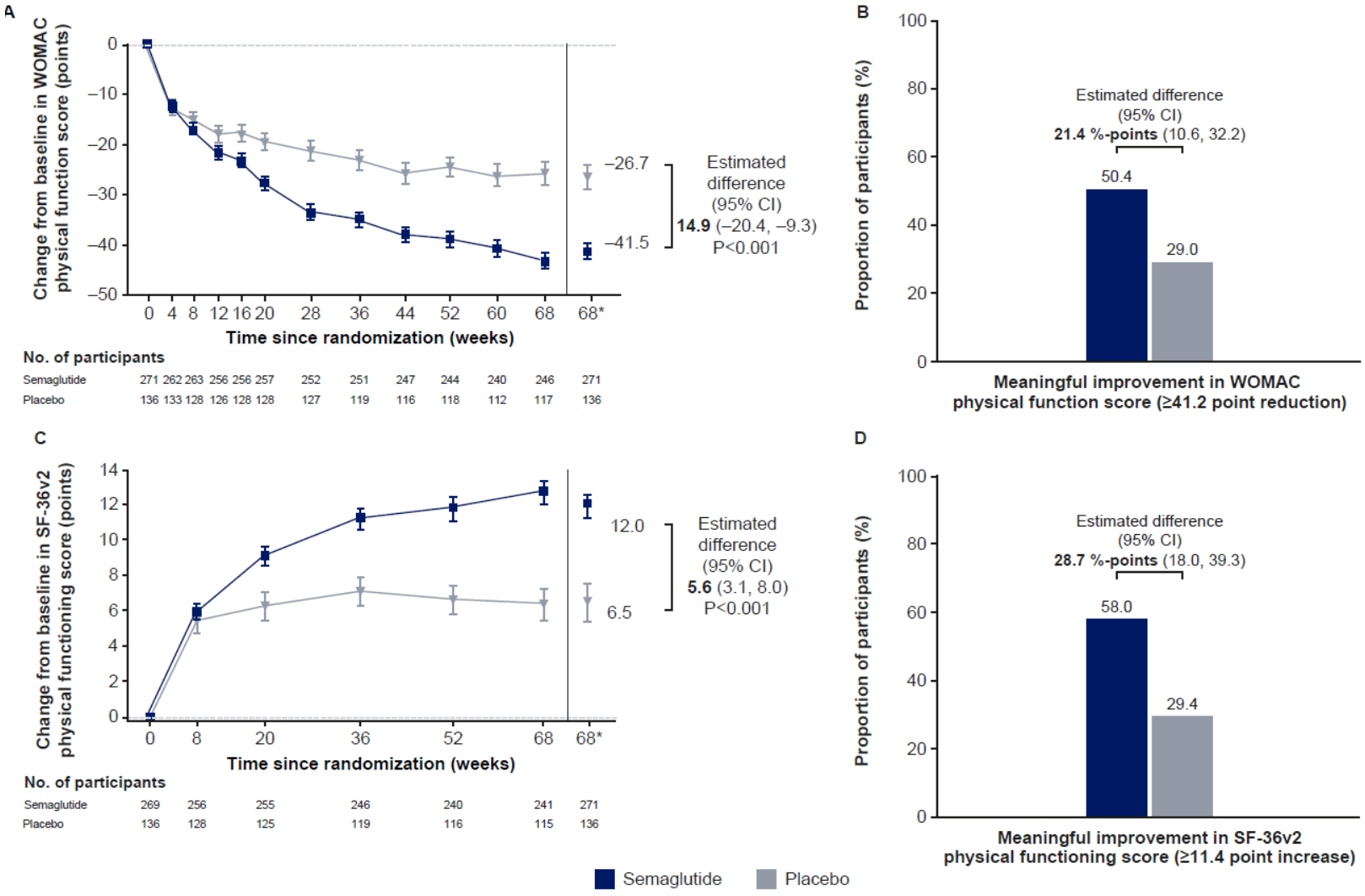


Data are observed values from the on-treatment period. Error bars are ± standard error of the mean. Numbers below the graph show the number of participants contributing to each mean.

*Estimated mean change at week 68 using the trial product estimand. Estimated difference was calculated using a mixed model for repeated measurement according to the trial product estimand.

CI denotes confidence interval, and WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

Figure S4. Change in WOMAC Physical Function Score and SF-36v2 Physical Functioning Score.

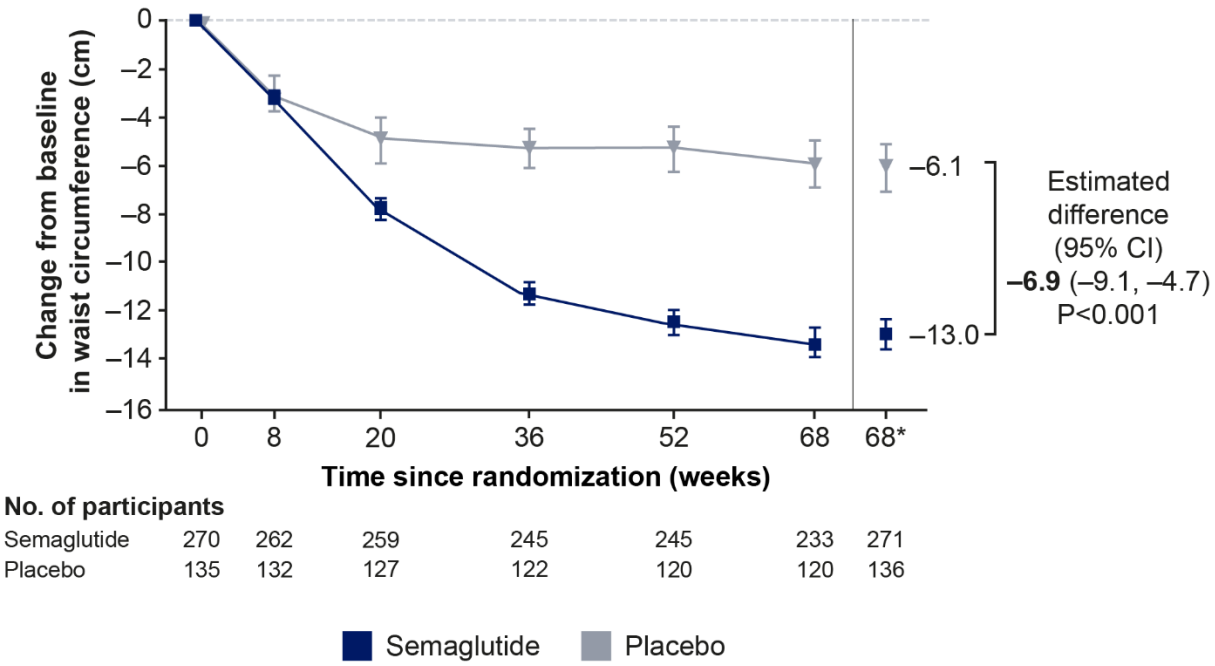


(A) and (C) Data are observed values from the in-trial period. (B) and (D) Proportions of participants reaching Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function and 36-Item Short Form survey (SF-36v2) physical functioning thresholds and differences were estimated from logistic regression according to the treatment policy estimand. Confidence intervals for the difference in proportions were obtained using the delta method. P values are reported for confirmatory secondary endpoint analyses only. Error bars in panels (A) and (C) are ± standard error of the mean. Numbers in the lower panels of (A) and (C) show the number of participants contributing to each mean. Odds ratios are reported in Supplementary Appendix, Table S3.

*Estimated mean change at week 68 using the treatment policy estimand. Estimated differences were calculated by analysis of covariance according to the treatment policy estimand.

CI denotes confidence interval.

Figure S5. Change in Waist Circumference.

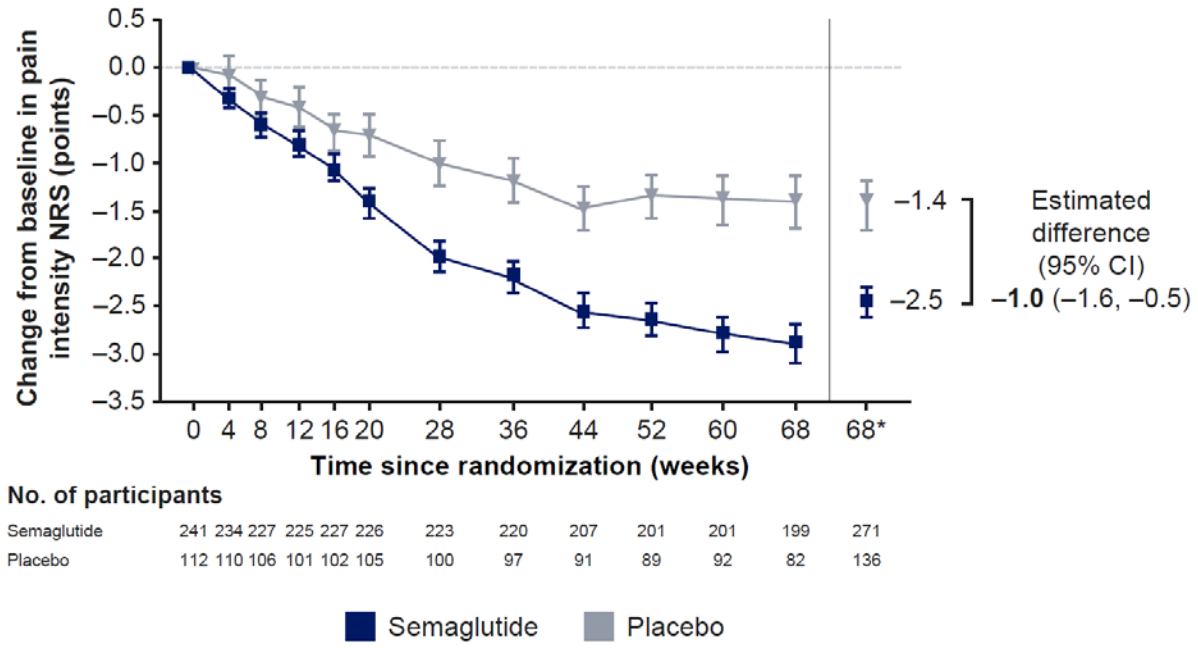


Data are observed values from the in-trial period. Error bars are ± standard error of the mean. Numbers below the graph show the number of participants contributing to each mean.

*Estimated mean change at week 68 using the treatment policy estimand. Estimated difference was calculated by analysis of covariance according to the treatment policy estimand.

CI denotes confidence interval.

Figure S6. Change in Pain Intensity (Numeric Rating Scale).

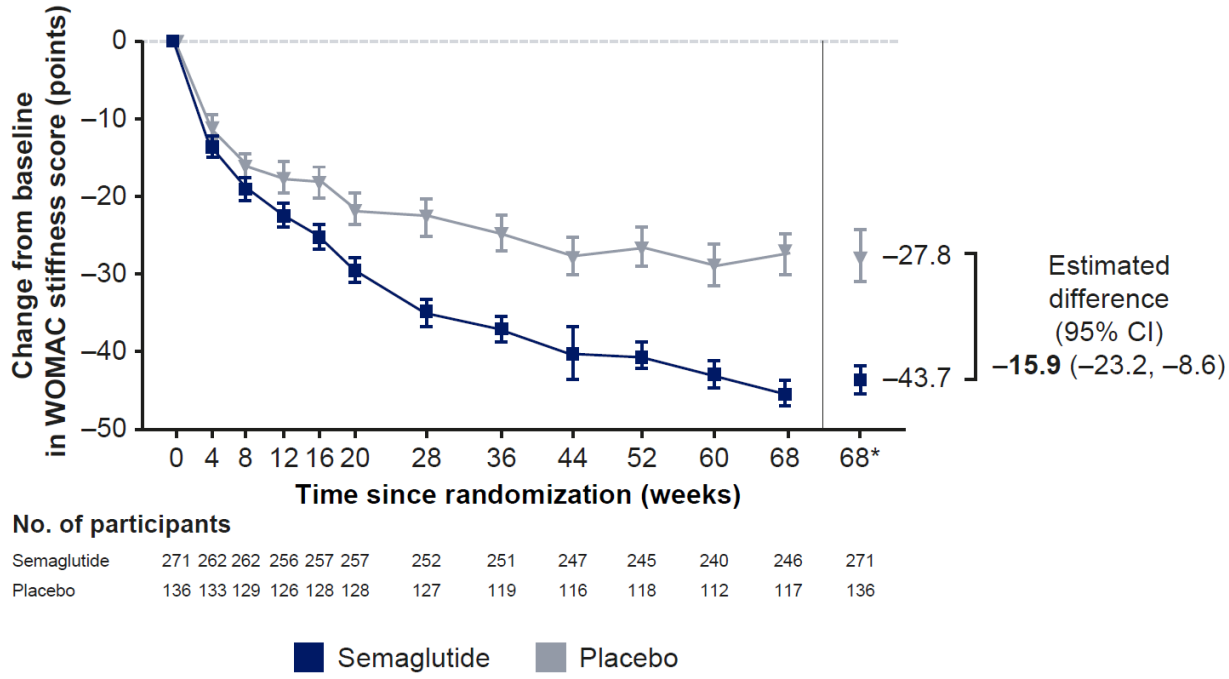


Data are observed values from the in-trial period. Error bars are ± standard error of the mean. Numbers below the graph show the number of participants contributing to each mean.

*Estimated mean change at week 68 using the treatment policy estimand. Estimated difference was calculated by analysis of covariance according to the treatment policy estimand.

CI denotes confidence interval, and NRS numeric rating scale.

Figure S7. Change in WOMAC Stiffness Score.

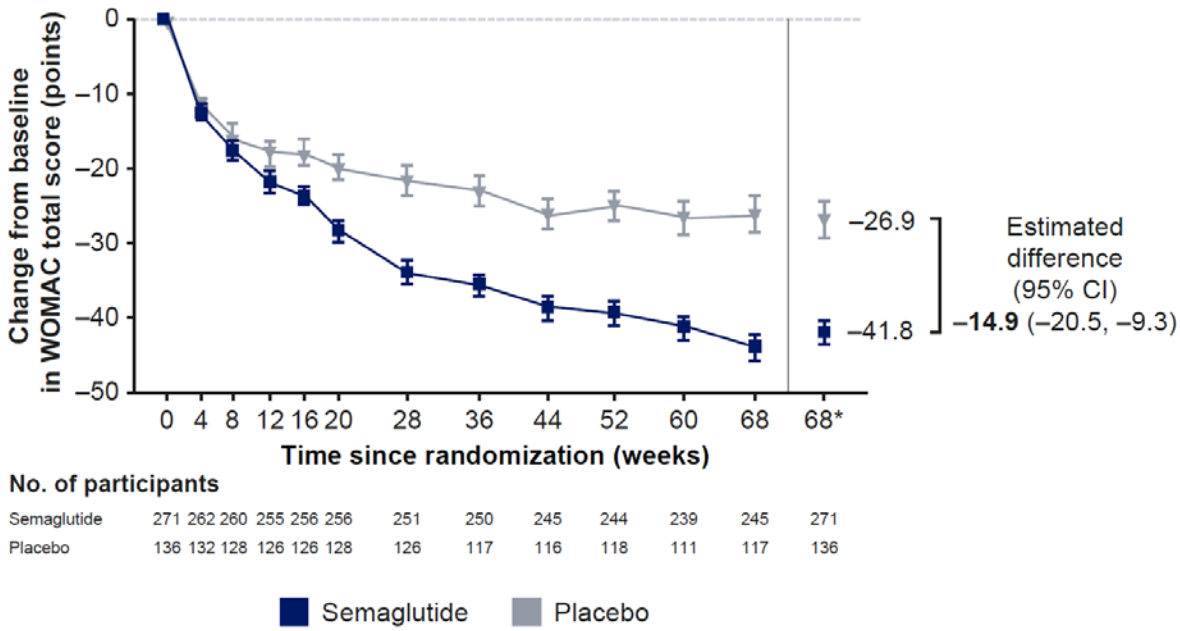


Data are observed values from the in-trial period. Error bars are ± standard error of the mean. Numbers below the graph show the number of participants contributing to each mean.

*Estimated mean change at week 68 using the treatment policy estimand. Estimated difference was calculated by analysis of covariance according to the treatment policy estimand.

CI denotes confidence interval, and WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

Figure S8. Change in WOMAC Total Score.



Data are observed values from the in-trial period. Error bars are ± standard error of the mean. Numbers below the graph show the number of participants contributing to each mean.

*Estimated mean change at week 68 using the treatment policy estimand. Estimated difference was calculated by analysis of covariance according to the treatment policy estimand.

CI denotes confidence interval, and WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

Supplementary Tables

Table S1. Detailed Baseline Characteristics of the Participants.

Characteristic	Semaglutide (N=271)	Placebo (N=136)	Total (N=407)
Age, years	56 (10)	56 (10)	56 (10)
Median (range)	56 (27, 83)	56 (31, 81)	56 (27, 83)
18 to <65, n (%)	222 (81.9)	108 (79.4)	330 (81.1)
65 to <75, n (%)	43 (15.9)	20 (14.7)	63 (15.5)
75 to <85, n (%)	6 (2.2)	8 (5.9)	14 (3.4)
≥85, n (%)	0	0	0
Sex, n (%)			
Female	228 (84.1)	104 (76.5)	332 (81.6)
Male	43 (15.9)	32 (23.5)	75 (18.4)
Race, n (%)			
White	168 (62.0)	80 (58.8)	248 (60.9)
Asian	16 (5.9)	6 (4.4)	22 (5.4)
Black or African American	18 (6.6)	13 (9.6)	31 (7.6)
American Indian or Alaska Native	37 (13.7)	11 (8.1)	48 (11.8)
Other	22 (8.1)	15 (11.0)	37 (9.1)
Not reported	10 (3.7)	11 (8.1)	21 (5.2)
Body weight, kg	108.7 (24.1)	108.5 (24.5)	108.6 (24.2)
Body mass index, kg/m^2			
Mean	40.5 (7.3)	40.0 (7.1)	40.3 (7.2)
<30, n (%)	0	1 (0.7)	1 (0.2)
30 to <35, n (%)	67 (24.7)	32 (23.5)	99 (24.3)
35 to <40, n (%)	84 (31.0)	56 (41.2)	140 (34.4)
≥40, n (%)	120 (44.3)	47 (34.6)	167 (41.0)
Waist circumference, cm*	118.3 (15.8)	119.7 (15.9)	118.7 (15.8)
WOMAC pain score	72.8 (15.6)	67.2 (16.0)	70.9 (16.0)
Systolic blood pressure, mmHg†	132 (14)	131 (15)	132 (15)
Diastolic blood pressure, mmHg†	82 (10)	82 (10)	82 (10)
Comorbidities, n (%)			
Asthma	19 (7.0)	19 (14.0)	38 (9.3)
Chronic kidney disease	2 (0.7)	0	2 (0.5)
Cardiovascular disease	13 (4.8)	8 (5.9)	21 (5.2)
Dyslipidemia	80 (29.5)	44 (32.4)	124 (30.5)

Gastroesophageal reflux disease	31 (11.4)	15 (11.0)	46 (11.3)
Gout	3 (1.1)	0	3 (0.7)
Hip osteoarthritis	4 (1.5)	2 (1.5)	6 (1.5)
Hypertension	128 (47.2)	68 (50.0)	196 (48.2)
Musculoskeletal pain	8 (3.0)	5 (3.7)	13 (3.2)
Non-alcoholic fatty liver disease/ non-alcoholic steatohepatitis	4 (1.5)	0	4 (1.0)
Obstructive sleep apnea	4 (1.5)	7 (5.1)	11 (2.7)
Psoriasis	6 (2.2)	2 (1.5)	8 (2.0)

Data include all participants in the full analysis set. Data are for the mean (standard deviation) unless stated otherwise. WOMAC denotes Western Ontario and McMaster Universities Osteoarthritis Index (scores were normalized and expressed on a scale of 0–100, with higher scores reflecting worse outcomes).

*Waist circumference data were available at baseline for 270 participants in the semaglutide group and 135 in the placebo group (405 participants in total).

†Blood pressure data were available at baseline for 269 participants in the semaglutide group and 135 in the placebo group (404 participants in total).

Table S2. Representativeness of Trial Participants.

Category	Example
Disease, problem, or condition under investigation	Obesity and knee osteoarthritis
Special consideration related to	
Sex and gender	Knee osteoarthritis affects women more than men.[2] In addition, the magnitude of relationship between BMI and knee osteoarthritis is stronger in women than in men.[3,4]
Age	The incidence and prevalence of knee osteoarthritis increases with increasing age.[2] The association between BMI and knee osteoarthritis is stronger in younger vs older age.[4]
Race or ethnic group	Black Americans have a greater prevalence and severity of lower extremity osteoarthritis versus White Americans.[5] Studies have also reported a 45% higher prevalence of radiographic and symptomatic knee osteoarthritis in Chinese versus White women, although no difference has been observed between Chinese and White men.[5]
Geography	Obesity is a risk factor for knee osteoarthritis, regardless of study country and sample size.[6] The prevalence of knee osteoarthritis varies across global regions, with the highest estimates from studies reporting data from 2000 to 2020 in Africa (21.0%) and Asia (19.2%), followed by North America (15.8%), Europe (13.4%), South America (4.1%), Oceania (3.1%).[2] It should be noted that significant heterogeneity within and between countries occurs across studies, and high prevalence rates may be influenced by varying numbers of studies in different regions.[2]
Other considerations	There are limited available epidemiologic data specifically for obesity-related knee osteoarthritis. Estimates for prevalence and incidence of knee osteoarthritis vary substantially across studies, owing to differences in populations studied (including age ranges), data sources, and definitions of osteoarthritis.[5,7] Studies reporting radiographic osteoarthritis, for example, tend to report higher prevalences compared with symptomatic or self-reported osteoarthritis; though notably, high levels of heterogeneity are seen even when utilizing the same definition.[7] There are limited studies that include analysis of body composition when considering associations between obesity and knee osteoarthritis. A nationwide study in Korean adults reported similar increased risk of knee osteoarthritis among those with general and central obesity, with the highest risk when both were present.[4]
Overall representativeness of this trial	The present study included a higher proportion of females (81.6%) than males (18.4%) compared with prevalence estimates of knee osteoarthritis. Biologic sex was reported by the participants; on the intake survey, they were asked, “What was your sex assigned at birth?”; Options were female and male. Gender was not recorded. Study participants were required to be aged ≥18 years to participate but had a mean age of 56 years, in line with the increased risk of knee osteoarthritis in older adults. The proportions of Black and Asian participants overall were small (7.6% and 5.4%, respectively), and there were no study sites in east Asian countries. In addition, participants had to meet more stringent definitions of knee osteoarthritis (clinical diagnosis of knee osteoarthritis with moderate radiographic changes and at least moderate pain) than many population-based studies to be eligible for this study.

BMI denotes body mass index.

Table S3. Odds Ratios for Categorical Study Endpoints.

Endpoint	Odds ratio (95% CI) for semaglutide (N=271) versus placebo (N=136)	P-value
Achievement of body weight reduction:		
≥5% from baseline at week 68	11.4 (6.6, 19.6)	P<0.001
≥10% from baseline at week 68	14.6 (7.4, 28.9)	P<0.001
≥15% from baseline at week 68*	18.9 (5.9, 61.0)	–
≥20% from baseline at week 68*	30.1 (2.2, 419.2)	–
Meaningful improvement in WOMAC pain score from baseline at week 68 (≥37.3 point reduction)*	2.7 (1.7, 4.3)	–
WOMAC pain score reduction:		
≥30% from baseline at week 68*	2.5 (1.6, 4.1)	–
≥50% from baseline at week 68*	3.4 (2.1, 5.5)	–
Meaningful improvement in WOMAC physical function score (≥41.2 point reduction*)	2.5 (1.5, 4.1)	–
Meaningful improvement in SF-36v2 physical functioning score (≥11.4 point increase)*	3.3 (2.0, 5.4)	–

*As supportive secondary endpoint analyses were not adjusted for multiplicity, P values are not reported for these endpoints.

The proportions of participants in the semaglutide vs placebo group achieving body weight reductions of ≥5%, ≥10%, ≥15% and ≥20% were 87.0% vs 29.2%, 70.4% vs 9.2%, 47.8% vs 2.5%, and 23.3% vs 0%, respectively. The odds ratio of reaching thresholds for each endpoint were estimated from logistic regression according to the treatment policy estimand.

CI denotes confidence interval, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index and SF-36v2 36-Item Short Form survey.

Table S4. Change in WOMAC Pain Scores from Baseline to Week 68 by Baseline BMI group.

Baseline BMI group	<35 kg/m^2		35–<40 kg/m^2		≥40 kg/m^2	
	Semaglutide (n=67)	Placebo (n=33)	Semaglutide (n=84)	Placebo (n=56)	Semaglutide (n=120)	Placebo (n=47)
Change from baseline to week 68, points	–47.6	–29.9	–39.1	–28.9	–40.3	–22.6
Estimated difference, points (95% CI)	–17.8 (–28.1, –7.4)		–10.3 (–19.7, –0.9)		–17.7 (–26.7, –8.8)	

Estimated mean change at week 68 using the treatment policy estimand (*post-hoc* analysis). Estimated differences were calculated by analysis of covariance according to the treatment policy estimand: Week 68 responses were analyzed using an analysis of covariance model with randomised treatment, subgroup and treatment by subgroup interaction as factors, and baseline value as covariate,

BMI denotes body mass index, CI confidence interval, and WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

Table S5. Serious Adverse Events Occurring in ≥1% of Either Treatment Group.

System Organ Class Preferred Term, n (%)	Semaglutide (N=269)	Placebo (N=135)
All events	27 (10.0)	11 (8.1)
Neoplasms: benign, malignant, and unspecified*	9 (3.3)	3 (2.2)
Metastatic breast cancer	2 (0.7)	0
Prostate cancer	2 (0.7)	1 (0.7)
Endometrial cancer (stage I)	1 (0.4)	0
Lung squamous cell carcinoma (stage II)	1 (0.4)	0
Malignant melanoma (stage III)	1 (0.4)	0
Papillary thyroid cancer	1 (0.4)	0
Teratoma benign	1 (0.4)	0
Adenocarcinoma of colon	0	1 (0.7)
Uterine leiomyoma	0	1 (0.7)
Gastrointestinal disorders	4 (1.5)	1 (0.7)
Lower abdominal pain	1 (0.4)	0
Upper abdominal pain	1 (0.4)	0
Chronic gastritis	1 (0.4)	0
Crohn's disease	1 (0.4)	0
Gastric ulcer hemorrhage	1 (0.4)	0
Anal fistula	0	1 (0.7)
Hepatobiliary disorders	3 (1.1)	1 (0.7)
Acute cholecystitis	2 (0.7)	0
Cholelithiasis	1 (0.4)	1 (0.7)
Reproductive system and breast disorders	3 (1.1)	0
Cervix disorder	1 (0.4)	0
Heavy menstrual bleeding	1 (0.4)	0
Vaginal prolapse	1 (0.4)	0
Surgical and medical procedures	3 (1.1)	2 (1.5)
Abdominoplasty	1 (0.4)	0
Knee arthroplasty	1 (0.4)	0
Mammoplasty	1 (0.4)	0
Sleeve gastrectomy	0	2 (1.5)
Infections and infestations	1 (0.4)	3 (2.2)
Arthritis bacterial	1 (0.4)	0
Abdominal abscess	0	1 (0.7)
Acute sinusitis	0	1 (0.7)
COVID-19 pneumonia	0	1 (0.7)
Plasmodium malariae infection	0	1 (0.7)

Serious adverse events occurring in ≥1% of either treatment group, at the system organ class level. Data are for the safety analysis set; adverse event reporting was selective (see Methods section for further details). *Including cysts and polyps.

Table S6. Adverse Events Leading to Permanent Treatment Discontinuation.

System Organ Class Preferred Term, n (%)	Semaglutide (N=269)	Placebo (N=135)
All events	18 (6.7)	4 (3.0)
Gastrointestinal disorders	6 (2.2)	0
Nausea	3 (1.1)	0
Abdominal pain	1 (0.4)	0
Abdominal pain upper	1 (0.4)	0
Crohn's disease	1 (0.4)	0
Vomiting	1 (0.4)	0
Neoplasms: benign, malignant, and unspecified*	5 (1.9)	2 (1.5)
Metastatic breast cancer	1 (0.4)	0
Endometrial cancer (stage I)	1 (0.4)	0
Lung squamous cell carcinoma (stage II)	1 (0.4)	0
Papillary thyroid cancer	1 (0.4)	0
Prostate cancer	1 (0.4)	1 (0.7)
Adenocarcinoma of colon	0	1 (0.7)
Metabolism and nutrition disorders	2 (0.7)	0
Dehydration	1 (0.4)	0
Hypoglycemia	1 (0.4)	0
General disorders and administration site conditions	1 (0.4)	0
Fatigue	1 (0.4)	0
Hepatobiliary disorders	1 (0.4)	0
Cholelithiasis	1 (0.4)	0
Investigations	1 (0.4)	0
Lipase increased	1 (0.4)	0
Musculoskeletal and connective tissue disorders	1 (0.4)	0
Arthralgia	1 (0.4)	0
Pain in extremity	1 (0.4)	0
Nervous system disorders	1 (0.4)	0
Transient ischemic attack	1 (0.4)	0
Infections and infestations	0	1 (0.7)
Gastroenteritis viral	0	1 (0.7)
Surgical and medical procedures	0	1 (0.7)
Sleeve gastrectomy	0	1 (0.7)

Data are for the safety analysis set; adverse event reporting was selective (see Methods section for further details). *Including cysts and polyps.

Table S7. Serious Malignant Neoplasm Adverse Events.

Preferred Term, n (%)	Semaglutide (N=269)	Placebo (N=135)
All events	8 (3.0)	2 (1.5)
Metastatic breast cancer	2 (0.7)	0
Prostate cancer	2 (0.7)	1 (0.7)
Endometrial cancer (stage I)	1 (0.4)	0
Lung squamous cell carcinoma (stage II)	1 (0.4)	0
Malignant melanoma (stage III)	1 (0.4)	0
Papillary thyroid cancer	1 (0.4)	0
Adenocarcinoma of colon	0	1 (0.7)

Data are for the safety analysis set.

Reference

1. Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims. December 2009. U.S. Food and Drug Administration, 2009 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims).
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Protocol

Protocol for: Bliddal H, Bays H, Czernichow S, et al. Once-weekly Semaglutide in persons with obesity and knee osteoarthritis. N Engl J Med 2024;391:1573-83. DOI: 10.1056/NEJMoa2403664

This trial protocol has been provided by the authors to give readers additional information about the work.

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes (page 93).
2. Original statistical analysis plan, final statistical analysis plan, summary of changes (page 206).

Protocol

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

Substance name: semaglutide

Universal Trial Number: U1111-1246-5824

EudraCT Number: 2020-000204-11

IND Number:126,360

Trial phase: 3b

In the following, Novo Nordisk A/S and its affiliates will be stated as "Novo Nordisk".

Table of Contents

Page

1 Protocol summary

1.1 Synopsis

The prevalence of obesity has reached epidemic proportions in most countries around the world and the prevalence is still increasing at an alarming rate. The medical and societal impacts are extensive, and obesity is one of the most significant public health challenges worldwide[1-7].

Obesity is associated with an increased risk of a variety of complications, including osteoarthritis (OA), affects physical and mental health and reduces health-related quality of life[8-22].

With the increasing prevalence of obesity, the health issues related to knee OA will intensify with huge consequence for society and the individual patient. Due to the pivotal role of the knee in basic mobility and locomotion, knee OA is associated with significant impairments and limitations to basic activities of daily living. The physical disability of knee OA arising from pain and loss of functional capacity reduces health-related quality of life and increases the risk of further morbidity.

Rationale:

Weight loss is strongly recommended as a primary management strategy in subjects with knee OA and obesity[23]. However, no specific guidance on how to achieve this is given, and no widely available and feasible means to sustain weight loss in subjects with knee OA and obesity have been presented.

There is a clear association between obesity and knee OA with obesity being a major risk factor for the incidence and progression of OA, and negatively influences disease outcomes[24, 25].

In accordance, American College of Rheumatology (ACR) guidelines strongly recommend weight loss in subjects with knee OA and obesity as first line treatment[23].

A significant relationship between weight loss above 10% of body weight and improvement in pain and function has been demonstrated in subjects with knee OA and obesity[26,27,28]. Pharmacotherapy may therefore serve as a valuable adjunct to lifestyle intervention for individuals with knee OA and obesity in order to achieve a sufficient and sustainable weight loss. In a recent phase 3a study (NN9536-4373) semaglutide s.c. 2.4 mg once-weekly led to a weight loss of 14.9% in subjects with overweight and obesity.

Objectives and endpoints:

Primary objective

To confirm superiority of semaglutide s.c. 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 OA in change from baseline to week 68 in body weight and knee OA-related pain.

Secondary objectives

To confirm superiority of semaglutide s.c. 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 OA in achieving body weight response criteria after 68 weeks from baseline as well as change from baseline to week 68 in knee OA-related and general physical function.

To compare the efficacy of semaglutide s.c. 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 OA in change from baseline to week 68 in waist circumference, knee OA-related stiffness, overall knee OA-related physical limitations and general health-related quality of life.

Primary estimand

The primary estimand is the average treatment effect of semaglutide s.c. 2.4 mg once-weekly relative to semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity, in patients with obesity and knee OA, measured by change from baseline to week 68 in body weight and knee OA-related pain, regardless of adherence to randomised treatment, regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injection or opioid medication) and regardless of compliance with washout period for pain medication (the latter only relevant in this context for knee OA-related pain) ("treatment policy" strategy).

Primary endpoints

Endpoint title	Time frame	Unit
Change in body weight	From baseline (week 0) to end of treatment (week 68)	%
Change in WOMAC pain score	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index

Confirmatory secondary endpoints

Endpoint title	Time frame	Unit
Achieving body weight reduction ≥5% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Achieving body weight reduction ≥10% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Change in WOMAC physical function score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 physical functioning score	From baseline (week 0) to end of treatment (week 68)	Score points

Overall design:

This is a 68-week, randomised, two-arm, double-blinded, multi-centre clinical trial comparing semaglutide s.c. 2.4 mg once-weekly with semaglutide placebo in subjects with moderate OA of one or both knees, pain due to knee OA, and obesity (BMI ≥30.0 kg/m^2).

Eligible subjects fulfilling all randomisation criteria at visit 2 will be randomised in a 2:1 manner to receive either semaglutide s.c. 2.4 mg or semaglutide placebo once-weekly as adjunct to a reduced-calorie diet and increased physical activity.

Key inclusion criteria:

- Male or female, age above or equal to 18 years at the time of signing informed consent
- Body Mass Index (BMI) ≥30.0 kg/m^2
- Clinical diagnosis of primary knee OA (American College of Rheumatology criteria) with moderate radiographic changes (Kellgren-Lawrence (KL) grades 2 or 3) in one or both knees
- Pain due to knee OA

Key exclusion criteria:

- Joint replacement in target knee
- Arthroscopy or injections into target knee within last 3 months prior to enrolment
- Active joint disease besides knee OA

Number of subjects:

Approximately 420 subjects will be screened to achieve 375 subjects randomly assigned to trial product.

Treatment groups and duration:

- The total trial duration for the individual subject will be approximately 76 weeks. The trial includes a screening period of approximately 2 weeks followed by randomisation. Dose escalation of semaglutide/semaglutide placebo will take place every 4 weeks during the first 16 weeks after randomisation. All subjects should aim at reaching the target dose of semaglutide 2.4 mg once-weekly. Following randomisation, visits are scheduled every 8th week until end-of-treatment (week 68). Follow-up period is 7 weeks after end-of-treatment.
- The following trial products will be supplied by Novo Nordisk A/S for the duration of the trial:
    - Semaglutide B 3.0 mg/mL PDS290 and semaglutide placebo, solution for injection, 3 mL PDS290 pre-filled injector

1.2 Flowchart

	Screening	Randomisation	Dose escalation period				Treatment period						End of treatment	End of trial
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Timing of Visit (Weeks)	-1	0	4	8	12	16	20	28	36	44	52	60	68	75
Visit Window (Days)	-7 to 0	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
SUBJECT RELATED INFORMATION AND ASSESSMENTS														
Informed Consent and Demography[a] (Appendix 1)	X													
Eligibility Criteria (5.1)	X	X												
Randomisation Criteria & Randomisation (5.5)		X												
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History/Concomitant Illness (8.2 /6.5)	X													
Tobacco Use[b] (5.3.1)	X													
Childbearing Potential (Appendix 4)	X													
Pregnancy Test[c] (8.3.5)	X	X		X		X	X	X	X	X	X	X	X	X
Knee Radiography (8.2.1)	X													

	Screening	Randomisation	Dose escalation period				Treatment period						End of treatment	End of trial
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Timing of Visit (Weeks)	-1	0	4	8	12	16	20	28	36	44	52	60	68	75
Visit Window (Days)	-7 to 0	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
EFFICACY														
Body Measurements (8.1.2)														
Body Weight	X	X		X			X		X		X		X	
Height	X													
Waist Circumference		X		X			X		X		X		X	
Clinical Outcome Assessments														
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (8.1.1)		X		X			X		X		X		X	
Patient Global Impression of Status (PGI-S)		X		X			X		X		X		X	
Patient Global Impression of Change (PGI-C)		X		X			X		X		X		X	
Short Form 36 V2.0 acute (SF-36) (8.1.3)		X		X			X		X		X		X	
Six-Minute Walking Test (8.1.3)		X											X	
SAFETY														
Adverse Event (8.3)		X	X	X	X	X	X	X	X	X	X	X	X	X
Technical Complaint (8.3.9)			X	X	X	X	X	X	X	X	X	X	X	
Vital Signs (8.2.3)														

	Screening	Randomisation	Dose escalation period				Treatment period						End of treatment	End of trial
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Timing of Visit (Weeks)	-1	0	4	8	12	16	20	28	36	44	52	60	68	75
Visit Window (Days)	-7 to 0	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Systolic Blood Pressure	X	X	X		X		X		X		X		X	X
Diastolic Blood Pressure	X	X	X		X		X		X		X		X	X
Pulse	X	X	X		X		X		X		X		X	X
Physical Examination (8.2.2)	X												X	
Laboratory Assessments (Appendix 2)														
Hemoglobin A1c ($HbA1_c$)	X													
ASSESSMENTS OF PAIN MEDICATION														
Pain Treatment (8)		X		X			X		X		X		X	
TRIAL MATERIAL														
IWRS Session	X	X		X		X	X	X	X	X	X	X	X	
Administration of Trial Product (6.1)														
Dispensing Visit		X		X		X	X	X	X	X	X	X		
Drug Accountability		X		X		X	X	X	X	X	X	X	X	
REMINDERS														
Criteria for discontinuation (7.1)			X	X	X	X	X	X	X	X	X	X		

	Screening	Randomisation	Dose escalation period				Treatment period						End of treatment	End of trial
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Timing of Visit (Weeks)	-1	0	4	8	12	16	20	28	36	44	52	60	68	75
Visit Window (Days)	-7 to 0	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Barriers and motivation interview (8)	X													
Diet and physical activity counselling (6.1.2)		X	X	X	X	X	X	X	X	X	X	X	X	
Hand out direction for use (6.1)		X												
Training in trial product, pen-handling		X	X	X	X	X	X							
Hand out dose reminder card (6.1)		X	X	X	X	X	X							
Hand out ID card	X													

[a] Demography consists of date of birth, sex, ethnicity, and race (according to local regulation).

[b] Smoking is defined as smoking at least one cigarette or equivalent daily.

[c] For all female subjects of child-bearing potential.

2 Introduction

Knee osteoarthritis and obesity

The prevalence of obesity has reached epidemic proportions in most countries around the world and the prevalence is still increasing at an alarming rate. The medical and societal impacts are extensive, and obesity is one of the most significant public health challenges worldwide[1-7].

Obesity is associated with an increased risk of a variety of complications including osteoarthritis (OA), type 2 diabetes (T2D), dyslipidaemia, hypertension, cardiovascular disease, obstructive sleep apnoea, non-alcoholic fatty liver disease, urinary incontinence, several types of cancers, and increased mortality.[8-22]

The risk of obesity-related complications increases with increasing body mass index (BMI) and body weight loss has been shown to have significant health benefits on many obesity-related complications as well as physical symptoms and health-related quality of life[29-36]. Lifestyle intervention in the form of diet and exercise is first line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss[37-46].

With the increasing prevalence of obesity, the health issues related to knee OA will intensify with huge consequence for society and the individual patient. Obesity and the increased weight bearing are attributable to development and progressions of knee OA being a highly disabling degenerative joint disease[21, 24]. Due to the pivotal role of the knee in basic mobility and locomotion, knee OA is associated with significant impairments and limitations to basic activities of daily living. The physical disability of knee OA arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity[25].

Weight loss is associated with a reduced risk of knee OA progression and improvement in pain and function regardless of the extent of radiological changes and knee OA grading[26, 47, 48]. However, in the IDEA trial only a reduction in baseline body weight of above 10% significantly reduced pain and improved function in subjects with knee OA and obesity[26].

Based on a systematic literature review, the ACR guidelines strongly recommends as primary management strategy that subjects with knee OA and obesity lose weight and participate in physical activity programme commensurate with their ability to perform these activities[23]. Furthermore, as obesity is an additional limiting factor in participating in physical activity programmes, weight loss will have both direct and indirect positive effect on management strategy and symptom relief in knee OA.

2.1 Trial rationale

Weight loss is strongly recommended as a primary management strategy in subjects with knee OA and obesity[23]. However, no specific guidance on how to achieve this is given, and no widely available and feasible means to sustain weight loss in subjects with knee OA and obesity have been presented.

Subjects with knee OA and obesity show a very specific pathophysiological profile compared to the population with knee OA without obesity. Subjects with knee OA and obesity have decreased quality of life, more pain and limited physical function compared to subjects with knee OA without obesity[23].

A reduction in baseline body weight loss above 10% significantly improves function and reduce pain in subjects with knee OA and obesity[26]. Semaglutide is a glucagon-like-peptide 1 (GLP-1) receptor agonist (RA) currently under development by Novo Nordisk A/S for weight management and treatment of obesity. Semaglutide is expected to provide a body weight loss of up to 10-15%[49].

The aim of the present trial is to investigate the effects of semaglutide s.c. 2.4 mg once-weekly on weight loss, knee OA-related pain and physical function, and health-related quality of life in a patient population with obesity and knee OA.

2.2 Background

2.2.1 Semaglutide

Semaglutide is a long-acting GLP-1 RA currently under development by Novo Nordisk A/S for weight management. Semaglutide has a half-life of approximately 160 hours, making it suitable for once-weekly dosing[50]. GLP-1 is a physiological regulator of appetite, and a postprandial GLP-1 response is present in several areas of the brain involved in appetite regulation[51].

Clinical[52-57] and non-clinical[57] data indicate that the body weight reducing effect of semaglutide is mainly mediated by a reduced energy intake.

A 52-week phase 2 dose-finding trial within weight management (NN9536-4153) has been completed. An overall monotone dose-dependent weight loss was observed across the 5 semaglutide doses tested (0.05 to 0.4 mg once-daily). The estimated weight loss at week 52 was 13.8% at the highest dose tested (0.4 mg once-daily) compared to the weight loss of 2.3% achieved by diet, exercise and placebo alone[49] . Based on results from this trial, a target dose of 2.4 mg of semaglutide s.c. once-weekly was used for the clinical phase 3a and 3b programme[49].

The 68-week phase 3a weight management trial, STEP 1 (NN9536-4373) has demonstrated clinical significant weight loss with semaglutide and is currently in the reporting phase. A total of 1,961 subjects were included in the trial: 1,306 randomised to semaglutide s.c. 2.4 mg once-weekly and

655 to placebo. At week 68, subjects in the semaglutide s.c. 2.4 mg once-weekly group achieved an average weight loss of 14.85% compared to 2.41% in the placebo group.

A comprehensive review of results from the non-clinical and clinical studies of semaglutide can be found in the current edition of the investigator's brochure (IB)[49] and any updates hereof.

2.3 Benefit-risk assessment

Main benefits and risks are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of semaglutide may be found in the IB[49] or any updates hereof.

2.3.1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Trial treatment(s)		
Gastrointestinal AE	Consistent with findings with other GLP-1 RAs, the most frequently reported adverse events (AE) in clinical trials with semaglutide were gastrointestinal AEs.	A low starting dose and dose escalation steps will be implemented to mitigate the risk of gastrointestinal AEs
Cholelithiasis	Events of cholelithiasis were the most frequently reported gallbladder events in the phase 2 weight management trial (NN9536-4153) and were in a few instances co-reported with the event adjudication committee confirmed pancreatitis	If cholelithiasis is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion
Pancreatitis	Pancreatitis has been observed with the use of GLP-1 RA drug class.	Subjects with a history of chronic pancreatitis or recent pancreatitis will not be enrolled in the trial. In addition, trial product should be discontinued in case of suspicion of pancreatitis in accordance to Section 7.1

Medullary thyroid cancer (MTC) (based on non-clinical data)	Proliferative thyroid C-cell changes were seen in the mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. No hyperplasia was observed in monkeys after 52 weeks exposure up to 13-fold above the clinical plasma exposure at 2.4 mg/week. In clinical trials with semaglutide, there have been no clinically relevant changes in calcitonin levels. The C-cell changes in rodents are mediated by the GLP-1 receptor, which is not expressed in the normal human thyroid. Accordingly, the risk of GLP-1 receptor-mediated C-cell changes in humans is considered to be low.	Exclusion criteria related to medical history of multiple endocrine neoplasia type 2 (MEN2) or MTC have been implemented.
Pancreatic cancer	There is currently no support from non-clinical studies, clinical trials or post-marketing data that GLP-1 RA based therapies increase the risk of pancreatic cancer, but pancreatic cancer has been classified as a potential class risk of GLP-1 RAs by European Medicines Agency.	Subjects with a history of malignant neoplasms within the past 5 years prior to screening will be excluded from the trial.
Allergic reactions	As is the case with all protein-based pharmaceuticals, subjects treated with semaglutide are at risk of developing immunogenic and allergic reactions.	Subjects with known or suspected hypersensitivity to semaglutide or related products will not be enrolled.
Trial procedures		
Pain analgesics washout period	There is a potential risk of increased pain	Washout period is short in duration. Use of rescue medication (acetaminophen) is allowed during wash out until 24 hours before visit
Other		
Pregnancy and fertility (based on non-clinical data)	Studies in animals have shown reproductive toxicity. There is limited data from the use of semaglutide in pregnant women.	Semaglutide should not be used during pregnancy. Exclusion and discontinuation criteria related to pregnancy have been implemented.

AE, adverse events; GLP-1 RA, Glucagon-like-peptide-1 receptor agonist; MTC, medullary thyroid cancer; MEN2, multiple endocrine neoplasia type 2

2.3.2 Benefit assessment

Subjects will be treated with a regimen anticipated to be better than or equal to the weight management they receive at the time of entry into the trial. Results from the phase 3a program has not yet been finalised and submitted to the authorities. However, results from the phase 2 trial (NN9536-4153) demonstrated that semaglutide s.c. once-daily as an adjunct to a reduced calorie diet and increased physical activity was effective for weight loss in subjects with obesity, while displaying a satisfactory tolerability profile. Overall, a monotone dose-dependent weight loss was observed across all tested doses of semaglutide (0.05 to 0.4 mg once-daily). The weight loss was 11.5 percentage points larger for the 0.4 mg group compared with placebo. Weight loss was accompanied by a consistent improvement in weight-related comorbidities, indicated by cardiovascular risk factors, lipid profile and glycaemic factors, as well as improvements in clinical outcome assessments.

In addition, it is expected that subjects will benefit from participation through close contact with the trial site and counselling by a dietician or a similar qualified healthcare professional, all of which will most likely result in intensified weight management. In addition, subjects will benefit from physical activity counselling and from improved physical function and knee pain reduction with body weight lowering. It is anticipated that all subjects will benefit from participation, but the effect will be greater in subjects randomised to semaglutide compared to placebo.

2.3.3 Overall benefit-risk conclusion

Necessary precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation in the trial. The safety profile for semaglutide generated from the clinical and non-clinical development programmes has not revealed any safety issues that would prohibit administration of semaglutide s.c. 2.4 mg once-weekly. Results from four phase 3a trials with semaglutide s.c. 2.4 mg once-weekly (NN9536-4373, -4374, -4375 and -4376) have demonstrated that semaglutide s.c. 2.4 mg once-weekly can provide a clinically meaningful weight loss. The anticipated benefits from diet and physical activity counselling will include all subjects participating in this trial.

Taking into account the measures taken to minimise risk to subjects participating in this trial, the potential risks identified in association with semaglutide are justified by the anticipated benefits that may be afforded to subjects with obesity and knee OA.

3 Objectives and endpoints

3.1 Primary, secondary and exploratory objective(s) and estimand(s)

Primary objectives

To confirm superiority of semaglutide s.c. 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 OA in change from baseline to week 68 in body weight and knee OA-related pain.

Secondary objectives

To confirm superiority of semaglutide s.c. 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 OA in achieving body weight response criteria after 68 weeks from baseline as well as change from baseline to week 68 in knee OA-related and general physical function.

To compare the efficacy of semaglutide s.c. 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 OA in change from baseline to week 68 in waist circumference, knee OA-related stiffness, overall knee OA-related physical limitations and general health-related quality of life.

Exploratory objectives

To compare the efficacy of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo as adjunct to a reduced-calorie diet and increased physical activity in subjects with obesity and knee OA in change from baseline to week 68 in use of analgesics and on walking distance.

Primary estimand

The primary clinical question of interest is: what is the average treatment effect of semaglutide s.c. 2.4 mg once-weekly relative to semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity, in patients with obesity and knee OA, measured by change from baseline to week 68 in body weight and knee OA-related pain, regardless of adherence to randomised treatment, regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injection or opioid medication) and regardless of compliance with washout period for pain medication (the latter only relevant in this context for knee OA-related pain) (“treatment policy” strategy).

The estimand is described by the following attributes (according to ICH E9(R1)):

- Treatment condition: The randomised treatment regardless of adherence or initiation of other anti-obesity therapies (as defined above) or other knee OA interventions (as defined above)

- Population: Patients with obesity and knee OA

- Endpoints: The two primary endpoints relative change in body weight and change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score both from baseline to week 68

- Remaining intercurrent events: The intercurrent events "treatment discontinuation for any reason", "initiation of other anti-obesity therapies" and "initiation of other knee OA interventions" are addressed by the treatment condition attribute. The remaining intercurrent event is "compliance with washout period for pain medication" (in general only applicable to WOMAC endpoints), which is handled by the treatment policy strategy.

- Population-level summary: Difference in mean changes between treatment conditions

A similar estimand applies to all secondary endpoints (confirmatory and supportive), which is called secondary estimand. The population-level summary for body weight response endpoints is the ratio of odds between treatment conditions.

Rationale for estimand: The primary (and secondary) estimand was requested by different regulatory authorities and it aims at reflecting how patients with obesity are treated in clinical practice

Additional estimand

An additional clinical question of interest is: what is the average treatment effect of semaglutide s.c. 2.4 mg once-weekly relative to semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity, in patients with obesity and knee OA, measured by change from baseline to week 68 in body weight and knee OA-related pain, had they remained on their randomised treatment for the entire planned duration of the trial, not initiated other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injection or opioid medication) and had they additionally complied with the washout period for pain medication (the latter only relevant in this context for knee OA-related pain) ("hypothetical" strategy).

The estimand is described by the following attributes (according to ICH E9(R1)):

- Treatment condition: The randomised treatment if patients had adhered for the entire duration of the trial, not initiated other anti-obesity therapies (as defined above) or other knee OA interventions (as defined above)
- Population: Patients with obesity and knee OA
- Endpoints: The two primary endpoints relative change in body weight and change in WOMAC pain score both from baseline to week 68
- Remaining intercurrent events: The intercurrent events "treatment discontinuation for any reason", "initiation of other anti-obesity therapies" and "initiation of other knee OA interventions" are addressed by the treatment condition attribute. The remaining intercurrent event is "compliance with washout period for pain medication" (in general only applicable to WOMAC endpoints), which is handled by the hypothetical strategy.
- Population-level summary: Difference in mean changes between treatment conditions

A similar additional estimand also applies to all secondary body weight endpoints as well as all secondary WOMAC endpoints (both confirmatory and supportive). The population-level summary for body weight response endpoints is the ratio of odds between treatment conditions.

Rationale for estimand: The additional estimand was requested by few regulatory authorities and aims at reflecting the treatment effect in the absence of intercurrent events.

3.2 Primary, secondary and exploratory endpoint(s)

3.2.1 Primary endpoints

Endpoint title	Time frame	Unit
Change in body weight	From baseline (week 0) to end of treatment (week 68)	%
Change in WOMAC pain score	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index

3.2.2 Secondary endpoints

The confirmatory and supportive secondary endpoints addressing the primary and secondary objectives are listed in Sections 3.2.2.1 and 3.2.2.2.

3.2.2.1 Confirmatory secondary endpoints

Endpoint title	Time frame	Unit
Achieving body weight reduction ≥5% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Achieving body weight reduction ≥10% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Change in WOMAC physical function score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 physical functioning score	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index, SF-36; Short Form (36) Health Survey

3.2.2.2 Supportive secondary endpoints

Endpoint title	Time frame	Unit
Change in waist circumference	From baseline (week 0) to end of treatment (week 68)	cm
Change in WOMAC stiffness score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in WOMAC total score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 role-physical score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 bodily pain score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 general health score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 vitality score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 social functioning score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 role-emotional score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 mental health score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 physical component summary	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 mental component summary	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index, SF-36; Short Form (36) Health Survey

3.2.3 Exploratory endpoint(s)

Endpoint title	Time frame	Unit
Change in pain medication (decrease/no change/increase)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Use of allowed rescue analgesics during washout period (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Change in 6 minutes walking distance	From baseline (week 0) to end of treatment (week 68)	Meters

4 Trial design

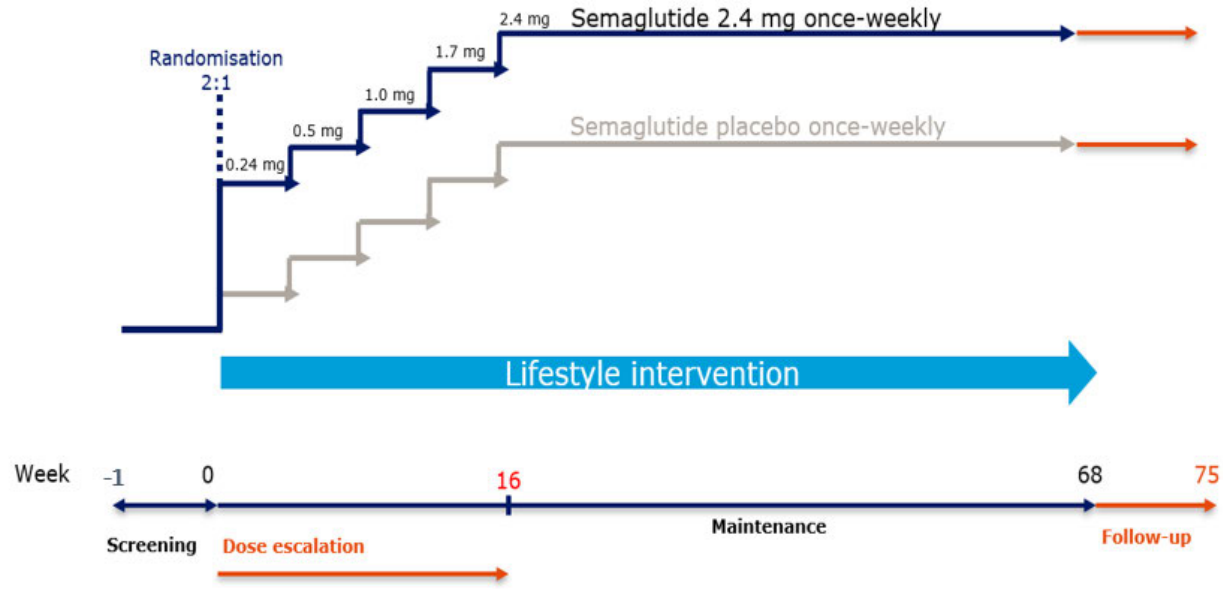
This trial is designed to evaluate weight loss and knee OA-related outcomes and will apply a targeted approach to collection of safety data focusing on serious adverse events (SAEs), adverse events (AEs) leading to discontinuation of trial product and other selected AEs. An adequate characterisation of the less serious and more common AEs is evaluated in the phase 3a trials (Section 2.2.1).

4.1 Overall design

This is a 68-week, randomised, two-arm, double-blinded, multi-centre clinical trial comparing semaglutide s.c. 2.4 mg once-weekly with semaglutide placebo in subjects with moderate OA of one or both knees, pain due to knee OA, and obesity (BMI ≥30.0 kg/m2).

Eligible subjects will be randomised in a 2:1 manner to receive either semaglutide s.c. 2.4 mg once-weekly or semaglutide placebo once-weekly as adjunct to a reduced-calorie diet and increased physical activity (Figure 4-1).

The trial includes a screening visit to assess the subject's eligibility followed by visits every 8th week until end-of-treatment (week 68). Follow-up period is 7 weeks after end-of-treatment.



mg; milligram

Figure 4-1 A schematic diagram of the trial design

4.2 Scientific rationale for trial design

The trial population will consist of subjects with obesity (≥ BMI 30.0 kg/m2) and knee OA ((primary knee OA according to the ACR criteria), ≥ 40 point in the WOMAC pain subscale, and radiological KL grade 2 or 3)[58]. The trial population is chosen to optimise the likelihood of achieving a clinical benefit with weight loss (reduction in knee OA-related pain and improved physical function) by including subjects with a clear medical need (obesity and knee OA). Although T2D is prevalent in the obesity population, it has been decided to exclude this group of subjects from the trial in order to get a homogenous study population.

The treatment duration of the trial is 68 weeks with an additional 7 weeks follow-up (without treatment). A 68-week treatment duration (including 52 weeks on target dose) is considered sufficient to realise the weight loss potential of the intervention as well as downstream effects on symptoms and function related to knee OA. The 7 weeks follow-up period is included to account for the exposure and long half-life of semaglutide.

A randomised, double-blinded, placebo-controlled, multi-centre trial design is chosen to minimise bias in the assessment of the effect and safety of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo, as an adjunct to a reduced calorie diet and increased physical activity.

In accordance with guideline for Clinical investigation of medicinal products used in the treatment of OA by the European Medicines Agency (EMA) pain medication required during the trial period is discontinued 72 hours in advance of assessment of symptomatic endpoints to avoid confounding effects[59]. During the washout rescue medication with acetaminophen is allowed as analgesic until 24 hours before visit if needed.

4.3 Justification for dose

Results from the phase 2 dose-finding trial for semaglutide in weight management (NN9536-4153) showed that the semaglutide s.c. 0.4 mg once-daily dose was most effective in terms of weight loss while displaying an acceptable tolerability profile. Using population pharmacokinetic modelling, it was estimated that a once-weekly maintenance dose of semaglutide s.c. 2.4 mg will result in similar C_{max} at steady-state as that obtained by the once-daily 0.4 mg semaglutide dose in trial NN9536-4153.

A maintenance dose of semaglutide s.c. 2.4 mg once-weekly was chosen for the phase 3 weight management development programme. The once-weekly dosing is anticipated to ease the burden of drug administration in clinical practice. Subjects will be initiated at a once-weekly dose of 0.24 mg and follow a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), until the target dose is reached after 16 weeks.

It is well known that to mitigate gastrointestinal side effects with GLP-1 RA treatment, dose escalation to the target dose is required. Based on experience from the semaglutide T2D development programme, a fixed dose escalation regimen was selected, with dose escalation every 4 weeks until the target dose is reached.

4.4 End of trial definition

The end of trial is defined as the date of the last visit of the last subject in the trial globally.

5 Trial population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Subjects are eligible to be included in the trial only if all of the following criteria apply:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male or female, age above or equal to 18 years at the time of signing informed consent
3. Body Mass Index (BMI) ≥30.0 kg/m2

4. Clinical diagnosis of knee OA (ACR criteria) with moderate radiographic changes (KL grades 2 or 3 as per central reading) in target knee. Target knee joint is defined as most symptomatic knee at screening. If pain in knees are equal target knee joint will be in the most dominant leg.
5. Pain due to knee OA (Section 5.5.1)
6. Willingness to complete 72-hour washout period of analgesics before all visits involving WOMAC questionnaire (acetaminophen is allowed as rescue medication).

5.2 Exclusion criteria

Subjects are excluded from the trial if any of the following criteria apply:

Knee OA-related:

1. Joint replacement in target knee
2. Arthroscopy or injections into target knee within the last 3 months prior to enrolment
3. Elective surgery scheduled during the trial duration period, except for minor surgical procedures
4. Active joint disease besides knee OA
5. Use of pain patches, medical marijuana or opioids
6. Symptomatic hip OA unless treated with hip replacement
7. Primary localisation of pain is not within target knee
8. Chronic widespread pain, including neuropathic pain

Obesity-related:

9. Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device, except for: (1) liposuction and/or abdominoplasty, if performed > 1 year before screening, (2) lap banding, if the band has been removed >1 year before screening, (3) intragastric balloon, if the balloon has been removed >1 year before screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year before screening.
10. A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records
11. Uncontrolled thyroid disease

Glycemia-related:

12. HbA1c ≥ 48 mmol/mol (6.5%) as measured by local laboratory at screening
13. History or presence of type 1 or type 2 diabetes (history of gestational diabetes is allowed)
14. Treatment with any GLP-1 RA within 90 days prior to the day of screening

General health and safety:

15. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma

16. Presence of pancreatitis within the last 180 days prior to screening
17. History or presence of chronic pancreatitis
18. End-stage renal disease or chronic or intermittent haemodialysis or peritoneal dialysis
19. Presence or history of malignant neoplasm within 5 years prior to the day of screening. Basal and squamous cell cancer and any carcinoma in-situ are allowed
20. Any of the following in the past 60 days prior to screening: myocardial infarction, stroke, hospitalisation for unstable angina or transient ischaemic attack
21. Subjects presently classified with heart failure New York Heart Association: Class IV
22. Known or suspected hypersensitivity to trial product(s) or related products
23. Previous participation in this trial. Participation is defined as signed informed consent
24. Participation in another clinical trial within 90 days before screening
25. Other subject(s) from the same household participating in any semaglutide trial
26. Female who is pregnant, breast feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method (highly effective contraceptive measures as required by local regulation or practice)
27. History of major depressive disorder within 2 years before screening
28. Diagnosis of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder)
29. History of a suicide attempt
30. Suicidal behaviour within 30 days before screening
31. Known or suspected abuse of alcohol or recreational drugs
32. Any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the subject's safety or compliance with the protocol

The criteria will be assessed at the investigator's discretion unless otherwise stated.

For country specific requirements, see Appendix 6 and for contraceptive requirements, see Appendix 4 .

5.3 Lifestyle considerations

To ensure alignment regarding performance of assessments across subjects and trial sites, the below restrictions apply.

5.3.1 Caffeine and tobacco

Subject should avoid caffeine and smoking at least 30 minutes prior to measuring their blood pressure.

5.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, eligibility criteria, and any SAEs. A screen failure session must be made in the interactive web response system (IWRS).

Individuals who do not meet the criteria for participation in this trial may not be rescreened. If the subject has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to the laboratory parameter, re-sampling is not allowed. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters. If the subject has failed inclusion criteria no. 4 due to incorrect position of the knee during the radiographic examination a reassessment is allowed.

5.5 Randomisation criteria

First dose must only be administered after assessments related to primary and secondary endpoints are completed.

5.5.1 Randomisation criteria

1. A score of at least 40 on the WOMAC pain subscale (range 0-100 normalised Numerical Rating Scale (NRS))
2. For subjects taking analgesics, attend randomisation visit after 72-hour washout period (rescue medication with acetaminophen allowed until 24 hours before visit) (Section 8.1.1)

To be randomised, all relevant randomisation criteria must be answered "yes".

A subject not fulfilling the randomisation criteria will be considered a randomisation failure, see Section 5.4 regarding screen failures.

6 Treatments

6.1 Treatments administered

All trial products listed in Table 6-1are considered investigational medicinal products (IMP). Trial product must only be used, if it appears clear and colourless.

Table 6-1 Investigational medicinal product provided by Novo Nordisk A/S

Trial product name:	Semaglutide B 3.0 mg/mL PDS290	Semaglutide Placebo
Dosage form	Solution for injection	Solution for injection
Route of administration	Subcutaneous	Subcutaneous
Dosing instruction:	Once-weekly	Once-weekly
Delivery device	3 mL PDS290 pre-filled pen-injector	3 mL PDS290 pre-filled pen-injector

- Dose escalation of semaglutide/semaglutide placebo should take place during the first 16 weeks after randomisation as described in Table 6-2. All subjects should aim at reaching the recommended target dose of 2.4 mg semaglutide s.c. once-weekly or the corresponding volume of semaglutide placebo.
- If a subject does not tolerate the recommended target dose of 2.4 mg once-weekly, the subject may stay at a lower dose level of 1.7 mg semaglutide s.c. once-weekly. This should only be allowed if the subject would otherwise discontinue trial product completely and if considered safe to continue trial product, as per the investigator's discretion. It is recommended that the subject makes at least one attempt to re-escalate to the recommended target dose of 2.4 mg semaglutide s.c. once-weekly, as per the investigator's discretion.
- It is recommended that the investigator consults Novo Nordisk in case of persistent deviations from the planned escalation regimen.
- The investigator must document that directions for use are given to the subject verbally and in writing at the first dispensing visit (as specified in the flowchart).
- A dose reminder card will be handed out to the subjects at each site visit during the dose escalation period. This is to remind the subjects of the dose to be taken until next site visit and provide a conversion of the dose to value shown in the dose counter. Once the target dose has been reached, the dose reminder card is only handed out as needed.

Table 6-2 Dose escalation and maintenance of semaglutide s.c. 2.4 mg /semaglutide placebo once-weekly

Trial product name	Dose	Value shown in dose counter	Duration
Dose escalation period			
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	0.24 mg	8*	4 weeks
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	0.5 mg	17*	4 weeks
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	1.0 mg	34*	4 weeks
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	1.7 mg	57*	4 weeks
Maintenance period			
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	2.4 mg	80*	52 weeks

*Conversion to dose is calculated based on 0.01 ml/value

- Subjects will be instructed to inject semaglutide/semaglutide placebo once-weekly at the same day of the week (to the extent possible) throughout the trial.
- Injections may be administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals.
- If a single dose of trial product is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 2 days (48 hours). If a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the subject should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week.
- If ≥ 2 consecutive doses of trial product are missed, the subject should be encouraged to recommence the treatment if considered safe as per the investigator's discretion and if the subject does not meet any of the discontinuation criteria (Section 7.1). The trial product should be continued as early as the situation allows. The missed doses should not affect the scheduled dosing day of the week. The start dose for re-initiation of trial product is at the investigator's discretion. In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk global medical expert.

Auxiliary supplies

Auxiliary supplies will be provided in accordance with the trial materials manual (TMM) please see Table 6-3.

Table 6-3 Auxiliary supplies provided by Novo Nordisk A/S

Auxiliary supply	Details
Needles	Needles for pre-filled pen system. Details provided in the TMM Only needles provided and approved by Novo Nordisk must be used for administration of trial product.
Directions for use (DFU)	DFU for 3 ml PDS290 pre-filled pen-injector. Not included in the dispensing unit and to be handed out separately.

6.1.1 Medical devices

Information about the PDS290 pre-filled pen-injector may be found in the IB[49] and any updates hereof.

Information about the use of the PDS290 pre-filled pen-injector for semaglutide 3.0 mg/mL and semaglutide placebo can be found in the DFU.

Training in the PDS290 pre-filled pen-injector

The investigator must document that training in the DFU has been given to the subjects verbally and in writing at the first dispensing visit. Training must be repeated, during the trial at regular intervals in order to ensure correct use of the medical device. Training is the responsibility of the investigator or a delegate.

6.1.2 Diet and Physical Activity counselling

All subjects in both treatment arms will receive counselling with regards to reduced calorie diet and physical activity taking subjects knee OA into consideration. Counselling should be done by a dietician or a similar qualified healthcare professional

6.1.2.1 Non-investigational medical device(s)

Non-investigational medical devices are listed in Section 6.1 as auxiliary supplies.

6.2 Preparation/handling/storage/accountability

Only subjects randomised to treatment may use trial product and only delegated site staff may supply or administer trial product.

Table 6-4 Trial product storage conditions

Trial product name	Storage conditions (not-in-use)	In-use conditions	In-use time
Semaglutide B 3.0 mg/mL PDS290	Store in refrigerator (2°C-8°C/36°F-46°F) Do not freeze Protect from light	In-use conditions will be available on the trial product label	In-use time will be available on the trial product label
Semaglutide placebo			

[a]In-use time starts when the product is taken out of the refrigerator in the subject's home

- Each site will be supplied with enough trial products for the trial on an ongoing basis. Trial product will be distributed to the sites according to screening and randomisation.
- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the TMM.
- The investigator or designee is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- The investigator or designee must instruct the subject in what to return at next visit.
- Drug accountability should be performed on a pen level and must be documented in the IWRS.
- The subject must return all used, partly used and unused trial product including empty packaging materials during the trial as instructed by the investigator.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- All returned, un-used, expired or damaged trial products (for technical complaint samples, see Section 10.5) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the site.

6.2.1 Shipment of trial product to subject's home

For selected countries and if permitted by local regulations, the investigator may offer to send trial product and auxiliaries from the trial site or pharmacy to the subject's home by courier service.

The process for sending trial product from the trial site or pharmacy to a subject's home is described in the "Trial site/pharmacy instruction for shipment of trial product to patients' homes" document. The document contains detailed instructions for preparing packaging and setting up the pick-up of trial product, handover of trial product from the trial site or pharmacy staff to the courier, required temperature monitoring of trial product, delivery to and receipt of trial product by the patient. The process for returning trial product to the trial site or pharmacy by courier is also described in this document.

Investigators, trial site/pharmacy staff and patients who will be involved in shipment of trial product to the subject's home will be adequately trained in this process.

6.3 Measures to minimise bias: Randomisation and blinding

Randomisation

- All subjects will be centrally screened and randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed at the trial visits summarised in the flowchart.

Blinding

- The active drug and placebo are visually identical for the following trial products:
    - Semaglutide B 3.0 mg/mL PDS290/Semaglutide placebo
- The IWRS is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subjects' treatment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Novo Nordisk prior to unblinding a subjects' treatment unless this could delay emergency treatment of the subject. If a subject's treatment is unblinded, Novo Nordisk (Global Safety department) must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation. The person breaking the blind must print the "code break confirmation" notification generated by the IWRS, sign and date the document. If IWRS is not accessible at the time of the blind break, the IWRS helpdesk should be contacted. Contact details are listed in Attachment 1. The subject will continue on trial product.

6.4 Treatment compliance

Drug treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to encourage subject compliance.

When subjects self-administer trial product(s) at home, compliance with trial product administration will be assessed and the assessment documented in source documents at each visit where information is available. If any suspicion of non-compliance arises, the site must enter into a dialogue with the subject, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Treatment compliance of trial product will be assessed by asking the subject about missed doses and current treatment dose at every visit. Information on treatment dose and periods > 14 days without treatment will be recorded in the case report form (CRF).

6.5 Concomitant medication

Any medication other than the trial product that the subject is receiving at the time of the first visit or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates
- Dose, unit and frequency (only to be recorded for analgesics at baseline)

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 8.3.

6.5.1 Rescue medication

During wash out use of acetaminophen for rescue medication (maximum of 4 g/day) is allowed until 24 hours before visit. Use of acetaminophen (day and dose) will be recorded at the visit related to the wash out period.

Rescue medication will not be supplied or reimbursed by Novo Nordisk.

6.6 Dose modification

Not applicable for this trial. Please refer to Section 6.1 for description of missed dose(s).

6.7 Treatment after end of trial

- There is no treatment following the end of trial.

- When discontinuing trial products, the subject should be transferred to a suitable marketed product at the discretion of the investigator.

7 Discontinuation of trial treatment and subject discontinuation/withdrawal

Treatment of a subject may be discontinued at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Efforts must be made to have subjects, who discontinue trial product, to continue in the trial. Subjects must be educated about the continued scientific importance of their data, even if they discontinue trial product. Only subjects who withdraw consent will be considered as withdrawn from the trial.

7.1 Discontinuation of trial treatment

- Discontinuation of treatment can be decided by both the investigator and the subject.
- Subjects who discontinue trial product should continue with the scheduled visits and assessments to ensure continued counselling and data collection.
    - If the subject does not wish to attend the scheduled clinic visits efforts should be made to have the visits converted to phone contacts. However, all effort should be made to have the subject attend at least the ‘end of treatment’ clinic visit containing the final data collection of primary and confirmatory secondary efficacy endpoints, and the ‘end of trial’ visit.
- The 'end of trial' visit is scheduled approximately 7 weeks after the final data collection, to ensure the safety of the subject. If the subject has discontinued trial product > 7 weeks prior to the 'end of treatment' visit, and the requirements for the follow-up period prior to the 'end of trial' visit is fulfilled, then 'end of trial' visit can be performed in combination with 'end of treatment' visit.
    - If the subject refuses to attend the ‘end of treatment’ and/or ‘end of trial’ visit, information about the attempts to follow up with the subject must be documented in the subject’s medical record.

The trial product must be discontinued, if any of the following applies for the subject:

1. Safety concern as judged by the investigator
2. Suspicion of pancreatitis
3. Pregnancy
4. Intention of becoming pregnant
5. Simultaneous use of an approved or non-approved IMP in another clinical trial

If pancreatitis is suspected appropriate actions should be initiated, including local measurements of amylase and lipase (see Appendix 3 for reporting).

Subjects meeting discontinuation of trial product criterion no. 2 are allowed to resume trial product if the Atlanta criteria[60] are not fulfilled and thus, the suspicion of pancreatitis is not confirmed, at the discretion of the investigator. Trial product may be resumed for subjects with a gallstone-induced pancreatitis in case of cholecystectomy.

Subjects meeting discontinuation of trial product criteria no. 1, 3 and 4 are allowed to resume trial product, if the criteria are no longer met (Section 7.1.1).

The primary reason for discontinuation of trial product must be specified in the end-of-treatment-form in the CRF, and final drug accountability must be performed. A treatment discontinuation status session must be made in the IWRS to indicate discontinuation of trial product.

7.1.1 Temporary discontinuation of trial treatment

If a subject has discontinued trial product due to temporary safety concern not related to trial product and is allowed to resume, the subject should follow the guide for missed doses (Section 6.1). Similarly, a subject who discontinues trial product on their own initiative should be encouraged to resume trial product (Section 6.1).

If a 'treatment' status session previously has been made in IWRS to indicate discontinuation of trial product, a new 'treatment status' session must be made to resume trial product.

7.1.2 Rescue criteria

Refer to Section 6.5.1 for description of rescue medication.

7.2 Subject discontinuation/withdrawal from the trial

A subject may withdraw consent at any time at his/her own request.

If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to the 'end of treatment' visit. See the flowchart for data to be collected.

Final drug accountability must be performed even if the subject is not able to come to the site. A treatment discontinuation status session must be made in the IWRS to indicate discontinuation of trial product.

If the subject withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the medical record.

Although a subject is not obliged to give his/her reason(s) for withdrawing, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the end of trial form in the CRF.

7.2.1 Replacement of subjects

Subjects who discontinue trial product or withdraw from trial will not be replaced.

7.3 Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the site.

The following actions must be taken if a subject fails to return to the site for a required visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial with a primary reason of ‘lost to follow-up’.

8 Trial assessments and procedures

- The following sections describe the assessments and procedures, while their timing is summarised in the flowchart.
- Informed consent must be obtained before any trial-related activity, see Section 10.1.3.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all inclusion criteria and none of the exclusion criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant site staff that can be contacted in case of emergency.

- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- Assessments should be carried out according to the clinic's standard of practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments.
- Source data of clinical assessments performed and recorded in the CRF must be available and will usually be the subject's medical records. Additional recording to be considered source data includes, but is not limited to laboratory reports, clinical outcome assessments.
- The barriers and motivation interview identify barriers to and motivation for lifestyle change and compliance with the protocol. The interview must be conducted at screening to assist in identifying subjects who are unable or unwilling to comply with protocol procedures as per the exclusion criteria. In addition, the interview will ensure that any minor barriers are addressed during lifestyle counselling.
    - The results of the interview will not be entered into the CRF. It will be at the investigator's discretion to evaluate the motivation of the subject and related eligibility.
- Review of patient reported outcome (PRO) instruments, laboratory report etc. must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the PRO instruments is needed, the subject must be questioned, and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.
- The investigator will evaluate changes in the subject's use of analgesics during the trial as detailed in the flowchart. The evaluation should review overall change from baseline until time of the evaluation, irrespective of the washout periods. The evaluation will be categorised as increase, decrease or no change as per the discretion of the investigator based on all available relevant information e.g. medical records and concomitant medication.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 for further details on laboratory samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart.

8.1.1 Western Ontario and McMaster Universities Osteoarthritis Index

Subjects should be given the opportunity to complete the questionnaire by themselves without interruption. The questionnaire takes approximately 5-10 minutes to complete[61].

- The WOMAC is a disease-specific questionnaire designed to assess pain, stiffness and physical function in subjects with hip and/or knee OA[62]. It consists of 24 items divided into three subscales concerning pain, stiffness and physical function. The WOMAC has a recall period of 48-hours.
- An 11-point numeric rating scale will be used to assess responses to individual items. Scores will be built according to the User's Manual (e.g. calculating percentages (range 0-100)). Higher scores on the WOMAC indicate worse pain, stiffness and functional limitations.
- For subjects taking analgesics, no analgesics with exception of acetaminophen until 24 hours before visit, may be taken 72-hours prior to completing the questionnaires allowing for 72-hour washout.
- WOMAC questionnaire will relate to target knee joint defined as most symptomatic knee at screening. If pain in knees are equal target knee joint will be in the most dominant leg.

8.1.2 Body measurements

- Body weight should be measured without shoes, on an empty bladder and only wearing light clothing. It should be measured on a digital scale and recorded in kilograms or pounds (one decimal) using the same scale throughout the trial.
- The scale must be calibrated yearly as a minimum.
- Height is measured without shoes in centimetres or inches (one decimal). BMI will be calculated by the CRF from screening data and must agree with inclusion criterion no. 3.
- Waist circumference is defined as:
    - abdominal circumference located midway between the lower rib margin and the iliac crest
    - Measures must be obtained in a standing position with a non-stretchable measuring tape and to the nearest cm or inch.
    - The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally. The same measuring tape should be used throughout the trial. The measuring tape will be provided by Novo Nordisk to ensure standardisation.

8.1.3 Clinical outcome assessments

Subject should be given the opportunity to complete the questionnaires by themselves without interruption. Each questionnaire takes approximately 10 minutes to complete.

The following PROs will be used:

- The WOMAC (Section 8.1.1)

- Short Form 36 v2-0 acute (SF-36)

SF-36 measures the subject's overall health-related quality of life. It is a 36-item generic measure of health status that yields 2 summary scores for physical health and mental health, and 8 domain scores[63].

- Patient Global Impression of Status (PGI-S) for physical function version 1.0
- Patient Global Impress of Change (PGI-C) for physical function version 1.0
- 6 Minute Walk Test (6MWT)

The 6MWT assesses the distance a subject can walk in 6 minutes. It is a direct and timed measure of walking ability, which is technically simple, reproducible, and when administrators are well trained, readily standardised. The goal is for the subject to walk as far as possible in six minutes without running. The subject is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway of 66 feet (20 m) (Figure 8-1). The primary outcome is the distance covered over 6 minutes[64, 65].

Specifically, all investigators and 6MWT clinical site administrators will receive a manual, providing details for administration of the 6MWT. In addition to the manual, each 6MWT clinical site administrator will have a checklist that must be completed prior to initiating each test administration to confirm and document that specific test administration criteria are met (e.g., the test is assessed along a flat, straight, undisturbed room that is at least 6 feet (1.8 m) wide; proper footwear as judged by the investigator is worn by the subject or otherwise noted)[66]. If the specific test administration criteria are not met, the 6MWT should not be performed.

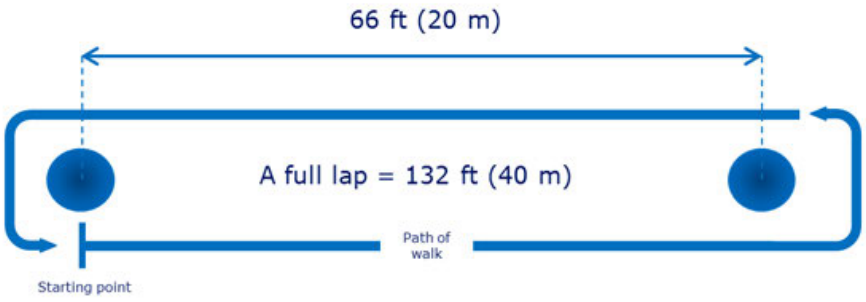


Figure 8-1 Walkway marking for the six-minute walk text

8.2 Safety assessments

Planned time points for all safety assessments are provided in the flowchart.

A **concomitant illness** is any illness that is already present at the time point from which AEs are collected or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Medical history is a medical event that the subject experienced prior to the time point from which AEs are collected. Only relevant and significant medical history as judged by the investigator should be recorded. Findings of specific medical history should be described in the Medical History/Concomitant Illness form.

- History of Gallbladder Disease
- History of Breast Neoplasm
- History of Colon Neoplasm
- History of Skin Cancer
- History of Psychiatric Disorder

In case of an abnormal and clinically significant finding fulfilling the definition of a concomitant illness or medical history, the investigator must record the finding on the Medical History/ Concomitant Illness form.

8.2.1 Radiographic examinations

- Results of a radiographic examination of the target knee, performed by a suitably qualified health care provider, will be evaluated by central reading. Results will be made available to the investigator before randomisation to assess eligibility.
- If the subject has had a radiographic examination performed within 90 days prior to screening, these images may be sent to for evaluation by central reading. The examination must be repeated before randomisation if the subject has experienced worsening of physical function since the last examination.
- The radiographs will be assessed using the KL grading system; a categorical grading scale of knee OA going from 0 to 4 by means of an evaluation of osteophytes, joint space narrowing, sclerosis and altered bone shapes[67, 68].

8.2.2 Physical examinations

- A physical examination will include assessments of the cardiovascular, musculoskeletal and respiratory system, general appearance, thyroid gland and abdomen.
- Body measurements (e.g. height and weight) will also be measured and recorded as specified in the flowchart.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.3 Vital signs

- The method for measuring systolic and diastolic blood pressure needs to follow the standard clinical practice at site

However, as a minimum:

- Vital sign assessment should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. no use of television, cell phones).
- Blood pressure and pulse rate measurements will be assessed sitting with a completely automated device. Manual techniques must be used only if an automated device is not available.
- Pulse rate will be measured in connection to the blood pressure measurements. Record the pulse rate for the last 2 blood pressure measurements in the CRF. The pulse rate is to be recorded as the mean of the last 2 measurement.

8.2.4 Clinical safety laboratory assessments

Not applicable for this trial.

8.3 Adverse events and serious adverse events

The investigator is responsible for detecting, documenting, recording and following up on all the events listed below:

- SAEs
- Following AEs irrespective of seriousness
    - AEs leading to permanent discontinuation of trial product
    - AEs requiring invasive knee procedures
    - AEs with additional data collection:
        - medication error (including abuse/misuse of trial product)
        - pancreatitis
- Pregnancies and pregnancy-related AEs
- Technical complaints

Note, that also events not allowed in accordance with the protocol e.g. bariatric surgery or knee replacement should, if they take place, be reported with both the procedure and medical condition specified.

The definition of AEs and SAEs can be found in Appendix 3, along with a description of AEs requiring additional data collection.

Some AEs require additional data collection on a specific event form. This always includes medication error, misuse and abuse of IMP. The relevant events are listed below in Table 8-1.

Table 8-1 AEs requiring additional data collection (serious and non-serious AEs)

Event type	AE requiring additional data collection
Medication error*	X
Misuse or abuse of trial product*	X
Pancreatitis	X

*Additional data for Misuse or abuse of trial product is reported on the medication error event form.

A detailed description of the events mentioned in the above table can be found in Appendix 3.

8.3.1 Time period and frequency for collecting AE and SAE information

All events specified in Section 8.3 (for events related to pregnancy, see Appendix 4) must be collected and reported. The events must be collected from the first trial-related activity after obtaining informed consent until the end of trial visit, at the time points specified in the flowchart.

Medical occurrences that take place or have onset prior to the time point from which AEs are collected will be recorded as concomitant illness/medical history. AE and SAE reporting timelines can be found in Appendix 3. All SAEs must be recorded and reported to Novo Nordisk or designee within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24-hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former trial subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related to the trial product or related to trial participation, the investigator must promptly notify Novo Nordisk.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about events.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs should be followed until final outcome of the event or the subject is lost to follow-up as described in Section 7.3. Further information on follow-up and final outcome of events is given in Appendix 3.

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk or designee of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial product under clinical investigation are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR).

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from Novo Nordisk will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of pregnancies in female subjects will be collected after the first-trial-related activity after obtaining informed consent and until the end of trial visit.

If a female subject becomes pregnant, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

8.3.6 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to Section 8.3.

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as an AE or SAE

Not applicable for this trial.

8.3.8 Adverse event of special interest

Not applicable for this trial.

8.3.9 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form.

Instructions for reporting technical complaints can be found in Appendix 5.

In order for Novo Nordisk to perform a complete investigation of reported SAEs, Novo Nordisk might ask the investigator to complete a technical complaint form.

8.4 Treatment of overdose

- Overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported AE was nausea. All subjects recovered without complications.
- There is no specific antidote for overdose with semaglutide. In the event of an overdose, appropriate supportive treatment should be initiated according to subject's clinical signs and symptoms.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.3 and Appendix 3 for further details.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE. A prolonged period of observation and treatment may be necessary, taking into account the long half-life of semaglutide of approximately one week.

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the subject.

For more information on overdose, also consult the current version of the investigator's brochure[49] and any updates hereof.

8.5 Pharmacokinetics

Not applicable for this trial.

8.6 Pharmacodynamics

Not applicable for this trial.

8.7 Genetics

Not applicable for this trial.

8.8 Biomarkers

Not applicable for this trial.

8.9 Immunogenicity assessments

Not applicable for this trial.

8.10 Health economics

Not applicable for this trial.

9 Statistical considerations

9.1 Statistical hypotheses

The tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo for the two primary and all confirmatory secondary endpoints are performed using a fixed-sequence statistical strategy and a weighted Holm-Bonferroni procedure (with weights one). For a detailed specification of statistical hypotheses for the two primary endpoints see Section 9.4.2.

This strategy tests the endpoints using a predefined hierarchical order; first the two primary endpoints: body weight change (%) and change in WOMAC pain score are tested at the significance level of 5% where the alpha is split between the two endpoints using 1% for body weight change (%) and 4 % for change in WOMAC pain score.

If superiority is not confirmed for both endpoints, then the testing will stop. If the test of superiority for one of the two primary endpoints is significant, then the alpha can be recycled for the other primary endpoint, which will be tested at the 5% significance level. If both hypotheses are rejected and superiority is confirmed, then the confirmatory secondary endpoints (starting with ≥5% body weight reduction) will be tested at the 5% level. Testing for superiority of confirmatory secondary endpoints can proceed only after a statistically significant result (p-value < 5%) on the previous endpoint.

9.2 Sample size determination

The trial is designed with an effective power of 90% and 67% to detect differences on the two primary endpoints and confirmatory secondary endpoints, respectively. The effective power was calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively which is a conservative approach. The power calculations for continuous endpoints are based on a t-test on the mean difference assuming equal variances, whereas those for the categorical endpoints are based on the Pearson chi-square test for two independent proportions.

Assumptions for these calculations are presented in Table 9-1 and are based on findings from NN9536-4153 and NN9536 phase 3a program (STEP) as well as on relevant publications on body weight loss and knee OA outcome (using WOMAC). Two studies, Bliddal et al. and Christensen et al., found that weight loss treatment (average weight loss 7.5% and 6.8% respectively) could lead to improvements in knee OA symptoms like pain and physical function (pain score: -8.4 (-10.4 vs -2.0) with baseline score 38.4 (SD=21.1) and -5.4 (-11.4 vs -6.0) with baseline score 36.7 (SD=21.3)

respectively; function score: -3.7 (-10.2 vs -6.5) with baseline score 39.2 (SD=21.4) and -9.9 (-14.9 vs -5.0) with baseline value 37.4 (SD=21.8) respectively) in obese subjects (average BMI at baseline 35.6 and 35.9 respectively)[27, 69]. Aforementioned score improvements were found in treatment completers. Item responses were collected using the VAS format of the questionnaire. Bliddal et al. reported normalised sum of scores (range 0-100) and Christensen et al. reported sum of scores, which were transformed to a 0-100 range for comparison purposes. Consequently, a treatment difference for the pain score was assumed to be -9 (-11 vs -2) with SD=20; for the function score it was assumed to be -9 (-15 vs -6) with SD=19 if treated with semaglutide s.c. 2.4 mg once-weekly vs semaglutide placebo for 68 weeks. Clement et al. identified a minimum clinically important difference of 11 for pain and 9 for function and a minimum important change of 21 for pain and 16 for function for improvement in WOMAC after total knee arthroplasty.[70] Although, it is planned to use the NRS format of the questionnaire in this trial, it is known that VAS and NRS are highly correlated (r>0.93) and that VAS derived assumptions for sample size calculation are adequate and can be translated to a setting where NRS is used[71]. It is planned that the WOMAC scores (derived from NRS responses) will be transformed to a 0-100 range based on which the corresponding endpoints will be calculated.

In relation to expected treatment effects it was assumed that 20% of subjects discontinue permanently and 60% of these are retrieved at week 68. All subjects in the placebo arm are assumed to have same effect as subjects who complete the trial on placebo. Retrieved subjects in the semaglutide s.c. 2.4 mg once-weekly arm are assumed to have an effect corresponding to half the treatment difference (compared to placebo) of subjects who complete the trial on semaglutide s.c. 2.4 mg once-weekly. Non-retrieved subjects in the semaglutide s.c. 2.4 mg once-weekly arm are assumed to have an effect corresponding to placebo.

Under these assumptions and a 2:1 randomisation ratio, the desired power of at least 90% for change in WOMAC pain score is obtained with 375 subjects randomised to either receive semaglutide s.c. 2.4 mg once-weekly (250) or placebo (125).

Table 9-1 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number of 375 randomised subjects

Order	Endpoint	Assumed mean (±SD) or proportion for completers		Expected mean (±SD) or proportion	Expected difference or proportion ratio	Marginal power (%)	Two-sided significance level (%) *	Effective power (%)
		Semaglutide s.c. 2.4 mg once-weekly	Semaglutide placebo	Semaglutide s.c. 2.4 mg once-weekly				
1	**% body weight change #**	14.0 (±10)	3.0 (±10)	12.5 (±11)	9.5%-points	>99	1	99
1	**WOMAC pain change #**	11.0 (±20)	2.0 (±20)	9.7 (±21)	7.7 score-points	90	4	90
2	5% responders	82%	42%	76%	1.8	>99	5	90
3	10% responders	66%	24%	60%	2.5	>99	5	90
4	WOMAC function change #	15.0 (±19)	6.0 (±19)	13.7 (±20)	7.7 score-points	94	5	84
5	SF-36 physical functioning change	6.0 (±10)	2.0 (±10)	5.4 (±11)	3.4 score-points	80	5	67

SD: Standard deviation; WOMAC: Western Ontario McMasters Osteoarthritis Index ; SF-36: Short Form (36) Health Survey.
*Significance level for confirmatory secondary endpoints reflects local alpha if all superiority hypotheses for endpoints higher in the statistical hierarchy were rejected
Shown as a positive number

As currently there are no NN trials utilizing WOMAC, see Table 9-2 for alternative power calculations to the main scenario assuming varying sample size, mean difference or standard deviation.

Table 9-2 Marginal power for WOMAC pain change (shown as a positive number) for alternative sample size, mean difference or standard deviation

Sample size	Expected mean for semaglutide placebo	Expected mean for semaglutide s.c. 2.4 mg once-weekly	Expected difference	Common SD	Marginal power (%)
Main scenario					
375	2	9.7	7.7	21	0.900
Varying sample size					
285	2	9.7	7.7	21	0.803
303	2	9.7	7.7	21	0.828
324	2	9.7	7.7	21	0.853
348	2	9.7	7.7	21	0.877
375	2	9.7	7.7	21	0.900
411	2	9.7	7.7	21	0.925
462	2	9.7	7.7	21	0.951
543	2	9.7	7.7	21	0.975
888	2	9.7	7.7	21	>.999
Varying mean difference					
375	2	5	**3**	21	0.226
375	2	6	**4**	21	0.375
375	2	7	**5**	21	0.545
375	2	8	**6**	21	0.708
375	2	9	**7**	21	0.837
375	2	10	**8**	21	0.921
375	2	11	**9**	21	0.968
375	2	12	**10**	21	0.989
375	2	13	**11**	21	0.997
375	2	14	**12**	21	>.999
375	2	15	**13**	21	>.999
Varying standard deviation					
375	2	9.7	7.7	**10**	>.999
375	2	9.7	7.7	**11**	>.999
375	2	9.7	7.7	**12**	>.999
375	2	9.7	7.7	**13**	>.999
375	2	9.7	7.7	**14**	0.998
375	2	9.7	7.7	**15**	0.996
375	2	9.7	7.7	**16**	0.990
375	2	9.7	7.7	**17**	0.981
375	2	9.7	7.7	**18**	0.967
375	2	9.7	7.7	**19**	0.949
375	2	9.7	7.7	**20**	0.927
375	2	9.7	7.7	**21**	0.900

375	2	9.7	7.7	**22**	0.871
375	2	9.7	7.7	**23**	0.840
375	2	9.7	7.7	**24**	0.807
375	2	9.7	7.7	**25**	0.773
375	2	9.7	7.7	**26**	0.740
375	2	9.7	7.7	**27**	0.706
375	2	9.7	7.7	**28**	0.673
375	2	9.7	7.7	**29**	0.642
375	2	9.7	7.7	**30**	0.611

SD: Standard deviation.

All above outlined sample size and power considerations are for the primary estimand for primary endpoints or the secondary estimand for confirmatory secondary endpoints (treatment policy strategy). It is assumed that up to 20% of subjects discontinue permanently and 60% of these are retrieved at week 68, which amounts to 8% expected missing data at week 68. Based on NN9536 STEP 1 trial 8.8% missing in-trial data was observed after 68 weeks for the primary estimand. Any superiority conclusions will be based on the primary or secondary estimand.

For the additional estimand (hypothetical strategy) however, data from retrieved subjects are not used. Hence, it is expected that up to 20% of data will be missing at week 68. Based on NN9536 STEP 1 trial 20.6% missing on-treatment data was observed after 68 weeks for the additional estimand. This included missing data not only due to treatment discontinuation, but also due to initiation of other anti-obesity therapies (<1%). For trial NN9536 4578 slightly higher missing on-treatment data is expected due to subjects initiating other knee OA interventions (<3%) and not complying with the washout period (<10%). In NN9536 STEP 1 trial it was seen that the treatment difference in mean changes for body weight was slightly higher and standard deviation was slightly lower for the additional estimand (using on-treatment data) than for the primary estimand (using in-trial data).

9.3 Populations for analyses

Two analysis sets are defined:

The *full analysis set (FAS)* includes all randomised subjects according to the intention-to-treat principle. The subjects in the *FAS* contribute to the evaluation as randomised.

The *safety analysis set (SAS)* includes all randomised subjects exposed to at least one dose of randomised treatment. The subjects in the *SAS* contribute to the evaluation as treated.

Any observation excluded from the analysis database will be documented before database lock with the reason for exclusion provided. Efficacy endpoints will be analysed using the FAS; safety endpoints will be analysed using the SAS.

Two observation periods are defined for each subject:

In-trial: The *in-trial period* is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site.

On-treatment (with trial product): A time-point is considered as "on-treatment" if any dose of trial product has been administered within the prior 2 weeks (14 days). The *on-treatment period* is defined as all times which are considered on-treatment.

In general, the *on-treatment period* will therefore be from the date of first trial product administration to date of last trial product administration excluding potential off-treatment time intervals triggered by at least two consecutive missed doses.

For the evaluation of AEs, the lag time for each on-treatment time interval is 7 weeks (49 days).

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

9.4 Statistical analyses

9.4.1 General considerations

A statistical analysis plan (SAP) will be written, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before breaking the blind to treatment assignment.

The last available and eligible observation at or before randomisation is used as the baseline value. If no assessments are available, the mean value at randomisation across all subjects is used as the baseline value.

9.4.2 Primary endpoint*(s)*

The primary endpoints are change in body weight (%) and change in WOMAC pain score from baseline (week 0) to end-of-treatment (week 68) as listed in Section 3.

Change from baseline to week 68 in body weight (%) is defined as

$$\% \text{ body weight change} = \frac{(\text{body weight at week 68} - \text{body weight at baseline})}{\text{body weight at baseline}} \times 100.$$

Change from baseline to week 68 in WOMAC pain score is defined as

WOMAC pain score change = WOMAC pain score at week 68 – WOMAC pain score at baseline.

All tests are tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo.

Let $\mu_{\text{semaglutide}}$ and $\mu_{\text{semaglutide placebo}}$ denote the true mean of % body weight change or WOMAC pain score change for semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo, respectively. The null and alternative hypotheses tested are

$$H_0: \mu_{semaglutide} \geq \mu_{semaglutide\ placebo}\ vs$$
$$H_A: \mu_{semaglutide} < \mu_{semaglutide\ placebo}.$$

The null hypotheses will be rejected and superiority claimed, if the upper limit of the estimated two-sided 95% CI is below 0.

Analyses addressing the primary estimand

The following statistical analyses and imputation methods are designed to address the primary estimand.

The analysis model for change in body weight (%) and change in WOMAC pain score will be a linear regression (ANCOVA) with randomised treatment as factor and either baseline body weight (kg) or baseline WOMAC pain score as covariate. The estimated treatment difference between semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

All available data at week 68 are used and missing values at week 68 will be imputed and the endpoint will be derived from the imputed values. The imputation approach for the primary analysis is a multiple imputation similar to the one described by McEvoy et al[72]. For subjects in the semaglutide s.c. 2.4 mg once-weekly and the semaglutide placebo arms, missing measurements at week 68 for non-retrieved subjects are imputed using assessments from retrieved subjects in each randomised treatment arm. This will be done according to the timing of last available observation during the on-treatment period (LAO-OT) as well as by taking sex, baseline BMI and baseline body weight into account. Missing measurements at week 68 for subjects on randomised treatment (at week 68) are imputed by sampling from available measurements at week 68 from subjects on randomised treatment in the relevant randomised treatment arms. Details of the multiple imputation approach are provided in the SAP.

Analysis addressing the additional estimand

The additional estimand for change in body weight (%) and change in WOMAC pain score will be assessed using a mixed model for repeated measurements (MMRM) approach.

Week 68 assessments for retrieved subjects are not used in this analysis. The MMRM will use assessments only from subjects who are taking the randomised treatment until end of treatment or until first discontinuation of randomised treatment. For subjects who experience other intercurrent events before completion or first discontinuing of randomised treatment, the date of initiating other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injections) will be used as latest date for using assessments in this MMRM. Additionally, for the MMRM analysing change in WOMAC pain score, assessments from subjects incompliant with the washout period for pain medication will not be used. The MMRM will be fitted using the change (% body weight change or change in WOMAC pain score) and the same factor and covariate as for the primary analysis all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

9.4.3 Secondary endpoints

9.4.3.1 Confirmatory secondary endpoints

The confirmatory secondary endpoints are listed in Section 3.

All tests are tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo.

Analyses addressing the secondary estimand

The confirmatory secondary endpoints addressing the secondary estimand will be analysed in a similar way as the primary endpoints addressing the primary estimand.

The statistical model for continuous confirmatory secondary endpoints will be the same linear regression as for the primary endpoints (ANCOVA) with treatment as a factor and the baseline value of the endpoint as covariate. The statistical model for confirmatory body weight responder endpoints is a logistic regression using randomised treatment as a factor and baseline body weight (kg) as covariate. The estimated odds ratio (OR) between semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval and corresponding p-value.

The imputation approach is the same multiple imputation using retrieved subjects as described in Section 9.4.2 and taking the baseline value of the endpoint into account.

Analyses addressing the additional estimand

The confirmatory secondary endpoint change in WOMAC physical function score addressing the additional estimand will be analysed using the same MMRM as described for the primary endpoint change in WOMAC pain score addressing the additional estimand with randomised treatment as a factor and the baseline value of the endpoint as covariate.

The confirmatory body weight responder endpoints addressing the additional estimand will be analysed using the same MMRM described for the primary endpoint change in body weight (%) addressing the additional estimand except that body weight (kg) will be used as response variable in the model. For subjects with missing body weight at week 68, individual values for body weight will be predicted from the MMRM and used to classify each subject as 5% or 10% responder or not. This classification will then be analysed using a logistic regression model with randomised treatment as a factor and baseline body weight (kg) as covariate.

9.4.3.2 Supportive secondary endpoints

For details on analyses of supportive secondary endpoints, please see the SAP.

9.4.4 Exploratory endpoints

For details on analyses of exploratory endpoints, please see the SAP.

9.4.5 Other safety analyses

For other safety analyse(s), please see the SAP.

9.4.6 Other analyse(s)

Not applicable for this trial.

9.4.6.1 Pharmacokinetic and/or pharmacodynamic modelling

Not applicable for this trial.

9.5 Interim analyses

Not applicable for this trial.

9.6 Data monitoring committee

Not applicable for this trial.

9.7 Reporting of the main part of the trial

Not applicable for this trial.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and trial oversight considerations

10.1.1 Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[73] and applicable ICH Good Clinical Practice (GCP) Guideline[74]
- Applicable laws and regulations
- The protocol, informed consent form, IB (as applicable) and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report (CTR) according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
- providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- ensuring submission of the CTR synopsis to the IRB/IEC
- reporting any potential serious breaches to the sponsor immediately after discovery

10.1.2 Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and one year after completion of the trial.
Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

10.1.3 Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the subject and answer all questions regarding the trial. This includes the use of an impartial witness where required according to local requirements.
- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.
- Subjects must be informed about their privacy rights.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[74], Declaration of Helsinki[73] and the IRB/IEC or site.
- The medical record must include a statement that written informed consent was obtained before any trial-related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial-related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form*(s)* during their participation in the trial.
- A copy of the informed consent form*(s)* must be provided to the subject.

10.1.4 Information to subjects during trial

The site will be offered a communication package for the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the subjects. The written information will be translated and adjusted to local requirements and distributed to the subject at the discretion of the investigator. The subject may receive a “welcome to the trial letter” and a “thank you for your participation letter” after completion of the trial. Further, the subject may receive other written information during the trial.

Different initiatives for subject retention will be implemented throughout this trial. Site retention activities may include cooking classes, group meetings and others. Materials and items will be supplied if locally acceptable. The retention items will be relevant for the subjects’ participation in the trial and/or their obesity and will not exceed local fair market value.

All written information to subjects must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

The initiatives for subject retention must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

10.1.5 Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the subject are transferred to Novo Nordisk.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.
- The subject must be informed about his/her privacy rights, including that his/her personal trial-related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee. The safety committee may recommend unblinding of any data for further analysis, and in this case an internal trial independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

10.1.6.2 Trial safety group

Not applicable for this trial.

10.1.6.3 Data monitoring committee

Not applicable for this trial.

10.1.6.4 Event adjudication committee

Not applicable for this trial.

10.1.7 Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements, such as those of the International Committee of Medical Journal Editors (ICMJE)[75], the Food and Drug Administration Amendment

Act (FDAAA)[76], European Commission Requirements[77-79] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The primary completion date is the last assessment of the primary endpoint, and is for this trial Last Subject First Treatment + 68 weeks corresponding to 'end of treatment' visit. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed 'end of treatment' visit. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The following will be provided as paper CRFs:
    - Pregnancy forms (Maternal forms 1A, 1B and 2 and Paternal form)
- The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:
    - AE forms
    - Safety information forms
    - Technical complaint forms (also to be used to report complaints on trial product not yet allocated to a subject)
- Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.
- The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

10.1.8.2 Monitoring

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.
- Monitors will review the subject's medical records and other source data, e.g. PROs, to ensure consistency and/or identify omissions compared to the CRF.

10.1.8.3 Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without delay and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the CRF or via listings from the trial database.

10.1.9 Source documents.

- All data entered in the eCRF must be verifiable in source documentation other than the CRF
- For ePROs, data in the service providers' database is considered source data.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

- It must be possible to verify subject's medical history in source documents, such as subject's medical record
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.
- Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

10.1.11 Trial and site closure

Novo Nordisk reserves the right to close the site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

Sites will be closed upon trial completion. A site is considered closed when all required documents and trial supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a site by Novo Nordisk or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines

- inadequate recruitment of subjects by the investigator
- discontinuation of further trial product development.

10.1.12 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

A qualified physician, who is an investigator or a sub investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents, including the subject identification code list must be kept in a secure locked facility so that no unauthorized persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of subjects to a specific qualified physician who will be readily available to subjects during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

10.1.13 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the trial or by persons for whom the said site or investigator are responsible. Novo Nordisk may pay additional costs incurred in relation to assessments relevant for following the safety of the subject. Investigator must contact Novo Nordisk on a case by case basis for whether the costs will be covered.

Novo Nordisk accepts liability in accordance with: Please refer to Appendix 6.

10.1.14 Publication policy

The information obtained during the conduct of this trial is considered confidential and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial.

The information obtained during this trial may be made available to other investigators who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted CTR for this trial.

One (or two) investigators will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators.

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

At the end of the trial, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases, the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

10.1.14.2 Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the trial concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[80]

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned publication.

Where required by the journal, the investigator from each site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

10.1.14.3 Site-specific publication(s) by investigator(s)

For a multicentre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the trial.

10.1.14.4 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database.

Individual investigators will have their own research subjects' data and will be provided with the randomisation code after results are available.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10-1 will be performed by the local laboratory
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. If additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.
- The investigator must review all laboratory results for concomitant illnesses and AEs.

Table 10-1 Protocol-required laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism[1]	$HbA1_c$
Pregnancy Testing	Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]
Notes: [1]For screening purposes only [2]Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.	

$HbA1_c$; glycated haemoglobin, IRB; institutional review board, IEC; independent ethics committee

10.3 Appendix 3: Adverse events: Definitions and procedures for recording, evaluation, follow-up, and reporting

10.3.1 Definition of AE

AE definition

An AE is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of an IMP, whether or not considered related to the IMP.

An AE can therefore be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of an IMP.

Events meeting the AE definition

- Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected
- Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected
- Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition
- Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent
- Obesity-related surgical procedures, total knee replacements and knee arthroscopy

A "lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.

Events NOT meeting the AE definition

- Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or other trial procedures performed before exposure to IMP.
- Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.
- Medical or surgical procedures (e.g. endoscopy, appendectomy). The condition that leads to the procedure is the AE. · Exceptions include; obesity-related surgical procedures, total knee replacements and knee arthroscopy. In these cases both the surgical procedure and the condition that leads to the procedure should be reported as AEs.
- Medical or surgical procedures not preceded by an AE or worsening of a known condition (exceptions are obesity-related surgical procedures, which for this trial should be reported as individual AE's).

10.3.2 Definition of an SAE

An SAE is an AE that fulfils at least one of the following criteria:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

- Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.
- Hospitalisation for elective treatment (e.g. elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE.

  Note:
  - Hospitalisations for administrative, trial-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs.
  - Hospital admissions for medical or surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Important medical event:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.

- The following adverse events must always be reported as SAEs using the important medical event criterion if no other seriousness criteria are applicable:
  - Suspicion of transmission of infectious agents via the IMP
  - Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of AEs requiring additional data collection

Description of AEs requiring additional data collection (on specific event form)

Adverse events requiring additional data collection
AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the safety of the trial product (see Table 8-1). The selection of these events is based on the non-clinical and clinical data with semaglutide, knowledge from the GLP-1 RA drug class as well as regulatory requirements.

Pancreatitis
Diagnosis of pancreatitis requires two of the following three features:

1. abdominal pain consistent with pancreatitis (onset of a persistent, severe, epigastric pain often radiating to the back)
2. serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal
3. characteristic findings of pancreatitis on imaging.

Medication error
A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the subject, such as:

- administration of wrong drug
  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- wrong route of administration, such as intramuscular instead of subcutaneous
- accidental administration of higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.
- missed doses or drug pauses are not to be reported as a medication error.

Misuse and abuse

- Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g. overdose to maximise effect)

- Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm)

Medication error, misuse and abuse must always be reported as an AE (e.g. accidental overdose, intentional overdose or other) on a separate AE form, and a medication error, misuse and abuse form must be completed. In case of a medication error and/or misuse and abuse resulting in a clinical consequence (e.g. hypoglycaemia or other), this must be reported on an additional AE form.

10.3.4 Recording and follow-up of AE and/or SAE

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the CRF.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- SAEs and AEs listed in Section 8.3 and AEs/SAEs in connection with pregnancies, must be recorded by the investigator in the CRF. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
- For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE-related forms, refer to "AE and SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

The investigator will assess severity for each event reported during the trial and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: An AE that is assessed as severe should not be confused with a SAE. Both AEs and SAEs can be assessed as severe.

Assessment of causality

- The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE.
- Relationship between an AE/SAE and the relevant IMP(s) should be assessed as:
  - Probable - Good reason and sufficient documentation to assume a causal relationship.
  - Possible - A causal relationship is conceivable and cannot be dismissed.
  - Unlikely - The event is most likely related to aetiology other than the IMP.
- Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.**
- The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented
- **Recovering/resolving:** The condition is improving, and the subject is expected to recover from the event. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- Note: For SAEs, this term is only applicable if the subject has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae:** The subject has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the subject has not improved, and the symptoms are unchanged, or the outcome is not known.

Note: This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).

- **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the subject is lost to follow-up.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology.

New or updated information will be recorded in the CRF.

10.3.5 Reporting of SAEs

SAE reporting via electronic CRF

- Relevant forms (AE form, safety information form and specific event forms) must be completed in the CRF.
- For reporting and sign-off timelines, see Figure 10-1 below.
- If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the CRF is unavailable for more than 5 calendar days, then the site will use the paper safety information form (see box below).
- The site will enter the SAE data into the CRF as soon as it becomes available.
- After the trial is completed, the trial database will be locked, and the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after CRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

AE and SAE reporting via paper CRF

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk in accordance with Section 10.1.5.

- For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting timelines (as illustrated in the figure below):
  - AE form within 24 hours
  - Safety information form within 5 calendar days
  - Both forms must be signed within 7 calendar days after first knowledge by the investigator.

The specific event form for AEs requiring additional data collection within 14 calendar days

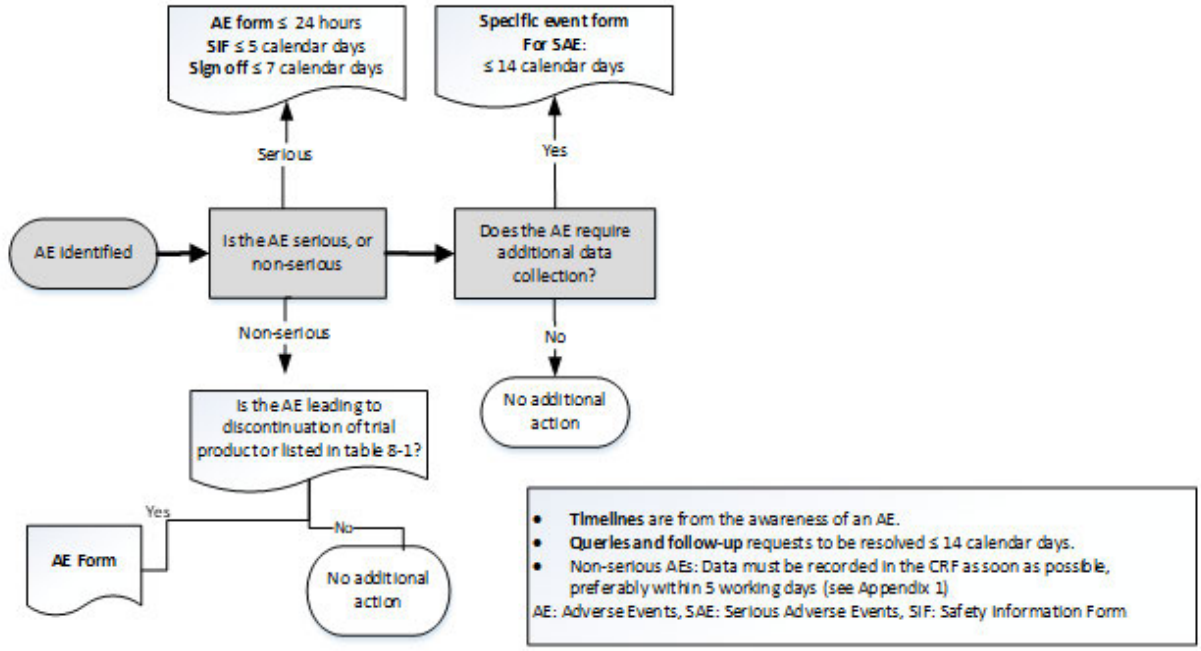


Figure 10-1 Decision tree for determining the event type and the respective forms to complete with associated timelines

Contact details for SAE reporting can be found in the investigator trial master file.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.
If fertility is unclear (e.g. amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of trial treatment, additional evaluation should be considered.

Females in the following categories are not considered WOCBP

1. Premenarcheal
2. Females with one or more of the following:
   Documented total hysterectomy
   Documented bilateral salpingectomy
   Documented bilateral oophorectomy

Females with permanent infertility due to an alternate medical cause other than the above (e.g. Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining trial enrolment.

3. Postmenopausal female:

- A postmenopausal state is defined as amenorrhoea for 12 months without an alternative medical cause.
- Females ≥ 50 years of age can be considered postmenopausal (irrespective of treatment with a hormonal contraception or hormone replacement therapy (HRT)) if they have both:
  - Amenorrhoea and
  - Documentation of 2 high follicle stimulating hormone (FSH) measurements in the postmenopausal range and one of these was observed ≥1 year prior to screening.
- Females ≥ 60 years of age can be considered postmenopausal.

Females on HRT and whose menopausal status is in doubt are considered of childbearing potential and will be required to use one of the highly effective contraception methods.

Note: Documentation regarding categories 1-3 can come from the site staff's review of subject's medical records, medical examination or medical history interview.

Contraception guidance

Male subjects
No contraception measures are required for male subjects as the risk of teratogenicity/fetotoxicity caused by transfer of semaglutide in seminal fluid is unlikely.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly as described in table below:

Table 10-1 Highly effective contraceptive methods

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:

• **Highly effective methods[b,f] that have low user dependency** (Failure rate of <1% per year when used consistently and correctly):
  • Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
  • Intrauterine device (IUD)
  • Intrauterine hormone-releasing system (IUS)[b]
  • Bilateral tubal occlusion
  • Vasectomized partner
  (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)
 	
• **Highly effective methods[b,f] that are user dependent** (Failure rate of <1% per year when used consistently and correctly):
  • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  o oral
  o intravaginal
  o transdermal
  o injectable
• Sexual abstinence
  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.

NOTES a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical trials. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

d)	Contraception should be utilised during the treatment period and for at least 49 days (corresponding to time needed to eliminate trial product) after the last dose of trial product. This period should be extended by 30 days in case of genotoxicity.

Pregnancy testing

- Additional pregnancy testing should be performed during the treatment period, if required locally (Appendix 6).
- WOCBP should only be included after a negative highly sensitive urine pregnancy test (refer to Appendix 2).
- A pregnancy test should be performed at the end of relevant systemic exposure (refer to Appendix 2).
- Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.

Collection of pregnancy information

Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy (see Figure 10-3).
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate which will be forwarded to Novo Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding ‘gestational’, ‘pregnancy-related’ or a similar term when reporting the AE/SAE.
- Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.

- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the IMP by the investigator will be reported to Novo Nordisk as described in Section 10.3. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

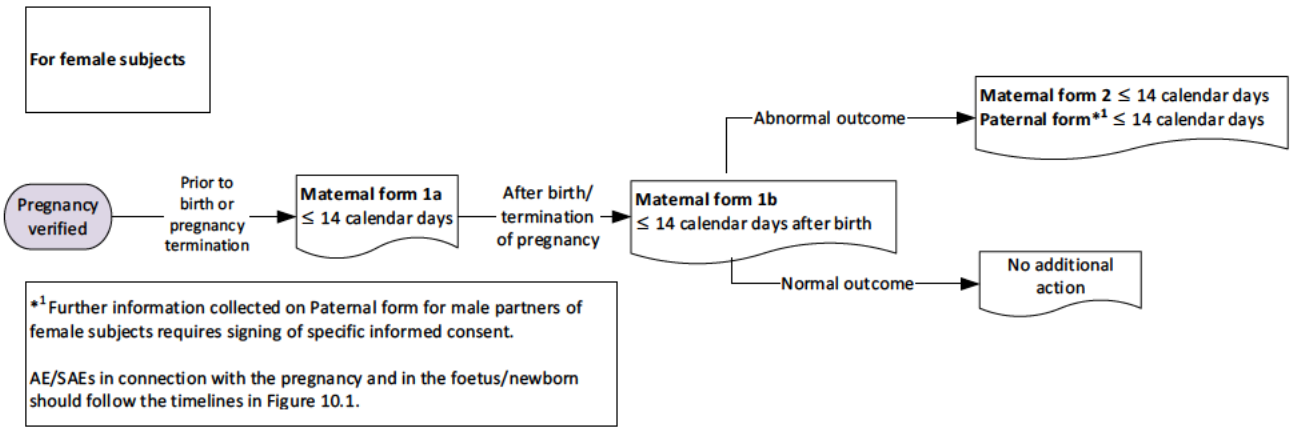


Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy

Any female subject who becomes pregnant while participating in the trial will discontinue IMP.

10.5 Appendix 5: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

10.5.1 Definition of technical complaint

Technical complaint definition
A technical complaint is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself.

Examples of technical complaints:

- Problems with the physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- Problems with packaging material including labelling
- Problems related to devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen-injector and the needle)

Time period for detecting technical complaints
All technical complaints which occur from the time of receipt of the product at site until the time of the last usage of the product must be collected for products predefined on the technical complaint form.

10.5.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk
Contact details for Customer Complaint Center, please refer to Attachment I. Technical complaints must be reported on a separate technical complaint form: 1. One technical complaint form must be completed for each affected DUN. 2. If DUN is not available, a technical complaint form for each batch, code or lot number must be completed.

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within: 24 hours if related to an SAE 5 days calendar for all other technical complaints If the CRF is unavailable, or when reporting a technical complaint on a trial product that is not yet allocated to subject, the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

Follow-up of technical complaints
The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples
The investigator must collect the technical complaint sample and all associated parts that were packed in the same DUN and notify the monitor within 5 calendar days of obtaining the sample at site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together. Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

10.5.3 Reporting of technical complaints

Reporting of technical complaints for Novo Nordisk products not included in technical complaint form
Technical complaints on Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk.

10.6 Appendix 6: Country-specific requirements

For Denmark:

Section 5.3 Exclusion criteria no. 26

Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered highly effective birth control.

For Canada:

Appendix 1 Section 10.1.10 Retention of clinical trial documentation

Part C, Division 5 of the Food and Drug Regulations [C.05.012] requires a 25 years retention period

For France:

1. Section 1.2 Flowchart

Ethnic origin and race: Collection not allowed in France.

Year of birth: Only year is collected for the date of birth.

Appendix 1 Section 10.1.13 Indemnity statement

The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX, Journal Officiel of 11 August 2004. "The sponsor is responsible for identification of the harmful consequences of the biomedical the research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research"

Section 5.3 Exclusion criteria no. 26

Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered highly effective birth control.

For Norway:

Section 5.3 Exclusion criteria no. 26

Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)

- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered highly effective birth control.

For Sweden:

Section 5.3 Exclusion criteria no. 26

Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered highly effective birth control.

For Spain:

Appendix 1 Section 10.1.10 Retention of clinical trial documentation

25 years according to the new Spanish Royal Decree 1090/2015

Section 5.3 Exclusion criteria no. 26

Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered highly effective birth control.

For Russia:

Appendix 1 Section 10.1.1 Regulatory and ethical considerations

The trial should be conducted in compliance with the protocol and Ministry of Healthcare of Russian Federation' order #200н from April, 01, 2016 "Approval of rules of good clinical practice and legal requirements of Russian Federation regulating circulation of medicines"

For US:

Appendix 1 Section 10.1.5 Data protection

In the United States, 21 CFR 312.62(c) and 21 CFR 812.140(d) require 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated;

or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified'.

10.7 Appendix 7: Abbreviations

6MWT	six-minute walking test
ACR	American College of Rheumatology
AE	adverse event
BMI	body mass index
CRF	case report form
CTR	clinical trial report
DFU	directions for use
DUN	dispensing unit number
eCRF	electronic case report form
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
GCP	Good Clinical Practice
GLP-1	glucose like peptide-1
$HbA1_c$	glycated haemoglobin
ICH	International Council for Harmonisation
IB	Investigator's Brochure
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
KL	Kellgren Lawrence
MEN2	multiple endocrine neoplasia type 2
MMRM	mixed model for repeated measures
MTC	medullary thyroid cancer
NRS	Numerical Rating Scale
OA	osteoarthritis
PGI-C	patient global impression of change
PGI-S	patient global impression of status

PRO	patient reported outcome
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
SF-36	Short Form (36) Health Survey
SUSAR	suspected unexpected serious adverse reaction
T2D	Type 2 Diabetes Mellitus
TMM	trial materials manual
WOCBP	woman of child bearing potential
WOMAC	Western Ontario McMasters Osteoarthritis Index

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9.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

.

Protocol

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

Substance name: semaglutide

Universal Trial Number: U1111-1246-5824

EudraCT Number: 2020-000204-11

IND Number:126,360

Trial phase: 3b

In the following, Novo Nordisk A/S and its affiliates will be stated as "Novo Nordisk".

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
Protocol version 3.0	21 April 2021	CA, CO, DK, FR, NO, RU, SA, ZA, ES, SE, US
Protocol version 2.0	23 Sep 2020	CA, CO, DK, FR, NO, RU, SA, ZA, ES, SE, US
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Protocol version 3.0 (21 April 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union[1] for the countries participating in the NN9536-4578 trial.

Overall rationale for preparing protocol, version 3.0:

The overall rationale for preparing protocol version 3.0 is 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 is to ensure interpretability of treatment effect. Furthermore, this version of the protocol includes an appendix to ensure subject safety and data integrity during COVID-19 and allows for co-participation in COVID-19 related trials.

Co-participation in other clinical trials is generally not allowed while participating in a Novo Nordisk trial. However, given the large societal impact of the COVID-19 pandemic, Novo Nordisk will allow for co-participation in trials with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions. For the current trial it has been evaluated that the safety profile of semaglutide is well established and based on current knowledge it is expected that co-participation in COVID-19 trials will not lead to unreasonable unforeseen risks for trial subjects. Exclusion criterion 25 and discontinuation criterion 5 regarding simultaneous participation in other trials has thus been amended, and changes have been made to registration of concomitant illness and handling of AEs.

Section # and name	**Description of change**	**Brief rationale**
Section 1.2 Flowchart	Addition of WOMAC assessments at V3, V5, V6, V8, V10, V12.	To have a more adequate frequency of time points for pain assessment to capture pain intensity change over the entire treatment course.
Section 1.2 Flowchart	PGI-S will not be assessed at V4 and V9.	Assessment removed as it will not be used in the analysis.
Section 1.2 Flowchart	PGI-C will not be assessed at V2, V4, and V9.	Assessment removed as it will not be used in the analysis.

Section 1.2 Flowchart	Addition of a pain and pain medication diary (training and review).	Daily pain scores are included as complementary evidence and permits averaging pain intensity by week to reduce the effect of daily variability. Recording pain medication enables a comparison of change in use of pain medication and grouping according to type of pain medication used.
Section 2.3 Benefit-risk assessment	Addition of risk of COVID-19 infection and overall neoplasms, and minor updates of text to reflect most recent data. Updated text on benefits.	To include the current risk of COVID-19 infection, overall neoplasms and allergic reactions as well as reflect the newest efficacy data in the benefit risk section.
Section 3.2 Primary, secondary and exploratory endpoint(s)	Addition and reorganisation of secondary and exploratory endpoints.	To include endpoints which reflect the data obtained in the pain and pain medication diary
Section 5.2 Exclusion criteria	Rephrased exclusion criteria 4 and 5.	Rephrased to avoid misinterpretation.
Section 5.2 Exclusion criteria	Amending the exclusion criterion 25, so that subjects are allowed to be included in the trial, while also participating in a COVID-19 trial.	To allow for simultaneous participation in current trial and a COVID-19 trial.
Section 6.5 Concomitant medication	Amending the use of a pain and pain medication diary and specifying that all pain medication is allowed.	Daily pain scores are included as complementary evidence and the use of pain medication will be used to analyse treatment effect in subjects grouped according to the pain medication they use.
Section 7.1 Discontinuation of trial treatment	Amending the discontinuation criterion 5, so that subjects are allowed to continue in the trial, while also participating in a COVID-19 trial.	To allow for simultaneous participation in current trial and a COVID-19 trial.
Section 8.1 Efficacy assessments	Rephrased the WOMAC description. Recall period is changed to 24-hours. Addition of a description of the pain and pain medication diary.	To have a more adequate pain outcome assessment recall period. The pain and pain medication diary is added to capture changes in pain and pain medication.
Section 8.2 Safety assessments	Inclusion of Cardiovascular Disorder and Procedure as part of the concomitant illness/medical history to be recorded in the eCRF.	To reflect the most updated eCRF.
Section 8.2 Safety assessments	Inclusion of COVID-19 as part of the concomitant illness/medical history to be recorded in the eCRF	When participation in a COVID-19 trial is allowed, the registration of any COVID-19 infections in the subjects is relevant.
Section 8.3 Adverse events and serious adverse events	Addition of COVID-19 related AEs to the list of AEs that the investigator is responsible for detecting, documenting, recording and following up on.	When participation in a COVID-19 trial is allowed, the handling of COVID-19 related AEs is relevant.
Section 9.4.2 Primary endpoint(s)	Addition of WOMAC pain score to be taken into account when imputing missing data.	To reflect both primary endpoints in the imputation.
Section 10.3.5 Reporting of SAEs	Inclusion of COVID-19 related AEs in the Figure 10-1 "Decision tree for determining the event type and the respective forms to complete with associated timelines".	When participation in a COVID-19 trial is allowed, the handling of COVID-19 related AEs is relevant to ensure alignment between Figure 10-1 and Section 8.3

Section 10.6 Appendix 6	Amending the appendix: Mitigations to ensure subject safety and data integrity during COVID-19	To have mitigations in place in case local restrictions due to a COVID-19 outbreak lead to lock-down of a site.
Section 10.7 Appendix 7	Deletion of country requirements for Russia	The text is included in the Agreement with sites.

Table of Contents

Page

1 Protocol summary

1.1 Synopsis

The prevalence of obesity has reached epidemic proportions in most countries around the world and the prevalence is still increasing at an alarming rate. The medical and societal impacts are extensive, and obesity is one of the most significant public health challenges worldwide[2-8].

Obesity is associated with an increased risk of a variety of complications, including osteoarthritis (OA), affects physical and mental health and reduces health-related quality of life[9-23].

With the increasing prevalence of obesity, the health issues related to knee OA will intensify with huge consequence for society and the individual patient. Due to the pivotal role of the knee in basic mobility and locomotion, knee OA is associated with significant impairments and limitations to basic activities of daily living. The physical disability of knee OA arising from pain and loss of functional capacity reduces health-related quality of life and increases the risk of further morbidity.

Rationale:

Weight loss is strongly recommended as a primary management strategy in subjects with knee OA and obesity[24]. However, no specific guidance on how to achieve this is given, and no widely available and feasible means to sustain weight loss in subjects with knee OA and obesity have been presented.

There is a clear association between obesity and knee OA with obesity being a major risk factor for the incidence and progression of OA, and negatively influences disease outcomes[25, 26].

In accordance, American College of Rheumatology (ACR) guidelines strongly recommend weight loss in subjects with knee OA and obesity as first line treatment[24].

A significant relationship between weight loss above 10% of body weight and improvement in pain and function has been demonstrated in subjects with knee OA and obesity[27,28, 29]. Pharmacotherapy may therefore serve as a valuable adjunct to lifestyle intervention for individuals with knee OA and obesity in order to achieve a sufficient and sustainable weight loss. In a recent phase 3a study (NN9536-4373) semaglutide s.c. 2.4 mg once-weekly led to a weight loss of 14.9% in subjects with overweight and obesity.

Objectives and endpoints:

Primary objective

To confirm superiority of semaglutide s.c. 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 OA in change from baseline to week 68 in body weight and knee OA-related pain.

Secondary objectives

To confirm superiority of semaglutide s.c. 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 OA in achieving body weight response criteria after 68 weeks from baseline as well as change from baseline to week 68 in knee OA-related and general physical function.

To compare the efficacy of semaglutide s.c. 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 OA in change from baseline to week 68 in waist circumference, knee OA-related stiffness, overall knee OA-related physical limitations, general health-related quality of life, and in use of analgesics.

Primary estimand

The primary estimand is the average treatment effect of semaglutide s.c. 2.4 mg once-weekly relative to semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity, in patients with obesity and knee OA, measured by change from baseline to week 68 in body weight and knee OA-related pain, regardless of adherence to randomised treatment, regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injection or opioid medication or medical marijuana) and regardless of compliance with washout period for pain medication (the latter only relevant in this context for knee OA-related pain) ("treatment policy" strategy).

Primary endpoints

Endpoint title	Time frame	Unit
Change in body weight	From baseline (week 0) to end of treatment (week 68)	%
Change in WOMAC pain score	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index

Confirmatory secondary endpoints

Endpoint title	Time frame	Unit
Achieving body weight reduction ≥5% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Achieving body weight reduction ≥10% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Change in WOMAC physical function score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 physical functioning score	From baseline (week 0) to end of treatment (week 68)	Score points

Overall design:

This is a 68-week, randomised, two-arm, double-blinded, multi-centre clinical trial comparing semaglutide s.c. 2.4 mg once-weekly with semaglutide placebo in subjects with moderate OA of one or both knees, pain due to knee OA, and obesity (BMI ≥30.0 kg/m^2).

Eligible subjects fulfilling all randomisation criteria at visit 2 will be randomised in a 2:1 manner to receive either semaglutide s.c. 2.4 mg or semaglutide placebo once-weekly as adjunct to a reduced-calorie diet and increased physical activity.

Key inclusion criteria:

- Male or female, age above or equal to 18 years at the time of signing informed consent
- Body Mass Index (BMI) ≥30.0 kg/m^2
- Clinical diagnosis of knee OA (American College of Rheumatology (ACR) criteria) with moderate radiographic changes (Kellgren-Lawrence (KL) grades 2 or 3 as per central

reading) in target knee. Target knee joint is defined as most symptomatic knee at screening. If pain in knees are equal target knee joint will be in the most dominant leg.

- Pain due to knee OA

Key exclusion criteria:

- Joint replacement in target knee
- Arthroscopy or injections into target knee within last 3 months prior to enrolment
- Any other joint disease in the target knee

Number of subjects:

Approximately 420 subjects will be screened to achieve 375 subjects randomly assigned to trial product.

Treatment groups and duration:

- The total trial duration for the individual subject will be approximately 76 weeks. The trial includes a screening period of approximately 2 weeks followed by randomisation. Dose escalation of semaglutide/semaglutide placebo will take place every 4 weeks during the first 16 weeks after randomisation. All subjects should aim at reaching the target dose of semaglutide 2.4 mg once-weekly. Following randomisation, visits are scheduled every 8th week until end-of-treatment (week 68). Follow-up period is 7 weeks after end-of-treatment.
- The following trial products will be supplied by Novo Nordisk A/S for the duration of the trial:
    - Semaglutide B 3.0 mg/mL PDS290 and semaglutide placebo, solution for injection, 3 mL PDS290 pre-filled injector

1.2 Flowchart

	Screening	Randomisation	Dose escalation period				Treatment period						End of treatment	End of trial
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Timing of Visit (Weeks)	-1	0	4	8	12	16	20	28	36	44	52	60	68	75
Visit Window (Days)	-7 to 0	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
SUBJECT RELATED INFORMATION AND ASSESSMENTS														
Informed Consent and Demography[a] (Appendix 1, Section 10.1)	X													
Eligibility Criteria (5.1)	X	X												
Randomisation Criteria & Randomisation (5.5)		X												
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History/Concomitant Illness (8.2 /6.5)	X													
Tobacco Use[b] (5.3.1)	X													
Childbearing Potential (Appendix 4, Section 10.4)	X													
Pregnancy Test[c] (8.3.5)	X	X		X		X	X	X	X	X	X	X	X	X
Knee Radiography (8.2.1)	X													
EFFICACY														
Body Measurements (8.1.2)														
Body Weight	X	X		X			X		X		X		X	
Height	X													
Waist Circumference		X		X			X		X		X		X	
Clinical Outcome Assessments														
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (8.1.1)		X	X	X	X	X	X	X	X	X	X	X	X	

	Screening	Randomisation	Dose escalation period				Treatment period						End of treatment	End of trial
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Timing of Visit (Weeks)	-1	0	4	8	12	16	20	28	36	44	52	60	68	75
Visit Window (Days)	-7 to 0	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Patient Global Impression of Status (PGI-S) Pain		X					X				X		X	
Patient Global Impression of Change (PGI-C) Pain							X				X		X	
Short Form 36 V2.0 acute (SF-36) (8.1.4)		X		X			X		X		X		X	
PGI-S Physical Function		X					X				X		X	
PGI-C Physical Function							X				X		X	
Six-Minute Walking Test (8.1.4)		X											X	
SAFETY														
Adverse Event (8.3)		X	X	X	X	X	X	X	X	X	X	X	X	X
Technical Complaint (8.3.9)			X	X	X	X	X	X	X	X	X	X	X	
Vital Signs (8.2.3)														
Systolic Blood Pressure	X	X	X		X		X		X		X		X	X
Diastolic Blood Pressure	X	X	X		X		X		X		X		X	X
Pulse	X	X	X		X		X		X		X		X	X
Physical Examination (8.2.2)	X												X	
Laboratory Assessments (Appendix 2, Section 10.2)														
Hemoglobin A1c ($HbA1_c$)	X													
TRIAL MATERIAL														
IWRS Session	X	X		X		X	X	X	X	X	X	X	X	
Administration of Trial Product (6.1)														

	Screening	Randomisation	Dose escalation period				Treatment period						End of treatment	End of trial
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Timing of Visit (Weeks)	-1	0	4	8	12	16	20	28	36	44	52	60	68	75
Visit Window (Days)	-7 to 0	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Dispensing Visit		X		X		X	X	X	X	X	X	X		
Drug Accountability		X		X		X	X	X	X	X	X	X	X	
REMINDERS														
Criteria for discontinuation (7.1)			X	X	X	X	X	X	X	X	X	X		
Barriers and motivation interview (8)	X													
Diet and physical activity counselling (6.1.2)		X	X	X	X	X	X	X	X	X	X	X	X	
Training in the use of the pain and pain medication diary	X													
Review of the pain and pain medication diary[d] (8.1.3)		X	X	X	X	X	X	X	X	X	X	X	X	
Hand out direction for use (6.1)		X												
Training in trial product, pen-handling		X	X	X	X	X	X							
Hand out dose reminder card (6.1)		X	X	X	X	X	X							
Hand out ID card	X													

[a] Demography consists of date of birth, sex, ethnicity, and race (according to local regulation).

[b] Smoking is defined as smoking at least one cigarette or equivalent daily.

[c] For all female subjects of child-bearing potential.

[d] The pain and pain medication diary should be filled in on a daily basis by the subject

2 Introduction

Knee osteoarthritis and obesity

The prevalence of obesity has reached epidemic proportions in most countries around the world and the prevalence is still increasing at an alarming rate. The medical and societal impacts are extensive, and obesity is one of the most significant public health challenges worldwide[2-8].

Obesity is associated with an increased risk of a variety of complications including osteoarthritis (OA), type 2 diabetes (T2D), dyslipidaemia, hypertension, cardiovascular disease, obstructive sleep apnoea, non-alcoholic fatty liver disease, urinary incontinence, several types of cancers, and increased mortality.[9-23]

The risk of obesity-related complications increases with increasing body mass index (BMI) and body weight loss has been shown to have significant health benefits on many obesity-related complications as well as physical symptoms and health-related quality of life[30-37]. Lifestyle intervention in the form of diet and exercise is first line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss[38-47].

With the increasing prevalence of obesity, the health issues related to knee OA will intensify with huge consequence for society and the individual patient. Obesity and the increased weight bearing are attributable to development and progressions of knee OA being a highly disabling degenerative joint disease[22, 25]. Due to the pivotal role of the knee in basic mobility and locomotion, knee OA is associated with significant impairments and limitations to basic activities of daily living. The physical disability of knee OA arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity[26].

Weight loss is associated with a reduced risk of knee OA progression and improvement in pain and function regardless of the extent of radiological changes and knee OA grading[27, 48, 49]. However, in the IDEA trial only a reduction in baseline body weight of above 10% significantly reduced pain and improved function in subjects with knee OA and obesity[27].

Based on a systematic literature review, the ACR guidelines strongly recommends as primary management strategy that subjects with knee OA and obesity lose weight and participate in physical activity programme commensurate with their ability to perform these activities[24]. Furthermore, as obesity is an additional limiting factor in participating in physical activity programmes, weight loss will have both direct and indirect positive effect on management strategy and symptom relief in knee OA.

2.1 Trial rationale

Weight loss is strongly recommended as a primary management strategy in subjects with knee OA and obesity[24]. However, no specific guidance on how to achieve this is given, and no widely available and feasible means to sustain weight loss in subjects with knee OA and obesity have been presented.

Subjects with knee OA and obesity show a very specific pathophysiological profile compared to the population with knee OA without obesity. Subjects with knee OA and obesity have decreased

quality of life, more pain and limited physical function compared to subjects with knee OA without obesity[24].

A reduction in baseline body weight loss above 10% significantly improves function and reduce pain in subjects with knee OA and obesity[27]. Semaglutide is a glucagon-like-peptide 1 (GLP-1) receptor agonist (RA) currently under development by Novo Nordisk A/S for weight management and treatment of obesity. Semaglutide is expected to provide a body weight loss of up to 10-15%[50].

The aim of the present trial is to investigate the effects of semaglutide s.c. 2.4 mg once-weekly on weight loss, knee OA-related pain and physical function, and health-related quality of life in a patient population with obesity and knee OA.

2.2 Background

2.2.1 Semaglutide

Semaglutide is a long-acting GLP-1 RA currently under development by Novo Nordisk A/S for weight management. Semaglutide has a half-life of approximately 160 hours, making it suitable for once-weekly dosing[51]. GLP-1 is a physiological regulator of appetite, and a postprandial GLP-1 response is present in several areas of the brain involved in appetite regulation[52].

Clinical[53-58] and non-clinical[58] data indicate that the body weight reducing effect of semaglutide is mainly mediated by a reduced energy intake.

A 52-week phase 2 dose-finding trial within weight management (NN9536-4153) has been completed. An overall monotone dose-dependent weight loss was observed across the 5 semaglutide doses tested (0.05 to 0.4 mg once-daily). The estimated weight loss at week 52 was 13.8% at the highest dose tested (0.4 mg once-daily) compared to the weight loss of 2.3% achieved by diet, exercise and placebo alone[50] . Based on results from this trial, a target dose of 2.4 mg of semaglutide s.c. once-weekly was used for the clinical phase 3a and 3b programme[50].

The 68-week phase 3a weight management trial, STEP 1 (NN9536-4373) has demonstrated clinical significant weight loss with semaglutide and is currently in the reporting phase. A total of 1,961 subjects were included in the trial: 1,306 randomised to semaglutide s.c. 2.4 mg once-weekly and 655 to placebo. At week 68, subjects in the semaglutide s.c. 2.4 mg once-weekly group achieved an average weight loss of 14.85% compared to 2.41% in the placebo group.

A comprehensive review of results from the non-clinical and clinical studies of semaglutide can be found in the current edition of the investigator's brochure (IB)[50] and any updates hereof.

2.3 Benefit-risk assessment

Main benefits and risks are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of semaglutide may be found in the IB[50] or any updates hereof.

2.3.1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Trial treatment(s)		
Gastrointestinal AE	Consistent with findings with other GLP-1 RAs, the most frequently reported adverse events (AE) in clinical trials with semaglutide were gastrointestinal AEs (such as nausea, vomiting and diarrhoea). In general, these reactions are mild or moderate in severity, of short duration, and dose dependent. In subjects treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating subjects with impaired renal function as it may cause a deterioration of renal function.	A low starting dose and dose escalation steps will be implemented to mitigate the risk of developing gastrointestinal symptoms. Subjects with GI symptoms are recommended to drink plenty of fluids to avoid volume depletion.
Cholelithiasis	Events of cholelithiasis were the most frequently reported gallbladder events in the clinical development programme for semaglutide 2.4 mg for weight management. In the phase 3a trials cholelithiasis was reported in 1.6% and led to cholecystitis in 0.6% of patients treated with semaglutide 2.4 mg.	If cholelithiasis is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion
Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 RA drug class. The frequency of adjudication-confirmed acute pancreatitis reported in phase 3a clinical trials was 0.2% for semaglutide 2.4 mg and <0.1% for placebo, respectively.	Subjects with a history of chronic pancreatitis or recent acute pancreatitis will not be enrolled in the trial. In addition, trial product should be discontinued in case of suspicion of acute pancreatitis in accordance to Section 7.1

Medullary thyroid cancer (MTC) (based on non-clinical data)	Proliferative thyroid C-cell changes were seen in the mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. No hyperplasia was observed in monkeys after 52 weeks exposure up to 13-fold above the clinical plasma exposure at 2.4 mg/week. In clinical trials with semaglutide, there have been no clinically relevant changes in calcitonin levels. The C-cell changes in rodents are mediated by the GLP-1 receptor, which is not expressed in the normal human thyroid. Accordingly, the risk of GLP-1 receptor-mediated C-cell changes in humans is considered to be low.	Exclusion criteria related to medical history of multiple endocrine neoplasia type 2 (MEN2) or MTC have been implemented~~.~~
Pancreatic cancer	There is currently no support from non-clinical studies, clinical trials or post-marketing data that GLP-1 RA based therapies increase the risk of pancreatic cancer, but pancreatic cancer has been classified as a potential class risk of GLP-1 RAs by European Medicines Agency.	Subjects with a history of malignant neoplasms within the past 5 years prior to screening will be excluded from the trial.
Allergic reactions	As is the case with all protein-based pharmaceuticals, treatment with semaglutide may evoke allergic reactions, including serious allergic reactions such as angioedema and anaphylactic reactions.	As a precaution, subjects with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this trial. In addition, subjects will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the trial product occurs.
Neoplasms (malignant and non-malignant)	Patients with overweight or obesity, have an increased risk of certain types of cancer. There is no evidence from clinical trials that GLP-1-based therapies increase the risk of neoplasms. However, in the semaglutide s.c. as well as oral semaglutide phase 3a trials for T2D, the proportion of subjects with neoplasms (malignant and non-malignant) were slightly higher with semaglutide than with comparator. The number of subjects exposed to semaglutide s.c. or oral semaglutide for a longer period is considered insufficient for a thorough assessment of the risk of neoplasms.	Subjects with a history of malignant neoplasms within the past 5 years prior to screening will not be enrolled in this trial. Basal and squamous cell skin cancer and any carcinoma in-situ is allowed

Risk of COVID-19 infection in relation to participation in study	Available data does not suggest an increased risk of infection or a more severe progression of infection when treated with semaglutide.	Detailed information about the known risks for semaglutide can be found in the investigator's brochure.
Trial procedures		
Pain analgesics washout period	There is a potential risk of increased pain	Washout period is short in duration. Use of rescue medication (acetaminophen) is allowed during wash out until 24 hours before visit
Risk of COVID-19 infection in relation to participation in study	Patients may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country	The risk of COVID-19 transmission in relation to site visits is overall considered to be low, however this may vary between geographical areas. To minimize the risk as much as possible, the following measures have been taken: Cautious patient recruitment planning ensures controlled patient enrolment in countries where the COVID-19 pandemic is evaluated to be sufficiently under control, and at sites where health care resources are evaluated to be adequate Study procedures including the number and frequency of study procedures and assessments have already during the protocol development been evaluated to limit the number of on-site visits. Additionally, we allow subjects that are treatment discontinued to convert on-site visits to phone (see Section 7.1). Physical contact between subjects and site staff will be limited to the extent possible, and protective measures will be implemented according to local practice. Appendix 6 (Section 10.6) includes mitigations that can be implemented to ensure subject safety and data integrity in case a COVID-19 outbreak leads to lock-down of sites which affects the ability to perform trial related procedures.
Other		
Pregnancy and fertility (based on non-clinical data)	Studies in animals have shown reproductive toxicity. There is limited data from the use of semaglutide in pregnant women.	Semaglutide should not be used during pregnancy. Exclusion and discontinuation criteria related to pregnancy have been implemented.

AE, adverse events; GLP-1 RA, Glucagon-like-peptide-1 receptor agonist; MTC, medullary thyroid cancer; MEN2, multiple endocrine neoplasia type 2

2.3.2 Benefit assessment

Subjects will be treated with a regimen anticipated to be better than or equal to the weight management they receive at the time of entry into the trial. The 68-week phase 3a weight

management trials, STEP 1 (NN9536-4373), have demonstrated clinically significant weight loss with semaglutide s.c. 2.4 mg once-weekly. Semaglutide s.c. 2.4 mg once-weekly was overall well-tolerated, and the safety and tolerability profile was consistent with other GLP-1 RAs.

In addition, it is expected that subjects will benefit from participation through close contact with the trial site and counselling by a dietician or a similar qualified healthcare professional, all of which will most likely result in intensified weight management. In addition, subjects will benefit from physical activity counselling and from improved physical function and knee pain reduction with body weight lowering. It is anticipated that all subjects will benefit from participation, but the effect will be greater in subjects randomised to semaglutide compared to placebo.

2.3.3 Overall benefit-risk conclusion

Necessary precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks (including the risk of transmission of infectious diseases such as COVID-19) and inconveniences of participation in the trial. The safety profile for semaglutide generated from the clinical and non-clinical development programmes has not revealed any safety issues that would prohibit administration of semaglutide s.c. 2.4 mg once-weekly. Results from four phase 3a trials with semaglutide s.c. 2.4 mg once-weekly (NN9536-4373, -4374, -4375 and -4376) have demonstrated that semaglutide s.c. 2.4 mg once-weekly can provide a clinically meaningful weight loss. The anticipated benefits from diet and physical activity counselling will include all subjects participating in this trial.

Taking into account the measures taken to minimise risk to subjects participating in this trial, the potential risks identified in association with semaglutide are justified by the anticipated benefits that may be afforded to subjects with obesity and knee OA.

3 Objectives and endpoints

3.1 Primary, secondary and exploratory objective(s) and estimand(s)

Primary objectives

To confirm superiority of semaglutide s.c. 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 OA in change from baseline to week 68 in body weight and knee OA-related pain.

Secondary objectives

To confirm superiority of semaglutide s.c. 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 OA in achieving body weight response criteria after 68 weeks from baseline as well as change from baseline to week 68 in knee OA-related and general physical function.

To compare the efficacy of semaglutide s.c. 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 OA in change from baseline to week 68 in waist circumference, knee OA-related stiffness, overall knee OA-related physical limitations, general health-related quality of life, and in use of analgesics.

Exploratory objectives

To compare the efficacy of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo as adjunct to a reduced-calorie diet and increased physical activity in subjects with obesity and knee OA in change from baseline to week 68 in selected SF-36 domain scores and on walking distance.

Primary estimand

The primary clinical question of interest is: what is the average treatment effect of semaglutide s.c. 2.4 mg once-weekly relative to semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity, in patients with obesity and knee OA, measured by change from baseline to week 68 in body weight and knee OA-related pain, regardless of adherence to randomised treatment, regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injection or opioid medication or medical marijuana) and regardless of compliance with washout period for pain medication (the latter only relevant in this context for knee OA-related pain) (“treatment policy” strategy).

The estimand is described by the following attributes (according to ICH E9(R1)):

- Treatment condition: The randomised treatment regardless of adherence or initiation of other anti-obesity therapies (as defined above) or other knee OA interventions (as defined above)
- Population: Patients with obesity and knee OA
- Endpoints: The two primary endpoints relative change in body weight and change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score both from baseline to week 68
- Remaining intercurrent events: The intercurrent events “treatment discontinuation for any reason”, “initiation of other anti-obesity therapies” and “initiation of other knee OA

interventions" are addressed by the treatment condition attribute. The remaining intercurrent event is "compliance with washout period for pain medication" (in general only applicable to WOMAC endpoints), which is handled by the treatment policy strategy.
- Population-level summary: Difference in mean changes between treatment conditions

A similar estimand applies to all secondary endpoints (confirmatory and supportive), which is called secondary estimand. The population-level summary for body weight response endpoints is the ratio of odds between treatment conditions.

Rationale for estimand: The primary (and secondary) estimand was requested by different regulatory authorities and it aims at reflecting how patients with obesity are treated in clinical practice.

Additional estimand

An additional clinical question of interest is: what is the average treatment effect of semaglutide s.c. 2.4 mg once-weekly relative to semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity, in patients with obesity and knee OA, measured by change from baseline to week 68 in body weight and knee OA-related pain, had they remained on their randomised treatment for the entire planned duration of the trial, not initiated other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injection or opioid medication or medical marijuana) and had they additionally complied with the washout period for pain medication (the latter only relevant in this context for knee OA-related pain) ("hypothetical" strategy).

The estimand is described by the following attributes (according to ICH E9(R1)):
- Treatment condition: The randomised treatment if patients had adhered for the entire duration of the trial, not initiated other anti-obesity therapies (as defined above) or other knee OA interventions (as defined above)
- Population: Patients with obesity and knee OA
- Endpoints: The two primary endpoints relative change in body weight and change in WOMAC pain score both from baseline to week 68
- Remaining intercurrent events: The intercurrent events "treatment discontinuation for any reason", "initiation of other anti-obesity therapies" and "initiation of other knee OA interventions" are addressed by the treatment condition attribute. The remaining intercurrent event is "compliance with washout period for pain medication" (in general only applicable to WOMAC endpoints), which is handled by the hypothetical strategy.
- Population-level summary: Difference in mean changes between treatment conditions

A similar additional estimand also applies to all secondary body weight endpoints as well as all secondary WOMAC endpoints (both confirmatory and supportive). The population-level summary for body weight response endpoints is the ratio of odds between treatment conditions.

Rationale for estimand: The additional estimand was requested by few regulatory authorities and aims at reflecting the treatment effect in the absence of intercurrent events.

3.2 Primary, secondary and exploratory endpoint(s)

3.2.1 Primary endpoints

Endpoint title	Time frame	Unit
Change in body weight	From baseline (week 0) to end of treatment (week 68)	%
Change in WOMAC pain score	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index

3.2.2 Secondary endpoints

The confirmatory and supportive secondary endpoints addressing the primary and secondary objectives are listed in Sections 3.2.2.1 and 3.2.2.2.

3.2.2.1 Confirmatory secondary endpoints

Endpoint title	Time frame	Unit
Achieving body weight reduction ≥5% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Achieving body weight reduction ≥10% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Change in WOMAC physical function score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 physical functioning score	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index, SF-36; Short Form (36) Health Survey

3.2.2.2 Supportive secondary endpoints

Endpoint title	Time frame	Unit
Change in waist circumference	From baseline (week 0) to end of treatment (week 68)	cm
Change in WOMAC stiffness score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in WOMAC total score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 bodily pain score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 physical component summary	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 mental component summary	From baseline (week 0) to end of treatment (week 68)	Score points
Use of allowed rescue analgesics during wash out	From baseline (week 0) to end of treatment (week 68)	Count of subjects
Amount of allowed rescue analgesics used during wash out	From baseline (week 0) to end of treatment (week 68)	Dose
Change in pain medication	From baseline (week 0) to end of treatment (week 68)	Dose
Change in pain intensity (NRS)	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index, SF-36; Short Form (36) Health Survey

3.2.3 Exploratory endpoint(s)

Endpoint title	Time frame	Unit
Change in 6 minutes walking distance	From baseline (week 0) to end of treatment (week 68)	Meters
Change in SF-36 role-physical score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 general health score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 vitality score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 social functioning score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 role-emotional score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 mental health score	From baseline (week 0) to end of treatment (week 68)	Score points

4 Trial design

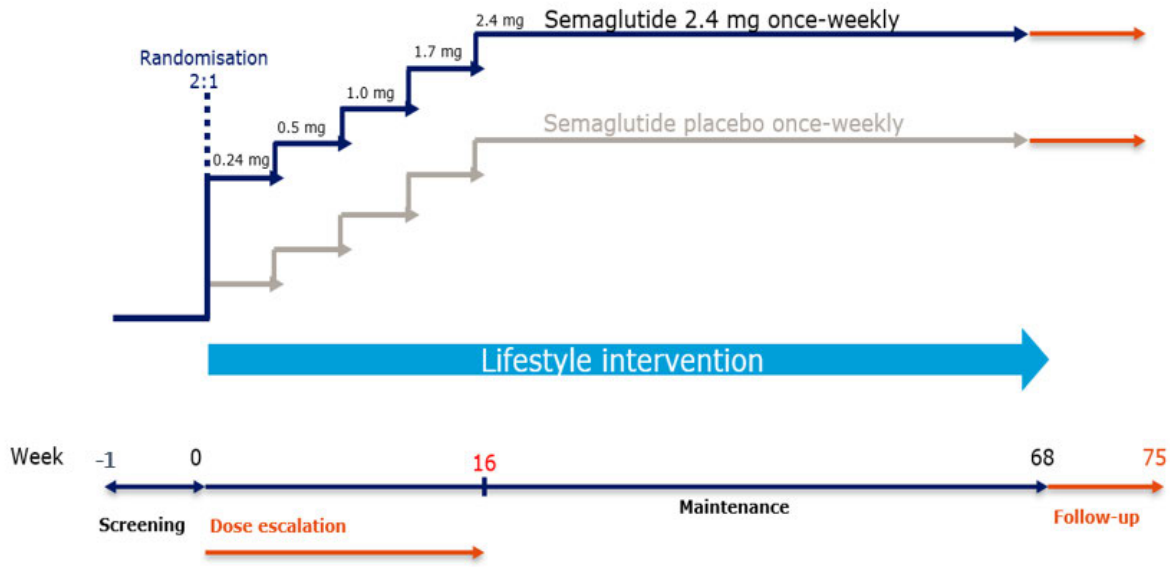
This trial is designed to evaluate weight loss and knee OA-related outcomes and will apply a targeted approach to collection of safety data focusing on serious adverse events (SAEs), adverse events (AEs) leading to discontinuation of trial product and other selected AEs. An adequate characterisation of the less serious and more common AEs is evaluated in the phase 3a trials (Section 2.2.1).

4.1 Overall design

This is a 68-week, randomised, two-arm, double-blinded, multi-centre clinical trial comparing semaglutide s.c. 2.4 mg once-weekly with semaglutide placebo in subjects with moderate OA of one or both knees, pain due to knee OA, and obesity (BMI ≥30.0 kg/m^2).

Eligible subjects will be randomised in a 2:1 manner to receive either semaglutide s.c. 2.4 mg once-weekly or semaglutide placebo once-weekly as adjunct to a reduced-calorie diet and increased physical activity (Figure 4-1).

The trial includes a screening visit to assess the subject's eligibility followed by visits every 8th week until end-of-treatment (week 68). Follow-up period is 7 weeks after end-of-treatment (week 75).



mg; milligram

Figure 4-1 A schematic diagram of the trial design

4.2 Scientific rationale for trial design

The trial population will consist of subjects with obesity (≥ BMI 30.0 kg/m^2) and knee OA ((primary knee OA according to the ACR criteria), ≥ 40 point in the WOMAC pain subscale, and radiological KL grade 2 or 3)[59]. The trial population is chosen to optimise the likelihood of achieving a clinical benefit with weight loss (reduction in knee OA-related pain and improved physical function) by including subjects with a clear medical need (obesity and knee OA). Although

T2D is prevalent in the obesity population, it has been decided to exclude this group of subjects from the trial in order to get a homogenous study population.

The treatment duration of the trial is 68 weeks with an additional 7 weeks follow-up (without treatment). A 68-week treatment duration (including 52 weeks on target dose) is considered sufficient to realise the weight loss potential of the intervention as well as downstream effects on symptoms and function related to knee OA. The 7 weeks follow-up period is included to account for the exposure and long half-life of semaglutide.

A randomised, double-blinded, placebo-controlled, multi-centre trial design is chosen to minimise bias in the assessment of the effect and safety of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo, as an adjunct to a reduced calorie diet and increased physical activity.

In accordance with guideline for Clinical investigation of medicinal products used in the treatment of OA by the European Medicines Agency (EMA) pain medication required during the trial period is discontinued 72 hours in advance of assessment of symptomatic endpoints to avoid confounding effects[60]. During the washout rescue medication with acetaminophen is allowed as analgesic until 24 hours before visit if needed.

4.3 Justification for dose

Results from the phase 2 dose-finding trial for semaglutide in weight management (NN9536-4153) showed that the semaglutide s.c. 0.4 mg once-daily dose was most effective in terms of weight loss while displaying an acceptable tolerability profile. Using population pharmacokinetic modelling, it was estimated that a once-weekly maintenance dose of semaglutide s.c. 2.4 mg will result in similar C_{max} at steady-state as that obtained by the once-daily 0.4 mg semaglutide dose in trial NN9536-4153.

A maintenance dose of semaglutide s.c. 2.4 mg once-weekly was chosen for the phase 3 weight management development programme. The once-weekly dosing is anticipated to ease the burden of drug administration in clinical practice. Subjects will be initiated at a once-weekly dose of 0.24 mg and follow a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), until the target dose is reached after 16 weeks.

It is well known that to mitigate gastrointestinal side effects with GLP-1 RA treatment, dose escalation to the target dose is required. Based on experience from the semaglutide T2D development programme, a fixed dose escalation regimen was selected, with dose escalation every 4 weeks until the target dose is reached.

4.4 End of trial definition

The end of trial is defined as the date of the last visit of the last subject in the trial globally.

5 Trial population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Subjects are eligible to be included in the trial only if all of the following criteria apply:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male or female, age above or equal to 18 years at the time of signing informed consent
3. Body Mass Index (BMI) ≥30.0 kg/m^2
4. Clinical diagnosis of knee OA (ACR criteria) with moderate radiographic changes (KL grades 2 or 3 as per central reading) in target knee. Target knee joint is defined as most symptomatic knee at screening. If pain in knees are equal target knee joint will be in the most dominant leg.
5. Pain due to knee OA (Section 5.5.1)
6. Willingness to complete 72-hour washout period of analgesics before all visits involving WOMAC questionnaire (acetaminophen is allowed as rescue medication).

5.2 Exclusion criteria

Subjects are excluded from the trial if any of the following criteria apply:

Knee OA-related:

1. Joint replacement in target knee
2. Arthroscopy or injections into target knee within the last 3 months prior to enrolment
3. Elective surgery scheduled during the trial duration period, except for minor surgical procedures
4. Any other joint disease in the target knee
5. Current use of medical marijuana or opioids
6. Symptomatic hip OA unless treated with hip replacement
7. Primary localisation of pain is not within target knee
8. Chronic widespread pain, including neuropathic pain

Obesity-related:

9. Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device, except for: (1) liposuction and/or abdominoplasty, if performed > 1 year before screening, (2) lap banding, if the band has been removed >1 year before screening, (3) intragastric balloon, if the balloon has been removed >1 year before screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year before screening.
10. A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records
11. Uncontrolled thyroid disease
12. Treatment with any medication for the indication of obesity within the past 90 days before screening

Glycemia-related:

13. $HbA_{1c} \geq 48$ mmol/mol (6.5%) as measured by local laboratory at screening
14. History or presence of type 1 or type 2 diabetes (history of gestational diabetes is allowed)
15. Treatment with any GLP-1 RA within 90 days prior to the day of screening

General health and safety:

16. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
17. Presence of acute pancreatitis within the last 180 days prior to screening
18. History or presence of chronic pancreatitis
19. End-stage renal disease or chronic or intermittent haemodialysis or peritoneal dialysis
20. Presence or history of malignant neoplasm within 5 years prior to the day of screening. Basal and squamous cell cancer and any carcinoma in-situ are allowed
21. Any of the following in the past 60 days prior to screening: myocardial infarction, stroke, hospitalisation for unstable angina or transient ischaemic attack
22. Subjects presently classified with heart failure New York Heart Association: Class IV
23. Known or suspected hypersensitivity to trial product(s) or related products
24. Previous participation in this trial. Participation is defined as signed informed consent
25. Participation in another clinical trial within 90 days before screening[a]
26. Other subject(s) from the same household participating in any semaglutide trial
27. Female who is pregnant, breast feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method (highly effective contraceptive measures as required by local regulation or practice)
28. History of major depressive disorder within 2 years before screening
29. Diagnosis of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder)
30. History of a suicide attempt
31. Suicidal behaviour within 30 days before screening
32. Known or suspected abuse of alcohol or recreational drugs
33. Any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the subject's safety or compliance with the protocol

[a] Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening.

The criteria will be assessed at the investigator's discretion unless otherwise stated.

For country specific requirements, see Appendix 7 (Section 10.7) and for contraceptive requirements, see Appendix 4 (Section 10.4).

5.3 Lifestyle considerations

To ensure alignment regarding performance of assessments across subjects and trial sites, the below restrictions apply.

5.3.1 Caffeine and tobacco

Subject should avoid caffeine and smoking at least 30 minutes prior to measuring their blood pressure.

5.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, eligibility criteria, and any SAEs. A screen failure session must be made in the interactive web response system (IWRS).

Individuals who do not meet the criteria for participation in this trial may not be rescreened. If the subject has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to the laboratory parameter, re-sampling is not allowed. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters. If the subject has failed inclusion criteria no. 4 due to incorrect position of the knee during the radiographic examination a reassessment is allowed.

5.5 Randomisation criteria

First dose must only be administered after assessments related to primary and secondary endpoints are completed.

5.5.1 Randomisation criteria

1. A score of at least 40 on the WOMAC version 3.1 pain subscale (range 0-100 normalised Numerical Rating Scale (NRS))
2. For subjects taking analgesics, attend randomisation visit after 72-hour washout period (rescue medication with acetaminophen allowed until 24 hours before visit) (Section 8.1.1)

To be randomised, all relevant randomisation criteria must be answered "yes".

A subject not fulfilling the randomisation criteria will be considered a randomisation failure, see Section 5.4 regarding screen failures.

6 Treatments

6.1 Treatments administered

- All trial products listed in Table 6-1 are considered investigational medicinal products (IMP).
- Trial product must only be used, if it appears clear and colourless.

Table 6-1 Investigational medicinal product provided by Novo Nordisk A/S

Trial product name:	Semaglutide B 3.0 mg/mL PDS290	Semaglutide Placebo
Dosage form	Solution for injection	Solution for injection
Route of administration	Subcutaneous	Subcutaneous
Dosing instruction:	Once-weekly	Once-weekly
Delivery device	3 mL PDS290 pre-filled pen-injector	3 mL PDS290 pre-filled pen-injector

- Dose escalation of semaglutide/semaglutide placebo should take place during the first 16 weeks after randomisation as described in Table 6-2. All subjects should aim at reaching the recommended target dose of 2.4 mg semaglutide s.c. once-weekly or the corresponding volume of semaglutide placebo.
- If a subject does not tolerate the recommended target dose of 2.4 mg once-weekly, the subject may stay at a lower dose level of 1.7 mg semaglutide s.c. once-weekly. This should only be allowed if the subject would otherwise discontinue trial product completely and if considered safe to continue trial product, as per the investigator's discretion. It is recommended that the subject makes at least one attempt to re-escalate to the recommended target dose of 2.4 mg semaglutide s.c. once-weekly, as per the investigator's discretion.
- It is recommended that the investigator consults Novo Nordisk in case of persistent deviations from the planned escalation regimen.
- The investigator must document that directions for use are given to the subject verbally and in writing at the first dispensing visit (as specified in the flowchart).
- A dose reminder card will be handed out to the subjects at each site visit during the dose escalation period. This is to remind the subjects of the dose to be taken until next site visit and provide a conversion of the dose to value shown in the dose counter. Once the target dose has been reached, the dose reminder card is only handed out as needed.

Table 6-2 Dose escalation and maintenance of semaglutide s.c. 2.4 mg /semaglutide placebo once-weekly

Trial product name	Dose	Value shown in dose counter	Duration
Dose escalation period			
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	0.24 mg	8*	4 weeks
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	0.5 mg	17*	4 weeks
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	1.0 mg	34*	4 weeks
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	1.7 mg	57*	4 weeks
Maintenance period			
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	2.4 mg	80*	52 weeks

*Conversion to dose is calculated based on 0.01 ml/value

- Subjects will be instructed to inject semaglutide/semaglutide placebo once-weekly at the same day of the week (to the extent possible) throughout the trial.
- Injections may be administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals.
- If a single dose of trial product is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 2 days (48 hours). If a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the subject should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week.
- If ≥ 2 consecutive doses of trial product are missed, the subject should be encouraged to recommence the treatment if considered safe as per the investigator's discretion and if the subject does not meet any of the discontinuation criteria (Section 7.1). The trial product should be continued as early as the situation allows. The missed doses should not affect the scheduled dosing day of the week. The start dose for re-initiation of trial product is at the investigator's discretion. In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk global medical expert.

Auxiliary supplies

- Auxiliary supplies will be provided in accordance with the trial materials manual (TMM) please see Table 6-3.

Table 6-3 Auxiliary supplies provided by Novo Nordisk A/S

Auxiliary supply	Details
Needles	Needles for pre-filled pen system. Details provided in the TMM Only needles provided and approved by Novo Nordisk must be used for administration of trial product.
Directions for use (DFU)	DFU for 3 ml PDS290 pre-filled pen-injector. Not included in the dispensing unit and to be handed out separately.

6.1.1 Medical devices

Information about the PDS290 pre-filled pen-injector may be found in the IB[50] and any updates hereof.

Information about the use of the PDS290 pre-filled pen-injector for semaglutide 3.0 mg/mL and semaglutide placebo can be found in the DFU.

Training in the PDS290 pre-filled pen-injector

The investigator must document that training in the DFU has been given to the subjects verbally and in writing at the first dispensing visit. Training must be repeated, during the trial at regular intervals in order to ensure correct use of the medical device. Training is the responsibility of the investigator or a delegate.

6.1.2 Diet and Physical Activity counselling

All subjects in both treatment arms will receive counselling with regards to reduced calorie diet and physical activity taking subjects knee OA into consideration. Counselling should be done by a dietician or a similar qualified healthcare professional

6.1.2.1 Non-investigational medical device(s)

Non-investigational medical devices are listed in Section 6.1 as auxiliary supplies.

6.2 Preparation/handling/storage/accountability

Only subjects randomised to treatment may use trial product and only delegated site staff may supply or administer trial product.

Table 6-4 Trial product storage conditions

Trial product name	Storage conditions (not-in-use)	In-use conditions	In-use time
Semaglutide B 3.0 mg/mL PDS290	Store in refrigerator (2°C-8°C/36°F-46°F) Do not freeze Protect from light	In-use conditions will be available on the trial product label	In-use time[a] will be available on the trial product label
Semaglutide placebo			

[a]In-use time starts when the product is taken out of the refrigerator in the subject's home

- Each site will be supplied with enough trial products for the trial on an ongoing basis. Trial product will be distributed to the sites according to screening and randomisation.
- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the TMM.
- The investigator or designee is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- The investigator or designee must instruct the subject in what to return at next visit.
- Drug accountability should be performed on a pen level and must be documented in the IWRS.
- The subject must return all used, partly used and unused trial product including empty packaging materials during the trial as instructed by the investigator.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- All returned, un-used, expired or damaged trial products (for technical complaint samples, see Section 10.5) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the site.

6.2.1 Shipment of trial product to subject's home

For selected countries and if permitted by local regulations, the investigator may offer to send trial product and auxiliaries from the trial site or pharmacy to the subject's home by courier service.

The process for sending trial product from the trial site or pharmacy to a subject's home is described in the "Trial site/pharmacy instruction for shipment of trial product to patients' homes" document. The document contains detailed instructions for preparing packaging and setting up the pick-up of trial product, handover of trial product from the trial site or pharmacy staff to the courier, required temperature monitoring of trial product, delivery to and receipt of trial product by the patient. The process for returning trial product to the trial site or pharmacy by courier is also described in this document.

Investigators, trial site/pharmacy staff and patients who will be involved in shipment of trial product to the subject's home will be adequately trained in this process.

6.3 Measures to minimise bias: Randomisation and blinding

Randomisation

- All subjects will be centrally screened and randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed at the trial visits summarised in the flowchart.

Blinding

- The active drug and placebo are visually identical for the following trial products:
  - Semaglutide B 3.0 mg/mL PDS290/Semaglutide placebo
- The IWRS is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subjects' treatment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Novo Nordisk prior to unblinding a subjects' treatment unless this could delay emergency treatment of the subject. If a subject's treatment is unblinded, Novo Nordisk (Global Safety department) must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation. The person breaking the blind must print the "code break confirmation" notification generated by the IWRS, sign and date the document. If IWRS is not accessible at the time of the blind break, the IWRS helpdesk should be contacted. Contact details are listed in Attachment 1. The subject will continue on trial product.

6.4 Treatment compliance

Drug treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to encourage subject compliance.

When subjects self-administer trial product(s) at home, compliance with trial product administration will be assessed and the assessment documented in source documents at each visit where information is available. If any suspicion of non-compliance arises, the site must enter into a dialogue with the subject, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Treatment compliance of trial product will be assessed by asking the subject about missed doses and current treatment dose at every visit. Information on treatment dose and periods > 14 days without treatment will be recorded in the case report form (CRF).

6.5 Concomitant medication

Any medication other than the trial product that the subject is receiving at the time of the first visit or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates

- For analgesics, subjects must record dose and frequency in the pain medication diary provided

During the trial subjects should not initiate any anti-obesity treatment (e.g. medication) which is not part of the trial procedures. If such treatment is initiated, the subject should be instructed to stop the anti-obesity treatment.

All pain medications are allowed during the trial, except for the use of opioids and medical marijuana at inclusion (Section 5.2). Initiation of opioids is discouraged during the trial. If such treatment is initiated, the subject should be instructed to stop the opioid treatment, and all other options must be tried before starting opioid medication. During the washout period (24 – 72 h before visits), subjects should not use any pain medication, with the exception of acetaminophen, and should not use any pain medication <24 h before visits.

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 8.3.

6.5.1 Rescue medication

During the washout period, use of acetaminophen for rescue medication (maximum of 4 g/day) is allowed until 24 hours before visit. Use of acetaminophen (dose and frequency) has to be recorded by the subjects in the pain medication diary.

Rescue medication will not be supplied or reimbursed by Novo Nordisk.

6.6 Dose modification

Not applicable for this trial. Please refer to Section 6.1 for description of missed dose(s).

6.7 Treatment after end of trial

- There is no treatment following the end of trial.
- When discontinuing trial products, the subject should be transferred to a suitable marketed product at the discretion of the investigator.

7 Discontinuation of trial treatment and subject discontinuation/withdrawal

Treatment of a subject may be discontinued at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Efforts must be made to have subjects, who discontinue trial product, to continue in the trial. Subjects must be educated about the continued scientific importance of their data, even if they discontinue trial product. Only subjects who withdraw consent will be considered as withdrawn from the trial.

7.1 Discontinuation of trial treatment

- Discontinuation of treatment can be decided by both the investigator and the subject.
- Subjects who discontinue trial product should continue with the scheduled visits and assessments to ensure continued counselling and data collection.
    - If the subject does not wish to attend the scheduled clinic visits efforts should be made to have the visits converted to phone contacts. However, all effort should be made to have the subject attend at least the ‘end of treatment’ clinic visit containing the final data collection of primary and confirmatory secondary efficacy endpoints, and the ‘end of trial’ visit.
- The 'end of trial' visit is scheduled approximately 7 weeks after the final data collection, to ensure the safety of the subject. If the subject has discontinued trial product > 7 weeks prior to the 'end of treatment' visit, and the requirements for the follow-up period prior to the 'end of trial' visit is fulfilled, then 'end of trial' visit can be performed in combination with 'end of treatment' visit.
    - If the subject refuses to attend the ‘end of treatment’ and/or ‘end of trial’ visit, information about the attempts to follow up with the subject must be documented in the subject’s medical record.

The trial product must be discontinued, if any of the following applies for the subject:

1. Safety concern as judged by the investigator
2. Suspicion of acute pancreatitis
3. Pregnancy
4. Intention of becoming pregnant
5. Simultaneous use of an approved or non-approved IMP in another clinical trial[a]

[a] Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator’s discretion without discontinuing trial product.

If acute pancreatitis is suspected appropriate actions should be initiated, including local measurements of amylase and lipase (see Appendix 3 (Section 10.3) for reporting).

Subjects meeting discontinuation of trial product criterion no. 2 are allowed to resume trial product if the Atlanta criteria[61] are not fulfilled and thus, the suspicion of acute pancreatitis is not confirmed, at the discretion of the investigator. Trial product may be resumed for subjects with a gallstone-induced pancreatitis in case of cholecystectomy.

Subjects meeting discontinuation of trial product criteria no. 1, 3 and 4 are allowed to resume trial product, if the criteria are no longer met (Section 7.1.1).

The primary reason for discontinuation of trial product must be specified in the end-of-treatment-form in the CRF, and final drug accountability must be performed. A treatment discontinuation status session must be made in the IWRS to indicate discontinuation of trial product.

7.1.1 Temporary discontinuation of trial treatment

If a subject has discontinued trial product due to temporary safety concern not related to trial product and is allowed to resume, the subject should follow the guide for missed doses (Section 6.1). Similarly, a subject who discontinues trial product on their own initiative should be encouraged to resume trial product (Section 6.1).

If a 'treatment' status session previously has been made in IWRS to indicate discontinuation of trial product, a new 'treatment status' session must be made to resume trial product.

7.1.2 Rescue criteria

Refer to Section 6.5.1 for description of rescue medication.

7.2 Subject discontinuation/withdrawal from the trial

A subject may withdraw consent at any time at his/her own request.

If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to the 'end of treatment' visit. See the flowchart for data to be collected.

Final drug accountability must be performed even if the subject is not able to come to the site. A treatment discontinuation status session must be made in the IWRS to indicate discontinuation of trial product.

If the subject withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the medical record.

Although a subject is not obliged to give his/her reason(s) for withdrawing, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the end of trial form in the CRF.

7.2.1 Replacement of subjects

Subjects who discontinue trial product or withdraw from trial will not be replaced.

7.3 Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the site.

The following actions must be taken if a subject fails to return to the site for a required visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial with a primary reason of ‘lost to follow-up’.

8 Trial assessments and procedures

- The following sections describe the assessments and procedures, while their timing is summarised in the flowchart.
- Informed consent must be obtained before any trial-related activity, see Section 10.1.3.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all inclusion criteria and none of the exclusion criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant site staff that can be contacted in case of emergency.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- Assessments should be carried out according to the clinic's standard of practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments.
- Source data of clinical assessments performed and recorded in the CRF must be available and will usually be the subject's medical records. Additional recording to be considered source data includes, but is not limited to laboratory reports, clinical outcome assessments.
- The barriers and motivation interview identify barriers to and motivation for lifestyle change and compliance with the protocol. The interview must be conducted at screening to assist in identifying subjects who are unable or unwilling to comply with protocol procedures as per the exclusion criteria. In addition, the interview will ensure that any minor barriers are addressed during lifestyle counselling.
    - The results of the interview will not be entered into the CRF. It will be at the investigator's discretion to evaluate the motivation of the subject and related eligibility.
- Subject's weight history must be recorded in the subject's medical record.
- Review of pain and pain medication diary, patient reported outcome (PRO) instruments, laboratory report etc. must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the PRO instruments is needed, the subject must be questioned, and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 (Section 10.2) for further details on laboratory samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart.

8.1.1 Western Ontario and McMaster Universities Osteoarthritis Index

Subjects should be given the opportunity to complete the questionnaire by themselves without interruption. The questionnaire takes approximately 5-10 minutes to complete[62].

- The WOMAC Osteoarthritis Index is a tri-dimensional, disease-specific, patient-reported outcome (PRO) measure[63]. It probes clinically-important, patient-relevant symptoms in the area of pain, stiffness and physical function in patients with osteoarthritis of the hip and/or knee. The index consists of 24 questions (5 pain, 2 stiffness, 17 physical function).
- The version used is the WOMAC 3.1 NRS version, an 11-point numeric rating scale with responses ranging from no symptom/difficulty (0) to extreme symptom/difficulty (10). The version used has a 24-hour recall period.
- Subscale scores for pain, stiffness and physical function and a total score will be calculated according to the guidelines provided in the WOMAC user manual.
- For subjects taking analgesics, no analgesics with exception of acetaminophen until 24 hours before visit, may be taken 72-hours prior to completing the questionnaires allowing for 72-hour washout.
- WOMAC questionnaire will relate to target knee joint defined as most symptomatic knee at screening. If pain in knees are equal target knee joint will be in the most dominant leg.

8.1.2 Body measurements

- Body weight should be measured without shoes, on an empty bladder and only wearing light clothing. It should be measured on a digital scale and recorded in kilograms or pounds (one decimal) using the same scale throughout the trial.
- The scale must be calibrated yearly as a minimum.
- Height is measured without shoes in centimetres or inches (one decimal). BMI will be calculated by the CRF from screening data and must agree with inclusion criterion no. 3.
- Waist circumference is defined as:
    - abdominal circumference located midway between the lower rib margin and the iliac crest
    - Measures must be obtained in a standing position with a non-stretchable measuring tape and to the nearest cm or inch.
    - The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally. The same measuring tape should be used throughout the trial. The measuring tape will be provided by Novo Nordisk to ensure standardisation.

8.1.3 Pain and pain medication diary

At screening, the subjects will be instructed in using an electronic pain and pain medication diary. In the diary, the subjects should record their:

- daily pain in the knee at its worst (NRS).
- daily use of pain medication and rescue pain medication (acetaminophen), including dose and frequency.

The investigator/site staff should review the diary for missing entries. The investigator should assist the subject in choosing the pain medication most often used and assist in choosing the correct category if the subject has chosen the category ‘Other’. If the subject has not taken any pain medication, this has to be recorded in the diary. Use of pain medication should also be reflected in EDC (standard concomitant medication form).

8.1.4 Clinical outcome assessments

Subject should be given the opportunity to complete the questionnaires by themselves without interruption. Each questionnaire takes approximately 10 minutes to complete.

The following PROs will be used:

- The WOMAC 3.1 NRS (Section 8.1.1)
- Patient Global Impression of Status (PGI-S) for Pain
- Patient Global Impression of Change (PGI-C) for Pain
- Short Form 36 v2.0 acute (SF-36)

The SF-36v2.0 is a 36-item commonly used generic PRO instrument measuring health-related quality of life and general health status across disease areas. The SF-36v2.0 for adults with a 1 week recall period (i.e. acute version) measures the individual overall health-related quality of life in 8 health domains (physical functioning, role limitation due to physical health problems [role-physical], bodily pain, general health, social functioning, role limitations due to emotional problems [role-emotional], vitality and mental health). Furthermore, it includes 2 aggregated scores: a physical component summary score and a mental component summary score[64].

- PGI-S for physical function
- PGI-C for physical function
- Knee pain NRS item

This is a single item measuring knee pain at its worst in the last 24 hours. This item is the pain diary described in Section 8.1.3. The response scale is a 11-point numeric rating scale from 0 (No knee pain) to 10 (Worst possible knee pain). The NRS item will relate to the target knee joint defined as the most symptomatic knee at screening. If pain in the knees are equal, the target knee joint will be in the most dominant leg.

- 6 Minute Walk Test (6MWT)

The 6MWT assesses the distance a subject can walk in 6 minutes. It is a direct and timed measure of walking ability, which is technically simple, reproducible, and when administrators are well trained, readily standardised. The goal is for the subject to walk as far as possible in six minutes without running. The subject is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway of 66 feet (20 m) (Figure 8-1). The primary outcome is the distance covered over 6 minutes[65, 66].

Specifically, all investigators and 6MWT clinical site administrators will receive a manual, providing details for administration of the 6MWT. In addition to the manual, each 6MWT clinical site administrator will have a checklist that must be completed prior to initiating each test administration to confirm and document that specific test administration criteria are met (e.g., the test is assessed along a flat, straight, undisturbed room that is at least 6 feet (1.8 m) wide; proper footwear as judged by the investigator is worn by the subject or otherwise noted)[67]. If the specific test administration criteria are not met, the 6MWT should not be performed.

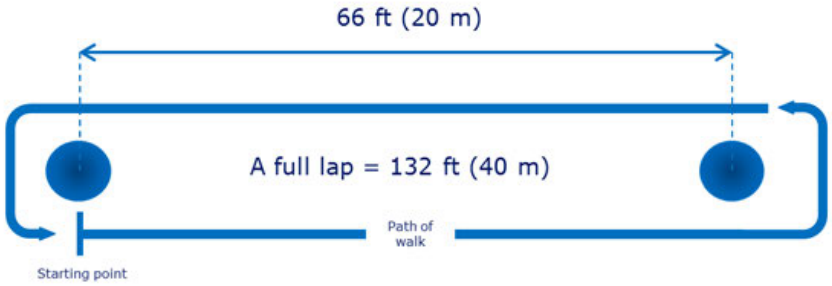


Figure 8-1 Walkway marking for the six-minute walk text

8.2 Safety assessments

Planned time points for all safety assessments are provided in the flowchart.

A **concomitant illness** is any illness that is already present at the time point from which AEs are collected or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Medical history is a medical event that the subject experienced prior to the time point from which AEs are collected. Only relevant and significant medical history as judged by the investigator should be recorded. Findings of specific medical history should be described in the Medical History/Concomitant Illness form.

The following concomitant illness/medical history should be recorded in the eCRF:

- History of breast neoplasm
- History of cardiovascular disorder and procedure
- History of dyslipidemia
- History of gallbladder disease and procedure
- History of gastrointestinal disorder and neoplasm
- History of musculoskeletal system disorder
- History of pancreatic disease
- History of psychiatric disorder
- History of skin cancer and skin disorder
- History of weight disorder
- Other relevant concomitant illness/medical history including COVID-19 and malignant neoplasm

In case of an abnormal and clinically significant finding fulfilling the definition of a concomitant illness or medical history, the investigator must record the finding on the Medical History/ Concomitant Illness form.

8.2.1 Radiographic examinations

- Results of a radiographic examination of the target knee, performed by a suitably qualified health care provider, will be evaluated by central reading. Results will be made available to the investigator before randomisation to assess eligibility.
- If the subject has had a radiographic examination performed within 90 days prior to screening, these images may be sent to for evaluation by central reading. The examination must be repeated before randomisation if the subject has experienced worsening of physical function since the last examination.
- The radiographs will be assessed using the KL grading system; a categorical grading scale of knee OA going from 0 to 4 by means of an evaluation of osteophytes, joint space narrowing, sclerosis and altered bone shapes[68, 69].

8.2.2 Physical examinations

- A physical examination will include assessments of the cardiovascular, musculoskeletal and respiratory system, general appearance, thyroid gland and abdomen.
- Body measurements (e.g. height and weight) will also be measured and recorded as specified in the flowchart.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.3 Vital signs

- The method for measuring systolic and diastolic blood pressure needs to follow the standard clinical practice at site

However, as a minimum:

- Vital sign assessment should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. no use of television, cell phones).
- Blood pressure and pulse rate measurements will be assessed sitting with a completely automated device. Manual techniques must be used only if an automated device is not available.
- Pulse rate will be measured in connection to the blood pressure measurements. Record the pulse rate for the last 2 blood pressure measurements in the CRF. The pulse rate is to be recorded as the mean of the last 2 measurement.

8.2.4 Clinical safety laboratory assessments

Not applicable for this trial.

8.3 Adverse events and serious adverse events

The investigator is responsible for detecting, documenting, recording and following up on all the events listed below:

- SAEs
- Following AEs irrespective of seriousness
    - AEs leading to permanent discontinuation of trial product
    - AEs requiring invasive knee procedures
    - AEs with additional data collection:

- medication error (including abuse/misuse of trial product)
- acute pancreatitis

- AEs of COVID-19[a]

- Pregnancies and pregnancy-related AEs
- Technical complaints

[a] Suspected COVID-19 should be reported if the clinical presentation is suggestive of COVID-19, even in the absence of a COVID-19 test or without a positive COVID-19 test result. In the absence of clinical symptoms, a positive COVID-19 test (antigen or antibody) should be reported, if available.

Note, that also events not allowed in accordance with the protocol e.g. bariatric surgery or knee replacement should, if they take place, be reported with both the procedure and medical condition specified.

The definition of AEs and SAEs can be found in Appendix 3 (Section 10.3), along with a description of AEs requiring additional data collection.

Some AEs require additional data collection on a specific event form. This always includes medication error, misuse and abuse of IMP. The relevant events are listed below in Table 8-1.

Table 8-1 AEs requiring additional data collection (serious and non-serious AEs)

Event type	AE requiring additional data collection
Medication error*	X
Misuse or abuse of trial product*	X
Acute pancreatitis	X

*Additional data for Misuse or abuse of trial product is reported on the medication error event form.

A detailed description of the events mentioned in the above table can be found in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All events specified in Section 8.3 (for events related to pregnancy, see Appendix 4 (Section 10.4) must be collected and reported. The events must be collected from the first trial-related activity after obtaining informed consent until the end of trial visit, at the time points specified in the flowchart.

Medical occurrences that take place or have onset prior to the time point from which AEs are collected will be recorded as concomitant illness/medical history. AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3). All SAEs must be recorded and reported to Novo Nordisk or designee within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24-hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former trial subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related to the trial product or related to trial participation, the investigator must promptly notify Novo Nordisk.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about events.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs should be followed until final outcome of the event or the subject is lost to follow-up as described in Section 7.3. Further information on follow-up and final outcome of events is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk or designee of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial product under clinical investigation are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR).

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from Novo Nordisk will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of pregnancies in female subjects will be collected after the first-trial-related activity after obtaining informed consent and until the end of trial visit.

If a female subject becomes pregnant, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

8.3.6 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to Section 8.3.

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as an AE or SAE

Not applicable for this trial.

8.3.8 Adverse event of special interest

Not applicable for this trial.

8.3.9 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form.

Instructions for reporting technical complaints can be found in Appendix 5 (Section 10.5).

In order for Novo Nordisk to perform a complete investigation of reported SAEs, Novo Nordisk might ask the investigator to complete a technical complaint form.

8.4 Treatment of overdose

- Overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported AE was nausea. All subjects recovered without complications.
- There is no specific antidote for overdose with semaglutide. In the event of an overdose, appropriate supportive treatment should be initiated according to subject's clinical signs and symptoms.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.3 and Appendix 3 (Section 10.3) for further details.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE. A prolonged period of observation and treatment may be necessary, taking into account the long half-life of semaglutide of approximately one week.

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the subject.

For more information on overdose, also consult the current version of the investigator's brochure[50] and any updates hereof.

8.5 Pharmacokinetics

Not applicable for this trial.

8.6 Pharmacodynamics

Not applicable for this trial.

8.7 Genetics

Not applicable for this trial.

8.8 Biomarkers

Not applicable for this trial.

8.9 Immunogenicity assessments

Not applicable for this trial.

8.10 Health economics

Not applicable for this trial.

9 Statistical considerations

9.1 Statistical hypotheses

The tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo for the two primary and all confirmatory secondary endpoints are performed using a fixed-sequence statistical strategy and a weighted Holm-Bonferroni procedure (with weights one). For a detailed specification of statistical hypotheses for the two primary endpoints see Section 9.4.2.

This strategy tests the endpoints using a predefined hierarchical order; first the two primary endpoints: body weight change (%) and change in WOMAC pain score are tested at the significance level of 5% where the alpha is split between the two endpoints using 1% for body weight change (%) and 4% for change in WOMAC pain score.

If superiority is not confirmed for both endpoints, then the testing will stop. If the test of superiority for one of the two primary endpoints is significant, then the alpha can be recycled for the other primary endpoint, which will be tested at the 5% significance level. If both hypotheses are rejected and superiority is confirmed, then the confirmatory secondary endpoints (starting with ≥5% body weight reduction) will be tested at the 5% level. Testing for superiority of confirmatory secondary endpoints can proceed only after a statistically significant result (p-value < 5%) on the previous endpoint.

9.2 Sample size determination

The trial is designed with an effective power of 90% and 67% to detect differences on the two primary endpoints and confirmatory secondary endpoints, respectively. The effective power was calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively which is a conservative approach. The power calculations for continuous endpoints are based on a t-test on the mean difference assuming equal variances, whereas those for the categorical endpoints are based on the Pearson chi-square test for two independent proportions.

Assumptions for these calculations are presented in Table 9-1 and are based on findings from NN9536-4153 and NN9536 phase 3a program (STEP) as well as on relevant publications on body weight loss and knee OA outcome (using WOMAC). Two studies, Bliddal et al. and Christensen et al., found that weight loss treatment (average weight loss 7.5% and 6.8% respectively) could lead to improvements in knee OA symptoms like pain and physical function (pain score: -8.4 (-10.4 vs -2.0) with baseline score 38.4 (SD=21.1) and -5.4 (-11.4 vs -6.0) with baseline score 36.7 (SD=21.3) respectively; function score: -3.7 (-10.2 vs -6.5) with baseline score 39.2 (SD=21.4) and -9.9 (-14.9 vs -5.0) with baseline value 37.4 (SD=21.8) respectively) in obese subjects (average BMI at baseline 35.6 and 35.9 respectively)[28, 70]. Aforementioned score improvements were found in treatment completers. Item responses were collected using the VAS format of the questionnaire. Bliddal et al. reported normalised sum of scores (range 0-100) and Christensen et al. reported sum of scores, which were transformed to a 0-100 range for comparison purposes. Consequently, a treatment difference for the pain score was assumed to be -9 (-11 vs -2) with SD=20; for the function score it was assumed to be -9 (-15 vs -6) with SD=19 if treated with semaglutide s.c. 2.4 mg once-weekly vs semaglutide placebo for 68 weeks. Clement et al. identified a minimum

clinically important difference of 11 for pain and 9 for function and a minimum important change of 21 for pain and 16 for function for improvement in WOMAC after total knee arthroplasty.[71] Although, it is planned to use the NRS format of the questionnaire in this trial, it is known that VAS and NRS are highly correlated (r>0.93) and that VAS derived assumptions for sample size calculation are adequate and can be translated to a setting where NRS is used[72]. It is planned that the WOMAC scores (derived from NRS responses) will be transformed to a 0-100 range based on which the corresponding endpoints will be calculated.

In relation to expected treatment effects it was assumed that 20% of subjects discontinue permanently and 60% of these are retrieved at week 68. All subjects in the placebo arm are assumed to have same effect as subjects who complete the trial on placebo. Retrieved subjects in the semaglutide s.c. 2.4 mg once-weekly arm are assumed to have an effect corresponding to half the treatment difference (compared to placebo) of subjects who complete the trial on semaglutide s.c. 2.4 mg once-weekly. Non-retrieved subjects in the semaglutide s.c. 2.4 mg once-weekly arm are assumed to have an effect corresponding to placebo.

Under these assumptions and a 2:1 randomisation ratio, the desired power of at least 90% for change in WOMAC pain score is obtained with 375 subjects randomised to either receive semaglutide s.c. 2.4 mg once-weekly (250) or placebo (125).

Table 9-1 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number of 375 randomised subjects

Order	Endpoint	Assumed mean (±SD) or proportion for completers		Expected mean (±SD) or proportion	Expected difference or proportion ratio	Marginal power (%)	Two-sided significance level (%) *	Effective power (%)
		Semaglutide s.c. 2.4 mg once-weekly	Semaglutide placebo	Semaglutide s.c. 2.4 mg once-weekly				
1	**% body weight change #**	14.0 (±10)	3.0 (±10)	12.5 (±11)	9.5%-points	>99	1	99
1	**WOMAC pain change #**	11.0 (±20)	2.0 (±20)	9.7 (±21)	7.7 score-points	90	4	90
2	5% responders	82%	42%	76%	1.8	>99	5	90
3	10% responders	66%	24%	60%	2.5	>99	5	90
4	WOMAC function change #	15.0 (±19)	6.0 (±19)	13.7 (±20)	7.7 score-points	94	5	84
5	SF-36 physical functioning change	6.0 (±10)	2.0 (±10)	5.4 (±11)	3.4 score-points	80	5	67

SD: Standard deviation; WOMAC: Western Ontario McMasters Osteoarthritis Index ; SF-36: Short Form (36) Health Survey.

*Significance level for confirmatory secondary endpoints reflects local alpha if all superiority hypotheses for endpoints higher in the statistical hierarchy were rejected
Shown as a positive number

As currently there are no NN trials utilizing WOMAC, see Table 9-2 for alternative power calculations to the main scenario assuming varying sample size, mean difference or standard deviation.

Table 9-2 Marginal power for WOMAC pain change (shown as a positive number) for alternative sample size, mean difference or standard deviation

Sample size	Expected mean for semaglutide placebo	Expected mean for semaglutide s.c. 2.4 mg once-weekly	Expected difference	Common SD	Marginal power (%)
Main scenario					
375	2	9.7	7.7	21	0.900
Varying sample size					
285	2	9.7	7.7	21	0.803
303	2	9.7	7.7	21	0.828
324	2	9.7	7.7	21	0.853
348	2	9.7	7.7	21	0.877
375	2	9.7	7.7	21	0.900
411	2	9.7	7.7	21	0.925
462	2	9.7	7.7	21	0.951
543	2	9.7	7.7	21	0.975
888	2	9.7	7.7	21	>.999
Varying mean difference					
375	2	5	**3**	21	0.226
375	2	6	**4**	21	0.375
375	2	7	**5**	21	0.545
375	2	8	**6**	21	0.708
375	2	9	**7**	21	0.837
375	2	10	**8**	21	0.921
375	2	11	**9**	21	0.968
375	2	12	**10**	21	0.989
375	2	13	**11**	21	0.997
375	2	14	**12**	21	>.999
375	2	15	**13**	21	>.999
Varying standard deviation					
375	2	9.7	7.7	**10**	>.999
375	2	9.7	7.7	**11**	>.999
375	2	9.7	7.7	**12**	>.999
375	2	9.7	7.7	**13**	>.999
375	2	9.7	7.7	**14**	0.998
375	2	9.7	7.7	**15**	0.996
375	2	9.7	7.7	**16**	0.990
375	2	9.7	7.7	**17**	0.981
375	2	9.7	7.7	**18**	0.967
375	2	9.7	7.7	**19**	0.949
375	2	9.7	7.7	**20**	0.927

375	2	9.7	7.7	**21**	0.900
375	2	9.7	7.7	**22**	0.871
375	2	9.7	7.7	**23**	0.840
375	2	9.7	7.7	**24**	0.807
375	2	9.7	7.7	**25**	0.773
375	2	9.7	7.7	**26**	0.740
375	2	9.7	7.7	**27**	0.706
375	2	9.7	7.7	**28**	0.673
375	2	9.7	7.7	**29**	0.642
375	2	9.7	7.7	**30**	0.611

SD: Standard deviation.

All above outlined sample size and power considerations are for the primary estimand for primary endpoints or the secondary estimand for confirmatory secondary endpoints (treatment policy strategy). It is assumed that up to 20% of subjects discontinue permanently and 60% of these are retrieved at week 68, which amounts to 8% expected missing data at week 68. Based on NN9536 STEP 1 trial 8.8% missing in-trial data was observed after 68 weeks for the primary estimand. Any superiority conclusions will be based on the primary or secondary estimand.

For the additional estimand (hypothetical strategy) however, data from retrieved subjects are not used. Hence, it is expected that up to 20% of data will be missing at week 68. Based on NN9536 STEP 1 trial 20.6% missing on-treatment data was observed after 68 weeks for the additional estimand. This included missing data not only due to treatment discontinuation, but also due to initiation of other anti-obesity therapies (<1%). For trial NN9536 4578 slightly higher missing on-treatment data is expected due to subjects initiating other knee OA interventions (<3%) and not complying with the washout period (<10%). In NN9536 STEP 1 trial it was seen that the treatment difference in mean changes for body weight was slightly higher and standard deviation was slightly lower for the additional estimand (using on-treatment data) than for the primary estimand (using in-trial data).

9.3 Populations for analyses

Two analysis sets are defined:

The *full analysis set (FAS)* includes all randomised subjects according to the intention-to-treat principle. The subjects in the *FAS* contribute to the evaluation as randomised.

The *safety analysis set (SAS)* includes all randomised subjects exposed to at least one dose of randomised treatment. The subjects in the *SAS* contribute to the evaluation as treated.

Any observation excluded from the analysis database will be documented before database lock with the reason for exclusion provided. Efficacy endpoints will be analysed using the FAS; safety endpoints will be analysed using the SAS.

Two observation periods are defined for each subject:

In-trial: The *in-trial period* is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site.

On-treatment (with trial product): A time-point is considered as "on-treatment" if any dose of trial product has been administered within the prior 2 weeks (14 days). The *on-treatment period* is defined as all times which are considered on-treatment.

In general, the *on-treatment period* will therefore be from the date of first trial product administration to date of last trial product administration excluding potential off-treatment time intervals triggered by at least two consecutive missed doses.

For the evaluation of AEs, the lag time for each on-treatment time interval is 7 weeks (49 days).

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

9.4 Statistical analyses

9.4.1 General considerations

A statistical analysis plan (SAP) will be written, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before breaking the blind to treatment assignment.

The last available and eligible observation at or before randomisation is used as the baseline value. If no assessments are available, the mean value at randomisation across all subjects is used as the baseline value.

9.4.2 Primary endpoint*(s)*

The primary endpoints are change in body weight (%) and change in WOMAC pain score from baseline (week 0) to end-of-treatment (week 68) as listed in Section 3.

Change from baseline to week 68 in body weight (%) is defined as

$$\%\ \text{body weight change} = \frac{(\text{body weight at week 68} - \text{body weight at baseline})}{\text{body weight at baseline}} \times 100.$$

Change from baseline to week 68 in WOMAC pain score is defined as

WOMAC pain score change = WOMAC pain score at week 68 – WOMAC pain score at baseline.

All tests are tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo.

Let $\mu_{\text{semaglutide}}$ and $\mu_{\text{semaglutide placebo}}$ denote the true mean of % body weight change or WOMAC pain score change for semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo, respectively. The null and alternative hypotheses tested are

$$H_0: \mu_{semaglutide} \geq \mu_{semaglutide\ placebo}\ vs$$
$$H_A: \mu_{semaglutide} < \mu_{semaglutide\ placebo}.$$

The null hypotheses will be rejected and superiority claimed, if the upper limit of the estimated two-sided 95% CI is below 0.

Analyses addressing the primary estimand

The following statistical analyses and imputation methods are designed to address the primary estimand.

The analysis model for change in body weight (%) and change in WOMAC pain score will be a linear regression (ANCOVA) with randomised treatment as factor and either baseline body weight (kg) or baseline WOMAC pain score as covariate. The estimated treatment difference between semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

All available data at week 68 are used and missing values at week 68 will be imputed and the endpoint will be derived from the imputed values. The imputation approach for the primary analysis is a multiple imputation similar to the one described by McEvoy et al[73]. For subjects in the semaglutide s.c. 2.4 mg once-weekly and the semaglutide placebo arms, missing measurements at week 68 for non-retrieved subjects are imputed using assessments from retrieved subjects in each randomised treatment arm. This will be done according to the timing of last available observation during the on-treatment period (LAO-OT) as well as by taking sex, baseline BMI and baseline body weight/WOMAC pain score into account. Missing measurements at week 68 for subjects on randomised treatment (at week 68) are imputed by sampling from available measurements at week 68 from subjects on randomised treatment in the relevant randomised treatment arms. Details of the multiple imputation approach are provided in the SAP.

Analysis addressing the additional estimand

The additional estimand for change in body weight (%) and change in WOMAC pain score will be assessed using a mixed model for repeated measurements (MMRM) approach.

Week 68 assessments for retrieved subjects are not used in this analysis. The MMRM will use assessments only from subjects who are taking the randomised treatment until end of treatment or until first discontinuation of randomised treatment. For subjects who experience other intercurrent events before completion or first discontinuing of randomised treatment, the date of initiating other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injections) will be used as latest date for using assessments in this MMRM. Additionally, for the MMRM analysing change in WOMAC pain score, assessments from subjects incompliant with the washout period for pain medication will not be used. The MMRM will be fitted using the change (% body weight change or change in WOMAC pain score) and the same factor and covariate as for the primary analysis all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

9.4.3 Secondary endpoints

9.4.3.1 Confirmatory secondary endpoints

The confirmatory secondary endpoints are listed in Section 3.

All tests are tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo.

Analyses addressing the secondary estimand

The confirmatory secondary endpoints addressing the secondary estimand will be analysed in a similar way as the primary endpoints addressing the primary estimand.

The statistical model for continuous confirmatory secondary endpoints will be the same linear regression as for the primary endpoints (ANCOVA) with treatment as a factor and the baseline value of the endpoint as covariate. The statistical model for confirmatory body weight responder endpoints is a logistic regression using randomised treatment as a factor and baseline body weight (kg) as covariate. The estimated odds ratio (OR) between semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval and corresponding p-value.

The imputation approach is the same multiple imputation using retrieved subjects as described in Section 9.4.2 and taking the baseline value of the endpoint into account.

Analyses addressing the additional estimand

The confirmatory secondary endpoint change in WOMAC physical function score addressing the additional estimand will be analysed using the same MMRM as described for the primary endpoint change in WOMAC pain score addressing the additional estimand with randomised treatment as a factor and the baseline value of the endpoint as covariate.

The confirmatory body weight responder endpoints addressing the additional estimand will be analysed using the same MMRM described for the primary endpoint change in body weight (%) addressing the additional estimand except that body weight (kg) will be used as response variable in the model. For subjects with missing body weight at week 68, individual values for body weight will be predicted from the MMRM and used to classify each subject as 5% or 10% responder or not. This classification will then be analysed using a logistic regression model with randomised treatment as a factor and baseline body weight (kg) as covariate.

9.4.3.2 Supportive secondary endpoints

For details on analyses of supportive secondary endpoints, please see the SAP.

9.4.4 Exploratory endpoints

For details on analyses of exploratory endpoints, please see the SAP.

9.4.5 Other safety analyses

For other safety analyse(s), please see the SAP.

9.4.6 Other analyse(s)

Not applicable for this trial.

9.4.6.1 Pharmacokinetic and/or pharmacodynamic modelling

Not applicable for this trial.

9.5 Interim analyses

Not applicable for this trial.

9.6 Data monitoring committee

Not applicable for this trial.

9.7 Reporting of the main part of the trial

Not applicable for this trial.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and trial oversight considerations

10.1.1 Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[74] and applicable ICH Good Clinical Practice (GCP) Guideline[75]
- Applicable laws and regulations
- The protocol, informed consent form, IB (as applicable) and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report (CTR) according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
- providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- ensuring submission of the CTR synopsis to the IRB/IEC
- reporting any potential serious breaches to the sponsor immediately after discovery

10.1.2 Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and one year after completion of the trial.
Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

10.1.3 Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the subject and answer all questions regarding the trial. This includes the use of an impartial witness where required according to local requirements.

- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.
- Subjects must be informed about their privacy rights.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[75], Declaration of Helsinki[74] and the IRB/IEC or site.
- The medical record must include a statement that written informed consent was obtained before any trial-related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial-related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form*(s)* during their participation in the trial.
- A copy of the informed consent form*(s)* must be provided to the subject.

10.1.4 Information to subjects during trial

The site will be offered a communication package for the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the subjects. The written information will be translated and adjusted to local requirements and distributed to the subject at the discretion of the investigator. The subject may receive a “welcome to the trial letter” and a “thank you for your participation letter” after completion of the trial. Further, the subject may receive other written information during the trial.

Different initiatives for subject retention will be implemented throughout this trial. Site retention activities may include cooking classes, group meetings and others. Materials and items will be supplied if locally acceptable. The retention items will be relevant for the subjects’ participation in the trial and/or their obesity and will not exceed local fair market value.

All written information to subjects must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

The initiatives for subject retention must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

10.1.5 Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the subject are transferred to Novo Nordisk.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or

leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.

- The subject must be informed about his/her privacy rights, including that his/her personal trial-related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee. The safety committee may recommend unblinding of any data for further analysis, and in this case an internal trial independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

10.1.6.2 Trial safety group

Not applicable for this trial.

10.1.6.3 Data monitoring committee

Not applicable for this trial.

10.1.6.4 Event adjudication committee

Not applicable for this trial.

10.1.7 Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements, such as those of the International Committee of Medical Journal Editors (ICMJE)[76], the Food and Drug Administration Amendment Act (FDAAA)[77], European Commission Requirements[1, 78, 79] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The primary completion date is the last assessment of the primary endpoint, and is for this trial Last Subject First Treatment + 68 weeks corresponding to 'end of treatment' visit (V13). If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed 'end of treatment' visit. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The following will be provided as paper CRFs:
    - Pregnancy forms (Maternal forms 1A, 1B and 2 and Paternal form)
- The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:
    - AE forms
    - Safety information forms
    - Technical complaint forms (also to be used to report complaints on trial product not yet allocated to a subject)
- Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.
- The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

10.1.8.2 Monitoring

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.

- Monitors will review the subject's medical records and other source data, e.g. PROs, to ensure consistency and/or identify omissions compared to the CRF.

10.1.8.3 Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without delay and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the CRF or via listings from the trial database.

10.1.9 Source documents.

- All data entered in the eCRF must be verifiable in source documentation other than the CRF
- For ePROs, data in the service providers' database is considered source data.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify subject's medical history in source documents, such as subject's medical record
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. This also applies for services outsourced to an external facility by the investigator. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.
- Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

10.1.11 Trial and site closure

Novo Nordisk reserves the right to close the site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

Sites will be closed upon trial completion. A site is considered closed when all required documents and trial supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a site by Novo Nordisk or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines
- inadequate recruitment of subjects by the investigator
- discontinuation of further trial product development.

10.1.12 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

A qualified physician, who is an investigator or a sub investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents, including the subject identification code list must be kept in a secure locked facility so that no unauthorized persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of subjects to a specific qualified physician who will be readily available to subjects during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

10.1.13 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the trial or by persons for whom the said site or investigator are responsible. Novo Nordisk may pay additional costs incurred in relation to assessments relevant for following the safety of the subject. Investigator must contact Novo Nordisk on a case by case basis for whether the costs will be covered.

Novo Nordisk accepts liability in accordance with: Please refer to Appendix 7 (Section 10.7).

10.1.14 Publication policy

The information obtained during the conduct of this trial is considered confidential and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial.

The information obtained during this trial may be made available to other investigators who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted CTR for this trial.

One (or two) investigators will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators.

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR is available. This includes the

right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

At the end of the trial, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases, the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

10.1.14.2 Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the trial concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[80]

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned publication.

Where required by the journal, the investigator from each site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

10.1.14.3 Site-specific publication(s) by investigator(s)

For a multicentre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the trial.

10.1.14.4 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database.

Individual investigators will have their own research subjects' data and will be provided with the randomisation code after results are available.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10-1 will be performed by the local laboratory
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. If additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.
- The investigator must review all laboratory results for concomitant illnesses and AEs.

Table 10-1 Protocol-required laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism[1]	• $HbA1_c$
Pregnancy Testing	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]
Notes: [1]For screening purposes only [2]Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.	

$HbA1_c$; glycated haemoglobin, IRB; institutional review board, IEC; independent ethics committee

10.3 Appendix 3: Adverse events: Definitions and procedures for recording, evaluation, follow-up, and reporting

10.3.1 Definition of AE

AE definition

An AE is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of an IMP, whether or not considered related to the IMP.
An AE can therefore be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of an IMP.

Events meeting the AE definition

- Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected
- Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected
- Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition
- Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent
- Obesity-related surgical procedures, total knee replacements and knee arthroscopy

A "lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.

Events NOT meeting the AE definition

- Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or other trial procedures performed before exposure to IMP.
- Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.
- Medical or surgical procedures (e.g. endoscopy, appendectomy). The condition that leads to the procedure is the AE. · Exceptions include; obesity-related surgical procedures, total knee replacements and knee arthroscopy. In these cases both the surgical procedure and the condition that leads to the procedure should be reported as AEs.
- Medical or surgical procedures not preceded by an AE or worsening of a known condition (exceptions are obesity-related surgical procedures, which for this trial should be reported as individual AE's).

10.3.2 Definition of an SAE

An SAE is an AE that fulfils at least one of the following criteria:
a. Results in death
b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation • Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment (e.g. elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE. • Note: • Hospitalisations for administrative, trial-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. • Hospital admissions for medical or surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect

f. Important medical event:
• Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
• The following adverse events must always be reported as SAEs using the important medical event criterion if no other seriousness criteria are applicable:
  • Suspicion of transmission of infectious agents via the IMP
  • Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of AEs requiring additional data collection

Description of AEs requiring additional data collection (on specific event form)
Adverse events requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the safety of the trial product (see Table 8-1). The selection of these events is based on the non-clinical and clinical data with semaglutide, knowledge from the GLP-1 RA drug class as well as regulatory requirements.

Acute pancreatitis
Diagnosis of acute pancreatitis requires two of the following three features:

1. abdominal pain consistent with acute pancreatitis (onset of a persistent, severe, epigastric pain often radiating to the back)
2. serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal
3. characteristic findings of acute pancreatitis on imaging.

Medication error
A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the subject, such as:

- administration of wrong drug
  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- wrong route of administration, such as intramuscular instead of subcutaneous
- accidental administration of higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.
- missed doses or drug pauses are not to be reported as a medication error.

Misuse and abuse

- Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g. overdose to maximise effect)
- Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm)

Medication error, misuse and abuse must always be reported as an AE (e.g. accidental overdose, intentional overdose or other) on a separate AE form, and a medication error, misuse and abuse form must be completed. In case of a medication error and/or misuse and abuse resulting in a clinical consequence (e.g. hypoglycaemia or other), this must be reported on an additional AE form.

10.3.4 Recording and follow-up of AE and/or SAE

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the CRF.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- SAEs and AEs listed in Section 8.3 and AEs/SAEs in connection with pregnancies, must be recorded by the investigator in the CRF. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
- For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE-related forms, refer to "AE and SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

The investigator will assess severity for each event reported during the trial and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: An AE that is assessed as severe should not be confused with a SAE. Both AEs and SAEs can be assessed as severe.

Assessment of causality

- The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE.
- Relationship between an AE/SAE and the relevant IMP(s) should be assessed as:
  - Probable - Good reason and sufficient documentation to assume a causal relationship.
  - Possible - A causal relationship is conceivable and cannot be dismissed.
  - Unlikely - The event is most likely related to aetiology other than the IMP.
- Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.**
- The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented
- **Recovering/resolving:** The condition is improving, and the subject is expected to recover from the event. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- Note: For SAEs, this term is only applicable if the subject has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae:** The subject has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the subject has not improved, and the symptoms are unchanged, or the outcome is not known.
  Note: This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the subject is lost to follow-up.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology.

New or updated information will be recorded in the CRF.

10.3.5 Reporting of SAEs

SAE reporting via electronic CRF

- Relevant forms (AE form, safety information form and specific event forms) must be completed in the CRF.
- For reporting and sign-off timelines, see Figure 10-1 below.
- If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the CRF is unavailable for more than 5 calendar days, then the site will use the paper safety information form (see box below).
- The site will enter the SAE data into the CRF as soon as it becomes available.
- After the trial is completed, the trial database will be locked, and the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a subject or receives updated data on a previously reported SAE

after CRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

AE and SAE reporting via paper CRF

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk in accordance with Section 10.1.5.
- For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting timelines (as illustrated in the figure below):
  - AE form within 24 hours
  - Safety information form within 5 calendar days
  - Both forms must be signed within 7 calendar days after first knowledge by the investigator.
- The specific event form for AEs requiring additional data collection within 14 calendar days

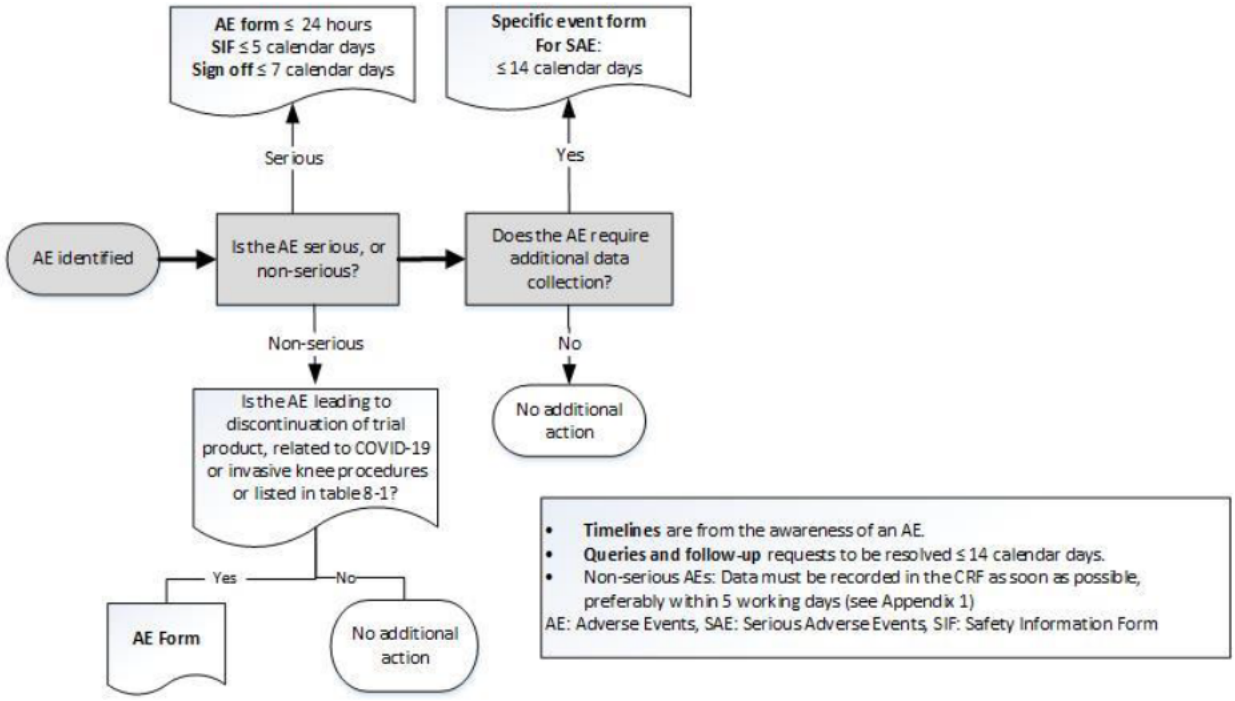


Figure 10-1 Decision tree for determining the event type and the respective forms to complete with associated timelines

Contact details for SAE reporting can be found in the investigator trial master file.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.
If fertility is unclear (e.g. amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of trial treatment, additional evaluation should be considered.

Females in the following categories are not considered WOCBP

1. Premenarcheal
2. Females with one or more of the following:
   - Documented total hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

Females with permanent infertility due to an alternate medical cause other than the above (e.g. Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining trial enrolment.

3. Postmenopausal female:
   - A postmenopausal state is defined as amenorrhoea for 12 months without an alternative medical cause.
   - Females ≥ 50 years of age can be considered postmenopausal (irrespective of treatment with a hormonal contraception or hormone replacement therapy (HRT)) if they have both:
     - Amenorrhoea and
     - Documentation of 2 high follicle stimulating hormone (FSH) measurements in the postmenopausal range and one of these was observed ≥1 year prior to screening.
   - Females ≥ 60 years of age can be considered postmenopausal.

Females on HRT and whose menopausal status is in doubt are considered of childbearing potential and will be required to use one of the highly effective contraception methods.

Note: Documentation regarding categories 1-3 can come from the site staff's review of subject's medical records, medical examination or medical history interview.

Contraception guidance

Male subjects
No contraception measures are required for male subjects as the risk of teratogenicity/fetotoxicity caused by transfer of semaglutide in seminal fluid is unlikely.

Female subjects
Female subjects of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly as described in table below:

Table 10-1 Highly effective contraceptive methods

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:
• **Highly effective methods[b,d] that have low user dependency** (Failure rate of <1% per year when used consistently and correctly): o Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b] o Intrauterine device (IUD) o Intrauterine hormone-releasing system (IUS)[b] o Bilateral tubal occlusion o Vasectomized partner (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.) • **Highly effective methods[b,d] that are user dependent** (Failure rate of <1% per year when used consistently and correctly): o Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] ▪ oral ▪ intravaginal ▪ transdermal ▪ injectable • Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.
NOTES a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical trials. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d) Contraception should be utilised during the treatment period and for at least 49 days (corresponding to time needed to eliminate trial product) after the last dose of trial product. This period should be extended by 30 days in case of genotoxicity.

Pregnancy testing

- Additional pregnancy testing should be performed during the treatment period, if required locally (Appendix 7, Section 10.7).
- WOCBP should only be included after a negative highly sensitive urine pregnancy test (refer to Appendix 2, Section 10.2).
- A pregnancy test should be performed at the end of relevant systemic exposure (refer to Appendix 2, Section 10.2).

- Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.

Collection of pregnancy information

Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy (see Figure 10-2).
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate which will be forwarded to Novo Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding 'gestational', 'pregnancy-related' or a similar term when reporting the AE/SAE.
- Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the IMP by the investigator will be reported to Novo Nordisk as described in Section 10.3. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

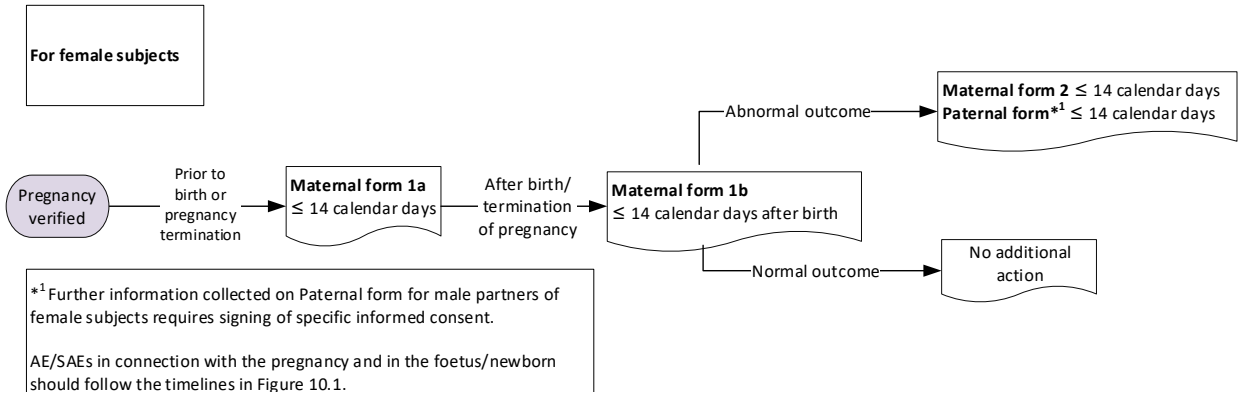


Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy

Any female subject who becomes pregnant while participating in the trial will discontinue IMP.

10.5 Appendix 5: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

10.5.1 Definition of technical complaint

Technical complaint definition
• A technical complaint is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself.

Examples of technical complaints:

- Problems with the physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- Problems with packaging material including labelling
- Problems related to devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen-injector and the needle)

Time period for detecting technical complaints
All technical complaints which occur from the time of receipt of the product at site until the time of the last usage of the product must be collected for products predefined on the technical complaint form.

10.5.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk
Contact details for Customer Complaint Center, please refer to Attachment I. Technical complaints must be reported on a separate technical complaint form: 1. One technical complaint form must be completed for each affected DUN. 2. If DUN is not available, a technical complaint form for each batch, code or lot number must be completed.

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within: • 24 hours if related to an SAE • 5 days calendar for all other technical complaints If the CRF is unavailable, or when reporting a technical complaint on a trial product that is not yet allocated to subject, the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

Follow-up of technical complaints
The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples
The investigator must collect the technical complaint sample and all associated parts that were packed in the same DUN and notify the monitor within 5 calendar days of obtaining the sample at site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together. Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

10.5.3 Reporting of technical complaints

Reporting of technical complaints for Novo Nordisk products not included in technical complaint form
Technical complaints on Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk.

10.6 Appendix 6: Mitigations to ensure subject safety and data integrity during COVID-19

In case local restrictions due to a COVID-19 outbreak lead to lock-down of a site, the site must contact Novo Nordisk to allow for implementation of mitigations mentioned in this appendix based on mutual agreement.

- Table 10-2 indicates the minimum requirements for assessments that should be performed during a lock-down, but sites should always try to follow the assessments outlined in Section 1.2 (original flowchart) to the extent possible. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.
- Sites should comply with local regulations, requirements and/or guidelines if they are issued.

10.6.1 Visits

- Screening (visit 1) and randomisation (visit 2) should always be performed as physical on-site visits. If a site is unable to perform these visits on-site, screening and randomisation of new subjects at that site should be on hold until on-site visits are possible.
- Visits 4, 7, 9, 11, 13, and 14 should be performed as physical on-site visits, if in any way possible.
- On-site visits (visits 3, 5, 6, 8, 10, and 12) can be converted to remote visits (video, phone or similar) or home visits.
- At each visit the investigator must indicate in the eCRF how the visit was performed and specify the reason for the preferred assessment method.

10.6.2 Assessments

- Assessments used for safety and the confirmatory endpoints should be prioritised. The preferred order for the method of assessment is: on-site, video, phone, home visit. Findings meeting the definition for an AE (refer to Appendix 3 [Section 10.3]) should be reported in the eCRF.
- If the assessments indicated in Table 10-2 cannot be performed as on-site visits or remote visits, they should be performed at the first possible timepoint following the originally scheduled visit in agreement with Novo Nordisk.

10.6.3 Minimum assessments following randomisation to be performed during lockdown

Table 10-2 Minimum assessments following randomisation to be performed during lockdown

	Dose escalation period				Treatment period						End of treatment	End of trial
Visit (V)	P3	V4	P5	P6	V7	P8	V9	P10	V11	P12	V13	V14
Timing of Visit (Weeks)	4	8	12	16	20	28	36	44	52	60	68	75
Visit Window (Days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
SUBJECT RELATED INFORMATION AND ASSESSMENTS												
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[c] (8.3.5)		X		X	X	X	X	X	X	X	X	X
EFFICACY												
Body Measurements (8.1.2)												
Body Weight		X			X		X		X		X	
Clinical Outcome Assessments												
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (8.1.1)	X	X	X	X	X	X	X	X	X	X	X	
Patient Global Impression of Status (PGI-S) Pain					X				X		X	
Patient Global Impression of Change (PGI-C) Pain					X				X		X	
Short Form 36 V2.0 acute (SF-36) (8.1.4)		X			X		X		X		X	
PGI-S Physical Function		X			X				X		X	
PGI-C Physical Function					X				X		X	
SAFETY												
Adverse Event (8.3)	X	X	X	X	X	X	X	X	X	X	X	X

	Dose escalation period				Treatment period						End of treatment	End of trial
Visit (V)	P3	V4	P5	P6	V7	P8	V9	P10	V11	P12	V13	V14
Timing of Visit (Weeks)	4	8	12	16	20	28	36	44	52	60	68	75
Visit Window (Days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Technical Complaint (8.3.9)	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs (8.2.3)												
Systolic Blood Pressure					X		X		X		X	X
Diastolic Blood Pressure					X		X		X		X	X
Pulse					X		X		X		X	X
Physical Examination (8.2.2)											X	
TRIAL MATERIAL												
IWRS Session		X		X	X	X	X	X	X	X	X	
Administration of Trial Product (6.1)												
Dispensing Visit		X			X		X		X			
Drug Accountability		X			X		X		X		X	
REMINDERS												
Criteria for discontinuation (7.1)	X	X	X	X	X	X	X	X	X	X		
Diet and physical activity counselling (6.1.2)	X	X	X	X	X	X	X	X	X	X	X	
Review of the pain and pain medication diary[d] (8.1.3)	X	X	X	X	X	X	X	X	X	X	X	
Training in trial product, pen-handling	X	X	X	X	X							
Hand out dose reminder card (6.1)	X	X	X	X	X							

[a] Demography consists of date of birth, sex, ethnicity, and race (according to local regulation).
[b] Smoking is defined as smoking at least one cigarette or equivalent daily.
[c] For all female subjects of child-bearing potential.
[d] The pain and pain medication diary should be filled in on a daily basis by the subject

10.7 Appendix 7: Country-specific requirements

For Denmark:

Section 5.3 Exclusion criteria no. 27

Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered highly effective birth control.

For Canada:

Appendix 1 Section 10.1.10 Retention of clinical trial documentation

Part C, Division 5 of the Food and Drug Regulations [C.05.012] requires a 25 years retention period

For France:

1. Section 1.2 Flowchart

Ethnic origin and race: Collection not allowed in France.

Year of birth: Only year is collected for the date of birth.

Appendix 1 Section 10.1.13 Indemnity statement

The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX, Journal Officiel of 11 August 2004. "The sponsor is responsible for identification of the harmful consequences of the biomedical the research for the person lending himself thereto and for

indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research"

Section 5.3 Exclusion criteria no. 27

Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered highly effective birth control.

For Norway:

Section 5.3 Exclusion criteria no. 27

Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner

- sexual abstinence

A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered highly effective birth control.

For Sweden:

Section 5.3 Exclusion criteria no. 27

Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered highly effective birth control.

For Spain:

Appendix 1 Section 10.1.10 Retention of clinical trial documentation

25 years according to the new Spanish Royal Decree 1090/2015

Section 5.3 Exclusion criteria no. 27

Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)

- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered highly effective birth control.

For US:

Appendix 1 Section 10.1.5 Data protection

In the United States, 21 CFR 312.62(c) and 21 CFR 812.140(d) require 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified'.

10.8 Appendix 8: Abbreviations

6MWT	six-minute walking test
ACR	American College of Rheumatology
AE	adverse event
BMI	body mass index
CRF	case report form
CTR	clinical trial report
DFU	directions for use
DUN	dispensing unit number
eCRF	electronic case report form
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
GCP	Good Clinical Practice
GLP-1	glucose like peptide-1
$HbA1_c$	glycated haemoglobin
ICH	International Council for Harmonisation
IB	Investigator's Brochure
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
KL	Kellgren Lawrence
MEN2	multiple endocrine neoplasia type 2
MMRM	mixed model for repeated measures
MTC	medullary thyroid cancer
NRS	Numerical Rating Scale
OA	osteoarthritis
PGI-C	patient global impression of change
PGI-S	patient global impression of status
PRO	patient reported outcome
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
SF-36	Short Form (36) Health Survey

SUSAR	suspected unexpected serious adverse reaction
T2D	Type 2 Diabetes Mellitus
TMM	trial materials manual
WOCBP	woman of child bearing potential
WOMAC	Western Ontario McMasters Osteoarthritis Index

10.9 Appendix 9: Protocol amendment history

Protocol version 2.0 (23 September 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union[1] for the countries participating in the NN9536-4578 trial.

Overall rationale for preparing protocol, version 2.0:

The rational for preparing protocol version 2.0 is to specify that anti-obesity treatment (e.g. medication) which is not part of the trial procedures is not allowed. This is to ensure alignment with the other clinical trials in the development of semaglutide for weight management and to ensure interpretability of treatment effect.

Section # and name	Description of change	Brief rational
Section 6.5 Concomitant medication	The following sentence was added to the protocol "*During the trial subjects should not initiate any anti-obesity treatment (e.g. medication) which is not part of the trial procedures. If such treatment is initiated, the subject should be instructed to stop the anti-obesity treatment*."	To not allow for other anti-obesity therapies (medication or bariatric surgery) is crucial to control the number of subjects actually on or starting other anti-obesity therapies at start or during the trial. By including wording of preventing other anti-obesity therapies in the trial protocol, it can be expected that only a small fraction of subjects will initiate other anti-obesity therapies (as seen in the phase 3a semaglutide trials NN9536-4373, -4374, -4375 and -4376), which is considered to be sufficiently small to not affect the conclusion of semaglutide being superior to placebo in subjects with obesity and knee OA.
Section 5.2 Exclusion criteria	The following exclusion criterion was added "*Treatment with any medication for the indication of obesity within the past 90 days before screening"*	Obesity medication taken within 90 days of the screening may influence metabolism and thus potentially affect the trial results.
Section 5.2 Exclusion criteria	Exclusion criteria 5 has been updated from "*Use of pain patches, medical marijuana or opioids*" to "*Use of medical marijuana or opioids*"	Pain patches containing NSAIDs are allowed in the trial, deleting "pain patches" avoids confusion.
Section 8.2 Safety assessment	The following concomitant illness/medical history was changed to the below History of breast neoplasm History of gallbladder disease and procedure History of gastrointestinal disorder and neoplasm History of musculoskeletal system disorder History of pancreatic disease History of psychiatric disorder History of skin cancer and skin disorder History of weight disorder	Revision and clarification of the specific topics of medical history and concomitant illness that will be recorded in the eCRF.

	Other relevant concomitant illness/medical history (this also includes malignant neoplasm)	
Throughout the protocol	Re-introduction of the specification of 'pancreatitis' as 'acute pancreatitis'	Due to error the 'acute' was missing from the risk acute pancreatitis. Re-introduction of the specification of 'pancreatitis' as 'acute pancreatitis' was done to ensure alignment with the naming of the Novo Nordisk safety committee endorsed risk for semaglutide.
Section 8 Trial assessments and procedures	The following sentence was added *Subject's weight history must be recorded in the subject's medical record.*	To specify that subject's weight history is recorded.

11 References

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9.1.1 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

If applicable, Protocol Attachment II is also located in the Trial Master File.

Content: Global key staff and Country key staff.

Statistical Analysis Plan

Trial ID: NN9536-4578

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

Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

Author

[redacted]

Biostatistics Obesity

Table of contents

Page

List of abbreviations

AE	*adverse event*
ANCOVA	*analysis of covariance*
BMI	*body mass index*
CI	*confidence interval*
FAS	*full analysis set*
ICH	*International Committee on Harmonisation*
LAO-OT	*last available observation during the on-treatment period*
LAO-OT-28	*last available observation during the on-treatment period until week 28*
MedDRA	*Medical Dictionary for Regulatory Activities*
MMRM	*mixed model for repeated measurements*
OA	*osteoarthritis*
OR	*odds ratio*
PYE	*patient years of exposure*
PYO	*patient years of observation*
SAE	*serious adverse event*
SAP	*statistical analysis plan*
SAS	*safety analysis set*
SD	*standard deviation*
SF-36	*Short Form (36) Health Survey*
TEAE	*treatment-emergent adverse event*
WOMAC	*Western Ontario McMasters Osteoarthritis Index*

1 Introduction

1.1 Trial information

1.1.1 Objective(s)

1.1.1.1 Primary objective

To confirm superiority of semaglutide s.c. 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 OA in change from baseline to week 68 in body weight and knee OA-related pain.

1.1.1.2 Secondary objectives

To confirm superiority of semaglutide s.c. 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 OA in achieving body weight response criteria after 68 weeks from baseline as well as change from baseline to week 68 in knee OA-related and general physical function.

To compare the efficacy of semaglutide s.c. 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 OA in change from baseline to week 68 in waist circumference, knee OA-related stiffness, overall knee OA-related physical limitations and general health-related quality of life.

1.1.1.3 Exploratory objectives

To compare the efficacy of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo as adjunct to a reduced-calorie diet and increased physical activity in subjects with obesity and knee OA in change from baseline to week 68 in use of analgesics and on walking distance.

1.1.2 Estimands

1.1.2.1 Primary estimand

The primary clinical question of interest is: what is the average treatment effect of semaglutide s.c. 2.4 mg once-weekly relative to semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity, in patients with obesity and knee OA, measured by change from baseline to week 68 in body weight and knee OA-related pain, regardless of adherence to randomised treatment, regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injection or opioid medication) and regardless of compliance with washout period for pain medication (the latter only relevant in this context for knee OA-related pain) ("treatment policy" strategy).

The estimand is described by the following attributes (according to ICH E9(R1)):

- Treatment condition: The randomised treatment regardless of adherence or initiation of other anti-obesity therapies (as defined above) or other knee OA interventions (as defined above)

- Population: Patients with obesity and knee OA

- Endpoints: The two primary endpoints relative change in body weight and change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score both from baseline to week 68

- Remaining intercurrent events: The intercurrent events "treatment discontinuation for any reason", "initiation of other anti-obesity therapies" and "initiation of other knee OA interventions" are addressed by the treatment condition attribute. The remaining intercurrent event is "compliance with washout period for pain medication" (in general only applicable to WOMAC endpoints), which is handled by the treatment policy strategy.

- Population-level summary: Difference in mean changes between treatment conditions

A similar estimand applies to all secondary endpoints (confirmatory and supportive), which is called secondary estimand. The population-level summary for body weight response endpoints is the ratio of odds between treatment conditions.

Rationale for estimand: The primary (and secondary) estimand was requested by different regulatory authorities and it aims at reflecting how patients with obesity are treated in clinical practice

1.1.2.2 Additional estimand

An additional clinical question of interest is: what is the average treatment effect of semaglutide s.c. 2.4 mg once-weekly relative to semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity, in patients with obesity and knee OA, measured by change from baseline to week 68 in body weight and knee OA-related pain, had they remained on their randomised treatment for the entire planned duration of the trial, not initiated other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injection or opioid medication) and had they additionally complied with the washout period for pain medication (the latter only relevant in this context for knee OA-related pain) ("hypothetical" strategy).

The estimand is described by the following attributes (according to ICH E9(R1)):

- Treatment condition: The randomised treatment if patients had adhered for the entire duration of the trial, not initiated other anti-obesity therapies (as defined above) or other knee OA interventions (as defined above)
- Population: Patients with obesity and knee OA
- Endpoints: The two primary endpoints relative change in body weight and change in WOMAC pain score both from baseline to week 68
- Remaining intercurrent events: The intercurrent events "treatment discontinuation for any reason", "initiation of other anti-obesity therapies" and "initiation of other knee OA interventions" are addressed by the treatment condition attribute. The remaining intercurrent event is "compliance with washout period for pain medication" (in general only applicable to WOMAC endpoints), which is handled by the hypothetical strategy.
- Population-level summary: Difference in mean changes between treatment conditions

A similar additional estimand also applies to all secondary body weight endpoints as well as all secondary WOMAC endpoints (both confirmatory and supportive). The population-level summary for body weight response endpoints is the ratio of odds between treatment conditions.

Rationale for estimand: The additional estimand was requested by few regulatory authorities and aims at reflecting the treatment effect in the absence of intercurrent events.

1.1.3 Endpoints

1.1.3.1 Primary endpoint

Endpoint title	Time frame	Unit
Change in body weight	From baseline (week 0) to end of treatment (week 68)	%
Change in WOMAC pain score	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index

1.1.3.2 Confirmatory secondary endpoints

Endpoint title	Time frame	Unit
Achieving body weight reduction ≥5% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Achieving body weight reduction ≥10% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Change in WOMAC physical function score	From baseline (week 0) to end of treatment (week 68)	Score points

Change in SF-36 physical functioning score	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index, SF-36; Short Form (36) Health Survey

1.1.3.3 Supportive secondary endpoints

Endpoint title	Time frame	Unit
Change in waist circumference	From baseline (week 0) to end of treatment (week 68)	cm
Change in WOMAC stiffness score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in WOMAC total score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 role-physical score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 bodily pain score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 general health score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 vitality score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 social functioning score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 role-emotional score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 mental health score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 physical component summary	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 mental component summary	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index, SF-36; Short Form (36) Health Survey

In addition to the protocol specified endpoints, the following supportive secondary endpoints are defined:

Endpoint title	Time frame	Unit
Achieving body weight reduction ≥15% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Achieving body weight reduction ≥20% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Change in body weight	From baseline (week 0) to week 28	%
Change in WOMAC pain score	From baseline (week 0) to week 28	Score points

1.1.3.4 Exploratory endpoint(s)

Endpoint title	Time frame	Unit

Change in pain medication (decrease/no change/increase)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Use of allowed rescue analgesics during washout period (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Change in 6 minutes walking distance	From baseline (week 0) to end of treatment (week 68)	Meters

1.1.4 Type of trial

This is a 68-week, randomised, two-arm, double-blinded, multi-centre clinical trial comparing semaglutide s.c. 2.4 mg once-weekly with semaglutide placebo in subjects with moderate OA of one or both knees, pain due to knee OA, and obesity (BMI ≥30.0 kg/m^2).

1.2 Scope of the statistical analysis plan

This statistical analysis plan (SAP) is based on the updated protocol for trial NN9536-4578 "Effect of subcutaneous semaglutide 2.4 mg once-weekly compared to placebo in subjects with obesity and knee osteoarthritis", version 1.0 (24 July 2020) and includes more detailed procedures for executing the statistical analyses of the primary and secondary endpoints.

2 Statistical considerations

2.1 Statistical hypotheses

The tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo for the two primary and all confirmatory secondary endpoints are performed using a fixed-sequence statistical strategy and a weighted Holm-Bonferroni procedure (with weights one). For a detailed specification of statistical hypotheses for the two primary endpoints see section 2.4.2.

This strategy tests the endpoints using a predefined hierarchical order; first the two primary endpoints: body weight change (%) and change in WOMAC pain score are tested at the significance level of 5% where the alpha is split between the two endpoints using 1% for body weight change (%) and 4 % for change in WOMAC pain score.

If superiority is not confirmed for both endpoints, then the testing will stop. If the test of superiority for one of the two primary endpoints is significant, then the alpha can be recycled for the other primary endpoint, which will be tested at the 5% significance level. If both hypotheses are rejected and superiority is confirmed, then the confirmatory secondary endpoints (starting with ≥5% body weight reduction) will be tested at the 5% level. Testing for superiority of confirmatory secondary endpoints can proceed only after a statistically significant result (p-value < 5%) on the previous endpoint.

2.2 Sample size determination

The trial is designed with an effective power of 90% and 67% to detect differences on the two primary endpoints and confirmatory secondary endpoints, respectively. The effective power was calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively which is a conservative approach. The power calculations for continuous endpoints are based on a t-test on the mean difference assuming equal variances, whereas those for the categorical endpoints are based on the Pearson chi-square test for two independent proportions.

Assumptions for these calculations are presented in Table 1 and are based on findings from NN9536-4153 and NN9536 phase 3a program (STEP) as well as on relevant publications on body weight loss and knee OA outcome (using WOMAC). Two studies, Bliddal et al. and Christensen et al., found that weight loss treatment (average weight loss 7.5% and 6.8% respectively) could lead to improvements in knee OA symptoms like pain and physical function (pain score: -8.4 (-10.4 vs -2.0) with baseline score 38.4 (SD=21.1) and -5.4 (-11.4 vs -6.0) with baseline score 36.7 (SD=21.3) respectively; function score: -3.7 (-10.2 vs -6.5) with baseline score 39.2 (SD=21.4) and -9.9 (-14.9 vs -5.0) with baseline value 37.4 (SD=21.8) respectively) in obese subjects (average BMI at baseline 35.6 and 35.9 respectively).[1, 2] Aforementioned score improvements were found in treatment completers. Item responses were collected using the VAS format of the questionnaire. Bliddal et al. reported normalised sum of scores (range 0-100) and Christensen et al. reported sum of scores, which were transformed to a 0-100 range for comparison purposes. Consequently, a treatment difference for the pain score was assumed to be -9 (-11 vs -2) with SD=20; for the function score it was assumed to be -9 (-15 vs -6) with SD=19 if treated with semaglutide s.c. 2.4 mg once-weekly vs semaglutide placebo for 68 weeks. Clement et al. identified a minimum clinically important difference of 11 for pain and 9 for function and a minimum important change of 21 for pain and 16 for function for improvement in WOMAC after total knee arthroplasty.[3] Although, it is planned to use the NRS format of the questionnaire in this trial, it is known that VAS and NRS are highly correlated (r>0.93) and that VAS derived assumptions for sample size calculation are adequate and can be translated to a setting where NRS is used[4]. It is planned that the WOMAC scores (derived from NRS responses) will be transformed to a 0-100 range based on which the corresponding endpoints will be calculated.

In relation to expected treatment effects it was assumed that 20% of subjects discontinue permanently and 60% of these are retrieved at week 68. All subjects in the placebo arm are assumed to have same effect as subjects who complete the trial on placebo. Retrieved subjects in the semaglutide s.c. 2.4 mg once-weekly arm are assumed to have an effect corresponding to half the treatment difference (compared to placebo) of subjects who complete the trial on semaglutide s.c. 2.4 mg once-weekly. Non-retrieved subjects in the semaglutide s.c. 2.4 mg once-weekly arm are assumed to have an effect corresponding to placebo.

Under these assumptions and a 2:1 randomisation ratio, the desired power of at least 90% for change in WOMAC pain score is obtained with 375 subjects randomised to either receive semaglutide s.c. 2.4 mg once-weekly (250) or placebo (125).

Table 1 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number of 375 randomised subjects

Order	Endpoint	Assumed mean (±SD) or proportion for completers		Expected mean (±SD) or proportion	Expected difference or proportion ratio	Marginal power (%)	Two-sided significance level (%) *	Effective power (%)
		Semaglutide s.c. 2.4 mg once-weekly	Semaglutide placebo	Semaglutide s.c. 2.4 mg once-weekly				
1	**% body weight change #**	14.0 (±10)	3.0 (±10)	12.5 (±11)	9.5%-points	>99	1	99
1	**WOMAC pain change #**	11.0 (±20)	2.0 (±20)	9.7 (±21)	7.7 score-points	90	4	90
2	5% responders	82%	42%	76%	1.8	>99	5	90
3	10% responders	66%	24%	60%	2.5	>99	5	90
4	WOMAC function change #	15.0 (±19)	6.0 (±19)	13.7 (±20)	7.7 score-points	94	5	84
5	SF-36 physical functioning change	6.0 (±10)	2.0 (±10)	5.4 (±11)	3.4 score-points	80	5	67

SD: Standard deviation; WOMAC: Western Ontario McMasters Osteoarthritis Index ; SF-36: Short Form (36) Health Survey.
*Significance level for confirmatory secondary endpoints reflects local alpha if all superiority hypotheses for endpoints higher in the statistical hierarchy were rejected
Shown as a positive number

As currently there are no Novo Nordisk trials utilizing WOMAC, see Table 2 for alternative power calculations to the main scenario assuming varying sample size, mean difference or standard deviation.

Table 2 Marginal power for WOMAC pain change (shown as a positive number) for alternative sample size, mean difference or standard deviation

Sample size	Expected mean for semaglutide placebo	Expected mean for semaglutide s.c. 2.4 mg once-weekly	Expected difference	Common SD	Marginal power (%)
Main scenario					
375	2	9.7	7.7	21	0.900
Varying sample size					
285	2	9.7	7.7	21	0.803
303	2	9.7	7.7	21	0.828
324	2	9.7	7.7	21	0.853
348	2	9.7	7.7	21	0.877
375	2	9.7	7.7	21	0.900
411	2	9.7	7.7	21	0.925
462	2	9.7	7.7	21	0.951
543	2	9.7	7.7	21	0.975
888	2	9.7	7.7	21	>.999
Varying mean difference					
375	2	5	**3**	21	0.226
375	2	6	**4**	21	0.375
375	2	7	**5**	21	0.545
375	2	8	**6**	21	0.708
375	2	9	**7**	21	0.837
375	2	10	**8**	21	0.921
375	2	11	**9**	21	0.968
375	2	12	**10**	21	0.989
375	2	13	**11**	21	0.997
375	2	14	**12**	21	>.999
375	2	15	**13**	21	>.999
Varying standard deviation					
375	2	9.7	7.7	**10**	>.999
375	2	9.7	7.7	**11**	>.999
375	2	9.7	7.7	**12**	>.999
375	2	9.7	7.7	**13**	>.999
375	2	9.7	7.7	**14**	0.998
375	2	9.7	7.7	**15**	0.996
375	2	9.7	7.7	**16**	0.990
375	2	9.7	7.7	**17**	0.981
375	2	9.7	7.7	**18**	0.967
375	2	9.7	7.7	**19**	0.949
375	2	9.7	7.7	**20**	0.927
375	2	9.7	7.7	**21**	0.900
375	2	9.7	7.7	**22**	0.871
375	2	9.7	7.7	**23**	0.840
375	2	9.7	7.7	**24**	0.807

375	2	9.7	7.7	**25**	0.773
375	2	9.7	7.7	**26**	0.740
375	2	9.7	7.7	**27**	0.706
375	2	9.7	7.7	**28**	0.673
375	2	9.7	7.7	**29**	0.642
375	2	9.7	7.7	**30**	0.611

SD: Standard deviation.

All above outlined sample size and power considerations are for the primary estimand for primary endpoints or the secondary estimand for confirmatory secondary endpoints (treatment policy strategy). It is assumed that up to 20% of subjects discontinue permanently and 60% of these are retrieved at week 68, which amounts to 8% expected missing data at week 68. Based on NN9536 STEP 1 trial 8.8% missing in-trial data was observed after 68 weeks for the primary estimand. Any superiority conclusions will be based on the primary or secondary estimand.

For the additional estimand (hypothetical strategy) however, data from retrieved subjects are not used. Hence, it is expected that up to 20% of data will be missing at week 68. Based on NN9536 STEP 1 trial 20.6% missing on-treatment data was observed after 68 weeks for the additional estimand. This included missing data not only due to treatment discontinuation, but also due to initiation of other anti-obesity therapies (<1%). For trial NN9536 4578 slightly higher missing on-treatment data is expected due to subjects initiating other knee OA interventions (<3%) and not complying with the washout period (<10%). In NN9536 STEP 1 trial it was seen that the treatment difference in mean changes for body weight was slightly higher and standard deviation was slightly lower for the additional estimand (using on-treatment data) than for the primary estimand (using in-trial data).

2.3 Definition of analysis sets

Two analysis sets are defined:

The *full analysis set (FAS)* includes all randomised subjects according to the intention-to-treat principle. The subjects in the *FAS* contribute to the evaluation as randomised.

The *safety analysis set (SAS)* includes all randomised subjects exposed to at least one dose of randomised treatment. The subjects in the *SAS* contribute to the evaluation as treated.

Any observation excluded from the analysis database will be documented before database lock with the reason for exclusion provided. Efficacy endpoints will be analysed using the FAS; safety endpoints will be analysed using the SAS.

Two observation periods are defined for each subject:

In-trial: The *in-trial period* is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site.

On-treatment (with trial product): A time-point is considered as "on-treatment" if any dose of trial product has been administered within the prior 2 weeks (14 days). The *on-treatment period* is defined as all times which are considered on-treatment.

In general, the *on-treatment period* will therefore be from the date of first trial product administration to date of last trial product administration excluding potential off-treatment time intervals triggered by at least two consecutive missed doses.

For the evaluation of AEs, the lag time for each on-treatment time interval is 7 weeks (49 days).

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

2.4 Statistical analyses

2.4.1 General considerations

The last available and eligible observation at or before randomisation is used as the baseline value. If no assessments are available, the mean value at randomisation across all subjects is used as the baseline value.

2.4.2 Primary endpoint*(s)*

The primary endpoints are change in body weight (%) and change in WOMAC pain score from baseline (week 0) to end-of-treatment (week 68) as listed in section 1.1.3.

Change from baseline to week 68 in body weight (%) is defined as

$$\%\ \text{body weight change} = \frac{(\text{body weight at week 68} - \text{body weight at baseline})}{\text{body weight at baseline}} \times 100.$$

Change from baseline to week 68 in WOMAC pain score is defined as

$$\text{WOMAC pain score change} = \text{WOMAC pain score at week 68} - \text{WOMAC pain score at baseline}.$$

All tests are tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo.

Let $\mu_{\text{semaglutide}}$ and $\mu_{\text{semaglutide placebo}}$ denote the true mean of % body weight change or WOMAC pain score change for semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo, respectively. The null and alternative hypotheses tested are

$$H_0: \mu_{semaglutide} \geq \mu_{semaglutide\ placebo}\ vs$$
$$H_A: \mu_{semaglutide} < \mu_{semaglutide\ placebo}.$$

The null hypotheses will be rejected and superiority claimed, if the upper limit of the estimated two-sided 95% CI is below 0.

Analyses addressing the primary estimand

The following statistical analyses and imputation methods are designed to address the primary estimand.

The analysis model for change in body weight (%) and change in WOMAC pain score will be a linear regression (ANCOVA) with randomised treatment as factor and either baseline body weight (kg) or baseline WOMAC pain score as covariate assuming equal variances. The estimated treatment difference between semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

Multiple imputation approach using retrieved subjects (RD-MI): The primary imputation approach for the primary estimand is a multiple imputation similar to the one described by McEvoy[1]. All available data at week 68 are used and missing values at week 68 will be imputed and the endpoint will be derived from the imputed values. For subjects in the semaglutide s.c. 2.4 mg once-weekly and the semaglutide placebo arms, missing measurements at week 68 for non-retrieved subjects are imputed using assessments from retrieved subjects in each randomised treatment arm. This will be done according to the timing of last available observation during the on-treatment period (LAO-OT) as well as by taking sex, baseline BMI and baseline body weight / WOMAC pain score into account. Missing measurements at week 68 for subjects on randomised treatment (at week 68) are imputed by sampling from available measurements at week 68 from subjects on randomised treatment in the relevant randomised treatment arms. The multiple imputation approach is done in three steps:

- **Imputation:** Defines an imputation model using retrieved subjects from FAS and done within groups defined by randomised treatment. The model will be a linear regression of body weight (kg) / WOMAC pain score at week 68 with sex (male/female), baseline BMI (kg/m^2) (in categories -<35, 35-<40, ≥40) and baseline body weight (kg) / WOMAC pain score and LAO-OT of body weight (kg) / WOMAC pain score as covariates. No interactions will be included. The grouping of timing will be done by quarters (intervals of 17 weeks). If timing by quarters is too restrictive, halves (intervals of 34 weeks) or excluding timing will be used. The timing by quarters or halves is defined as too restrictive if the imputation model cannot be fit due to inadequate numbers of retrieved subjects in 1 or more groups. If the imputation model still cannot be fit after excluding timing then the model will be further reduced until the model can be fit. Reduction will be done in a fixed order by first removing sex, then collapsing the two

highest baseline BMI groups into one (≥35) and finally removing baseline BMI group. If no LAO-OT exists post-baseline then the LAO-OT will be the baseline body weight / WOMAC pain score and the timing will be 0. If any subjects are on-treatment with missing values at week 68, an imputation model for missing body weight / WOMAC pain score at week 68 will be defined using subjects on-treatment and with available observations at week 68 in a similar way. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 68 body weight / WOMAC pain score values for each randomised treatment arm. This will be done 1,000 times and results in 1,000 complete data sets.

- **Analysis**: Analysis of each of the 1,000 complete data sets, using the analysis models (ANCOVA and logistic regression) results in 1,000 times 2 estimations.
- **Pooling**: Integrates the 1,000 times 2 estimation results into two final results using Rubin's formula.

Based on NN9536-4153 phase 2 results 1,000 copies should be sufficient to establish stable results. If 1,000 copies are insufficient, 10,000 copies will be used. The multiple imputations will be generated using Novo Nordisk trial number 95364578 as seed number. In addition to the seed number, it is specified that the dataset is sorted by subject ID.

Sensitivity analyses

Jump to reference multiple imputation approach (J2R-MI): Missing values of body weight / WOMAC pain score at week 68 for both the semaglutide 2.4 mg and semaglutide placebo group are imputed by sampling among all available assessments at week 68 in the semaglutide placebo group. This approach makes the assumption that subjects instantly after discontinuation lose any effect of randomised treatment beyond what can be expected from semaglutide placebo treatment as adjunct to reduced-calorie diet and increased physical activity[6]. The multiple imputation approach is done as above with the first step replaced by

- **Imputation**: Defines an imputation model using semaglutide placebo subjects from FAS with a week 68 measurement. The model will be a linear regression of body weight (kg) /WOMAC pan score at week 68 with sex (male/female), BMI (kg/m^2) (in categories -<35, 35-<40, ≥40 as factors and baseline body weight (kg) / WOMAC pain score as covariate. No interactions will be included. If the imputation model cannot be fit due to inadequate numbers of retrieved subjects in 1 or more groups, then the imputation model will be reduced until the model can be fit. Reduction will be done in a fixed order by first removing sex, then collapsing the two highest baseline BMI-groups into one (≥35) and finally removing baseline BMI-group. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 68 body weight / WOMAC pain score

values for each randomised treatment arm. This will be done 1,000 times and results in 1,000 complete data sets.

Tipping-point multiple imputation analysis (TP-MI): First, missing data are imputed according to the primary multiple imputation approach. Then, a penalty is added to the imputed values at week 68. The approach is to explore a range of penalties for both treatment groups, and the impact these would have on the study conclusions. The 2-dimensional space of penalties covering the range from -30% to 30% (for body weight change) / -50 to 50 (for WOMAC pain score) will be explored for both treatment groups. This sensitivity analysis evaluates the robustness of the superiority conclusions to departures from the observed change in body weight / WOMAC pain score in both treatment groups.

ANCOVA for unequal variances: An alternative analysis model similar to the primary analysis model (ANCOVA), following the primary imputation approach (RD-MI), but assuming unequal variances instead of equal variances. The analysis model includes randomised treatment as factor and either baseline body weight (kg) or baseline WOMAC pain score as covariate. The estimated treatment difference between semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

Analysis addressing the additional estimand

The additional estimand for change in body weight (%) and change in WOMAC pain score will be assessed using a mixed model for repeated measurements (MMRM) approach.

Week 68 assessments for retrieved subjects are not used in this analysis. The MMRM will use assessments only from subjects who are taking the randomised treatment until end of treatment or until first discontinuation of randomised treatment. For subjects who experience other intercurrent events before completion or first discontinuing of randomised treatment, the date of initiating other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injections) will be used as latest date for using assessments in this MMRM. Additionally, for the MMRM analysing change in WOMAC pain score, assessments from subjects incompliant with the washout period for pain medication will not be used. The MMRM will be fitted using the change (% body weight change or change in WOMAC pain score) and the same factor and covariate as for the primary analysis all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

2.4.3 Secondary endpoints

2.4.3.1 Confirmatory secondary endpoints

All tests are tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo.

Analyses addressing the secondary estimand

The confirmatory secondary endpoints addressing the secondary estimand will be analysed in a similar way as the primary endpoints addressing the primary estimand.

The statistical model for continuous confirmatory secondary endpoints will be the same linear regression as for the primary endpoints (ANCOVA) with treatment as a factor and the baseline value of the endpoint as covariate. The statistical model for confirmatory body weight responder endpoints is a logistic regression using randomised treatment as a factor and baseline body weight (kg) as covariate. The estimated odds ratio (OR) between semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval and corresponding p-value.

The imputation approach is the same multiple imputation using retrieved subjects as described in section 2.4.12.4.2 and taking the baseline value of the endpoint into account.

Sensitivity analyses for confirmatory secondary endpoints

For all continuous confirmatory secondary endpoints a sensitivity analysis using jump to reference as imputation approach will be carried out. For all confirmatory body weight responder endpoints a sensitivity analysis using non-retrieved subjects as non-responders will be carried out.

Analyses addressing the additional estimand

The confirmatory secondary endpoint change in WOMAC physical function score addressing the additional estimand will be analysed using the same MMRM as described for the primary endpoint change in WOMAC pain score addressing the additional estimand with randomised treatment as a factor and the baseline value of the endpoint as covariate.

The confirmatory body weight responder endpoints addressing the additional estimand will be analysed using the same MMRM described for the primary endpoint change in body weight (%) addressing the additional estimand except that body weight (kg) will be used as response variable in the model. For subjects with missing body weight at week 68, individual values for body weight will be predicted from the MMRM and used to classify each subject as 5% or 10% responder or not. This classification will then be analysed using a logistic regression model with randomised treatment as a factor and baseline body weight (kg) as covariate.

2.4.3.2 Supportive secondary endpoints

Analyses addressing the secondary estimand

The supportive secondary endpoints addressing the secondary estimand will be analysed in a similar way as the primary endpoints addressing the primary estimand.

The statistical model for continuous confirmatory secondary endpoints will be the same linear regression as for the primary endpoints (ANCOVA) with treatment as a factor and the baseline value of the endpoint as covariate. The statistical model for confirmatory body weight responder endpoints is a logistic regression using randomised treatment as a factor and baseline body weight (kg) as covariate. The estimated odds ratio (OR) between semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval and corresponding p-value.

The imputation approach is the same multiple imputation using retrieved subjects as described in section 2.4.12.4.2 and taking the baseline value of the endpoint into account. For the analyses of change in WOMAC pain score and % change in body weight from baseline (week 0) to week 28, imputation will be done according to the timing of last available observation during the on-treatment period until week 28 (LAO-OT-28). The imputation model will be a linear regression of body weight (kg) / WOMAC pain score at week 28 with sex (male/female), baseline BMI (kg/m2) (in categories -<35, 35-<40, ≥40) and baseline body weight (kg) / WOMAC pain score and LAO-OT-28 of body weight (kg) / WOMAC pain score as covariates. The grouping of timing will be done by quarters (intervals of 7 weeks). If timing by quarters is too restrictive, halves (intervals of 14 weeks) or excluding timing will be used. If any subjects are on-treatment with missing values at week 28, an imputation model for missing body weight / WOMAC pain score at week 28 will be defined using subjects on-treatment and with available observations at week 28 in a similar way. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 28 body weight / WOMAC pain score values for each randomised treatment arm.

Analyses addressing the additional estimand

Supportive secondary body weight and WOMAC endpoints addressing the additional estimand will be analysed using the same MMRM as described for the primary endpoint change in WOMAC pain score addressing the additional estimand with randomised treatment as a factor and the baseline value of the endpoint as covariate.

Supportive secondary body weight responder endpoints addressing the additional estimand will be analysed using the same MMRM described for the primary endpoint change in body weight (%) addressing the additional estimand except that body weight (kg) will be used as response variable in the model. For subjects with missing body weight at week 68, individual values for body weight will be predicted from the MMRM and used to classify each subject as 15% or 20% responder or not. This classification will then be analysed using a logistic regression model with randomised treatment as a factor and baseline body weight (kg) as covariate.

2.4.4 Exploratory endpoints

Descriptive statistics will be provided for exploratory endpoints.

2.4.5 Safety endpoints

Adverse events will be defined as "treatment-emergent" (TEAE), if the onset of the event occurs in the on-treatment period. TEAEs and SAEs will be summarised by descriptive statistics, such as frequencies and rates. No formal statistical inference will be carried out based on the number of TEAEs and SAEs. All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

3 Change log

SAP Change log

Version	Reason for change
1.0	New

4 References

1. Bliddal H, Leeds AR, Stigsgaard L, Astrup A, Christensen R. Weight loss as treatment for knee osteoarthritis symptoms in obese patients: 1-year results from a randomised controlled trial. Ann Rheum Dis. 2011;70(10):1798-803.
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Statistical Analysis Plan

Trial ID: NN9536-4578

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

Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

Author

[redacted]

Biostatistics

Table of contents Page

List of abbreviations

AE	*adverse event*
ANCOVA	*analysis of covariance*
BMI	*body mass index*
FAS	*full analysis set*
ICH	*International Council for Harmonisation*
J2R-MI	*jump to reference multiple imputation*
LAO-OT	*last available observation during the on-treatment period*
MedDRA	*Medical Dictionary for Regulatory Activities*
MMRM	*mixed model for repeated measurements*
NRS	*numerical rating scale*
NSAIDs	*non-steroidal anti-inflammatory drugs*
OA	*osteoarthritis*
OR	*odds ratio*
PYE	*patient years of exposure*
PYO	*patient years of observation*
RD-MI	*retrieved dropout multiple imputation*
SAE	*serious adverse event*
SAP	*statistical analysis plan*
SAS	*safety analysis set*
SD	*standard deviation*
SF-36	*Short Form (36) Health Survey*
TEAE	*treatment-emergent adverse event*
TP-MI	*tipping-point multiple imputation*
VAS	*visual analogue scale*
WOMAC	*Western Ontario McMasters Osteoarthritis Index*

Version history

This statistical analysis plan (SAP) is based on the updated protocol for trial NN9536-4578 "Effect of subcutaneous semaglutide 2.4 mg once-weekly compared to placebo in subjects with obesity and knee osteoarthritis", version 3.0 (21 April 2021).

SAP version	Change	Rationale
1.0 (03 August 2020)	Not applicable	Original version
2.0 (03 May 2021)	The following supportive secondary endpoints have been added: • Amount of allowed rescue analgesics used during wash out • Change in pain intensity (NRS) • Achieving WOMAC pain reduction ≥30% (yes/no) • Achieving WOMAC pain reduction ≥50% (yes/no) • Achieving pain intensity (NRS) reduction ≥30% (yes/no) • Achieving pain intensity (NRS) reduction ≥50% (yes/no) The following supportive secondary endpoints are no longer in scope: • Change in body weight from baseline to week 28 • Change in WOMAC pain score from baseline to week 28 The exploratory endpoint "Change in pain medication (decrease/no change/increase)" has been renamed to "Change in pain medication" with dose as units. The following supportive secondary endpoints have been recategorized as exploratory endpoints: • Change in SF-36 role-physical score • Change in SF-36 vitality score • Change in SF-36 social functioning score • Change in SF-36 role-emotional score • Change in SF-36 mental health score	The overall rationale for preparing protocol version 3.0 was to include a pain and pain medication diary, to update supportive secondary endpoints and adjust WOMAC assessments with respect to frequency and recall period.
3.0 (20 September 2021)	It has been specified in section 2.4.1 how the composite WOMAC scores are derived. It has been specified in more detail how missing WOMAC pain scores are handled in section 2.4.2 and 2.4.3.2, 2.4.3. For the endpoints related to change in WOMAC scores it is specified that imputation of missing values is done at the item level and not at the composite score level.	Correspondence with the Food and Drug Administration, US, has prompted further specification of how missing data in the WOMAC

	For the tipping-point multiple imputation analysis of the WOMAC pain score, the penalties added has been changed from -50/50 to -5/5 since WOMAC scores will be reported on a 0-10 point scale and not on a 0-100 point scale. In section 2.2 the following sentence has been deleted: "It is planned that the WOMAC scores (derived from NRS responses) will be transformed to a 0-100 range based on which the corresponding endpoints will be calculated."	questionnaire are handled.
4.0 (28 February 2022)	The final reporting scale of WOMAC scores was set to be on the 0-100 range in order to comply with the protocol, specifically the randomisation criterion:" A score of at least 40 on the WOMAC version 3.1 pain subscale (range 0-100 normalised Numerical Rating Scale (NRS))". In consequence… • the following sentence was again added to section 2.2: "It is planned that the WOMAC scores (derived from NRS responses) will be transformed to a 0-100 range based on which the corresponding endpoints will be calculated.", • section 2.4.1 describing how the composite WOMAC scores are derived was updated to reflect final reporting scale, i.e. normalisation to 0-100, • for the tipping-point multiple imputation analysis of the WOMAC pain score, the penalties were changed back from -5/5 to -50/50 since WOMAC scores will be reported on a 0-100 point scale. The following endpoints were added to section 1.1.3.3: "Subject achieving threshold(s) for clinically meaningful within-subject change in WOMAC pain score" (similar for WOMAC physical function score and SF-36 physical functioning score), where the responder thresholds are a direct result of the analyses described in the PAP. The process of deriving response definition values is described in brief in section 2.4.3.2. In section 2.4.2 the imputation approach for WOMAC (item) scores was clarified. In section 2.4.3 it was added that risk differences will be reported for binary endpoints.	Compliance with protocol and finalisation of the psychometric analysis report (PAP).
5.0 (17 May 2023)	In the estimand description, the relevance of washout compliance intercurrent event was clarified for secondary endpoints.	Correspondence with the Food and Drug Administration, US, has prompted further clarifications on

	The endpoint "Change in SF-36 general health score" has been moved from supportive secondary to exploratory in alignment with protocol. Supportive secondary endpoint of "Change in pain medication" was changed to "Use of pain medication" to reflect descriptive character of the endpoint. The calculation of WOMAC scores, including handling of partially missing assessments, has been clarified in details in section 2.4.1. In this section it was also clarified that SF-36 scores are norm based scores obtained from dedicated software. In section 2.4.2 it has been clarified that the primary endpoint related to WOMAC is derived based on transformed and normalized WOMAC score as described in 2.4.1. Prompted by FDA feedback, the decision on imputing data on the item level was retracted and it was clarified that missing WOMAC assessments will be imputed on the score level. In section 2.4.2 additional sensitivity analysis was added for the primary endpoint of change in WOMAC pain score to address potential date/visit mismatch for 7 subjects. Tables Table 2-4, Table 2-5, Table 2-7, Table 2-8 were added to give an overview of all planned analysis on all endpoints. In section 2.4.3 it has been clarified that MMRM on endpoints related to WOMAC and SF-36 analysis addressing additional estimand will not use assessments not collected in compliance with the washout period for pain medication. In section 2.4.3.1 the description of analyses were updated to include the confirmatory secondary endpoint of change in SF-36 physical functioning. In section 2.4.3.2 it was clarified that pain intensity (NRS) for each subject will be calculated as the mean of the available daily pain scores reported from 4 up to 7 days prior to the visit. The exclusion of data reported in washout period for pain intensity was done to facilitate interpretation of the results without imposed limitations on pain medication use. Additionally, it was noted that all endpoints derived from pain	WOMAC scores calculation (including handling of partially missing assessment).

	medication diary (use of pain medication and endpoints related to use of allowed rescue analgesics during washout period) will be analysed descriptively and descriptive statistics to be used were listed. Also, detailed definitions for deriving endpoints related to rescue analgesics from pain medication diary were specified. The final thresholds are established based on FAS and prior to unblinding as per FDA request. This has been reflected in section 2.4.3.2 and the description of preliminary thresholds evaluation has been removed as no longer relevant. A table Table 2-6 summarising thresholds for meaningful within-patient change used in the PROs responder definitions was added in section 2.4.3.2.	
6.0 (13 Nov 2023)	In section 2.4.2 the reduction procedure for imputation model was optimized and the description of further step in the procedure was added. In section 2.4.3.1 the imputation approach for endpoints related to pain intensity (NRS) was changed to J2R-MI.	Corrections to imputation model reduction and imputation approach for endpoints related to pain intensity (NRS) were prompted by issues related to fitting the imputation model due to low availability of retrieved data for these endpoints.

1 Introduction

1.1 Trial information

1.1.1 Objective(s)

1.1.1.1 Primary objective

To confirm superiority of semaglutide s.c. 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 OA in change from baseline to week 68 in body weight and knee OA-related pain.

1.1.1.2 Secondary objectives

To confirm superiority of semaglutide s.c. 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 OA in achieving body weight response criteria after 68 weeks from baseline as well as change from baseline to week 68 in knee OA-related and general physical function.

To compare the efficacy of semaglutide s.c. 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 OA in change from baseline to week 68 in waist circumference, knee OA-related stiffness, overall knee OA-related physical limitations and general health-related quality of life.

1.1.1.3 Exploratory objectives

To compare the efficacy of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo as adjunct to a reduced-calorie diet and increased physical activity in subjects with obesity and knee OA in change from baseline to week 68 in use of analgesics and on walking distance.

1.1.2 Estimands

1.1.2.1 Primary estimand

The primary clinical question of interest is: what is the average treatment effect of semaglutide s.c. 2.4 mg once-weekly relative to semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity, in patients with obesity and knee OA, measured by change from baseline to week 68 in body weight and knee OA-related pain, regardless of adherence to randomised treatment, regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injection or opioid medication) and regardless of compliance with washout period for pain medication (the latter only relevant in this context for knee OA-related pain) ("treatment policy" strategy).

The estimand is described by the following attributes (according to ICH E9(R1)):

- Treatment condition: The randomised treatment regardless of adherence or initiation of other anti-obesity therapies (as defined above) or other knee OA interventions (as defined above)
- Population: Patients with obesity and knee OA

- Endpoints: The two primary endpoints relative change in body weight and change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score both from baseline to week 68
- Remaining intercurrent events: The intercurrent events "treatment discontinuation for any reason", "initiation of other anti-obesity therapies" and "initiation of other knee OA interventions" are addressed by the treatment condition attribute. The remaining intercurrent event is "compliance with washout period for pain medication" (in general only applicable to WOMAC endpoints), which is handled by the treatment policy strategy
- Population-level summary: Difference in mean changes between treatment conditions

A similar estimand applies to secondary endpoints (confirmatory, supportive) and exploratory endpoints related to body weight, waist circumference, WOMAC, SF-36 and pain intensity (NRS), which is called secondary estimand. The population-level summary for body weight response and WOMAC pain response endpoints is the ratio of odds between treatment conditions.

Rationale for estimand: The primary (and secondary) estimand was requested by different regulatory authorities and it aims at reflecting how patients with obesity are treated in clinical practice

1.1.2.2 Additional estimand

An additional clinical question of interest is: what is the average treatment effect of semaglutide s.c. 2.4 mg once-weekly relative to semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity, in patients with obesity and knee OA, measured by change from baseline to week 68 in body weight and knee OA-related pain, had they remained on their randomised treatment for the entire planned duration of the trial, not initiated other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injection or opioid medication) and had they additionally complied with the washout period for pain medication (the latter only relevant in this context for knee OA-related pain) ("hypothetical" strategy).

The estimand is described by the following attributes (according to ICH E9(R1)):

- Treatment condition: The randomised treatment if patients had adhered for the entire duration of the trial, not initiated other anti-obesity therapies (as defined above) or other knee OA interventions (as defined above)
- Population: Patients with obesity and knee OA
- Endpoints: The two primary endpoints relative change in body weight and change in WOMAC pain score both from baseline to week 68
- Remaining intercurrent events: The intercurrent events "treatment discontinuation for any reason", "initiation of other anti-obesity therapies" and "initiation of other knee OA interventions" are addressed by the treatment condition attribute. The remaining intercurrent event is "compliance with washout period for pain medication" (in general only applicable to WOMAC endpoints), which is handled by the hypothetical strategy.
- Population-level summary: Difference in mean changes between treatment conditions

A similar additional estimand applies to secondary endpoints (confirmatory and supportive) and exploratory endpoints related to body weight, waist circumference, WOMAC, SF-36 and pain intensity (NRS). The remaining intercurrent event of "compliance with washout period for pain medication" is considered relevant for all WOMAC and SF-36 related endpoints. The population-level summary for body weight response and WOMAC pain response endpoints is the ratio of odds between treatment conditions.

Rationale for estimand: The additional estimand was requested by few regulatory authorities and aims at reflecting the treatment effect in the absence of intercurrent events.

1.1.3 Endpoints

1.1.3.1 Primary endpoints

Endpoint title	Time frame	Unit
Change in body weight	From baseline (week 0) to end of treatment (week 68)	%
Change in WOMAC pain score	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index

1.1.3.2 Confirmatory secondary endpoints

Endpoint title	Time frame	Unit
Achieving body weight reduction ≥5% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Achieving body weight reduction ≥10% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Change in WOMAC physical function score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 physical functioning score	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index, SF-36; Short Form (36) Health Survey

1.1.3.3 Supportive secondary endpoints

Endpoint title	Time frame	Unit
Change in waist circumference	From baseline (week 0) to end of treatment (week 68)	cm
Change in WOMAC stiffness score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in WOMAC total score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 bodily pain score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 physical component summary	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 mental component summary	From baseline (week 0) to end of treatment (week 68)	Score points
Use of allowed rescue analgesics during wash out	From baseline (week 0) to end of treatment (week 68)	Count of subjects

Amount of allowed rescue analgesics used during wash out	From baseline (week 0) to end of treatment (week 68)	Dose
Use of pain medication	From baseline (week 0) to end of treatment (week 68)	Dose
Change in pain intensity (NRS)	From baseline (week 0) to end of treatment (week 68)	Score points

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index, SF-36; Short Form (36) Health Survey

In addition to the protocol specified endpoints, the following supportive secondary endpoints are defined:

Endpoint title	Time frame	Unit
Achieving body weight reduction ≥15% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Achieving body weight reduction ≥20% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Achieving WOMAC pain reduction ≥30% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Achieving WOMAC pain reduction ≥50% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Achieving threshold(s) for clinically meaningful within-subject change in WOMAC pain score	From baseline (week 0) to end of treatment (week 68)	Count of subjects
Achieving threshold(s) for clinically meaningful within-subject change in WOMAC physical function score	From baseline (week 0) to end of treatment (week 68)	Count of subjects
Achieving threshold(s) for clinically meaningful within-subject change in SF-36 physical functioning score	From baseline (week 0) to end of treatment (week 68)	Count of subjects
Achieving pain intensity (NRS) reduction ≥30% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject
Achieving pain intensity (NRS) reduction ≥50% (yes/no)	From baseline (week 0) to end of treatment (week 68)	Count of subject

1.1.3.4 Exploratory endpoint(s)

Endpoint title	Time frame	Unit
Change in 6 minutes walking distance	From baseline (week 0) to end of treatment (week 68)	Meters
Change in SF-36 role-physical score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 general health score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 vitality score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 social functioning score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 role-emotional score	From baseline (week 0) to end of treatment (week 68)	Score points
Change in SF-36 mental health score	From baseline (week 0) to end of treatment (week 68)	Score points

1.1.4 Type of trial

This is a 68-week, randomised, two-arm, double-blinded, multi-centre clinical trial comparing semaglutide s.c. 2.4 mg once-weekly with semaglutide placebo in subjects with moderate OA of one or both knees, pain due to knee OA, and obesity (BMI ≥30.0 kg/m^2).

1.2 Scope of the statistical analysis plan

This statistical analysis plan (SAP) is based on the updated protocol for trial NN9536-4578 "Effect of subcutaneous semaglutide 2.4 mg once-weekly compared to placebo in subjects with obesity and knee osteoarthritis", version 3.0 (21 April 2021) and includes more detailed procedures for executing the statistical analyses.

2 Statistical considerations

2.1 Statistical hypotheses

The tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo for the two primary and all confirmatory secondary endpoints are performed using a fixed-sequence statistical strategy and a weighted Holm-Bonferroni procedure (with weights one). For a detailed specification of statistical hypotheses for the two primary endpoints see section 2.4.2.

This strategy tests the endpoints using a predefined hierarchical order; first the two primary endpoints: body weight change (%) and change in WOMAC pain score are tested at the significance level of 5% where the alpha is split between the two endpoints using 1% for body weight change (%) and 4% for change in WOMAC pain score.

If superiority is not confirmed for both endpoints, then the testing will stop. If the test of superiority for one of the two primary endpoints is significant, then the alpha can be recycled for the other primary endpoint, which will be tested at the 5% significance level. If both hypotheses are rejected and superiority is confirmed, then the confirmatory secondary endpoints (starting with ≥5% body weight reduction) will be tested at the 5% level. Testing for superiority of confirmatory secondary endpoints can proceed only after a statistically significant result (p-value < 5%) on the previous endpoint.

2.2 Sample size determination

The trial is designed with an effective power of 90% and 67% to detect differences on the two primary endpoints and confirmatory secondary endpoints, respectively. The effective power was calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively which is a conservative approach. The power calculations for continuous endpoints are based on a t-test on the mean difference assuming equal variances, whereas those for the categorical endpoints are based on the Pearson chi-square test for two independent proportions.

Assumptions for these calculations are presented in Table 2-1 and are based on findings from NN9536-4153 and NN9536 phase 3a program (STEP) as well as on relevant publications on body weight loss and knee OA outcome (using WOMAC). Two studies, Bliddal et al. and Christensen et al., found that weight loss treatment (average weight loss 7.5% and 6.8% respectively) could lead to improvements in knee OA symptoms like pain and physical function (pain score: -8.4 (-10.4 vs -2.0) with baseline score 38.4 (SD=21.1) and -5.4 (-11.4 vs -6.0) with baseline score 36.7 (SD=21.3) respectively; function score: -3.7 (-10.2 vs -6.5) with baseline score 39.2 (SD=21.4) and -9.9 (-14.9 vs -5.0) with baseline value 37.4 (SD=21.8) respectively) in obese subjects (average BMI at baseline 35.6 and 35.9 respectively)[4, 5]. Aforementioned score improvements were found in treatment completers. Item responses were collected using the visual analogue scale (VAS) format of the questionnaire. Bliddal et al. reported normalised sum of scores (range 0-100) and Christensen et al. reported sum of scores, which were transformed to a 0-100 range for comparison purposes. Consequently, a treatment difference for the pain score was assumed to be -9 (-11 vs -2) with SD=20; for the function score it was assumed to be -9 (-15 vs -6) with SD=19 if treated with semaglutide s.c. 2.4 mg once-weekly vs semaglutide placebo for 68 weeks. Clement et al. identified a minimum clinically important difference of 11 for pain and 9 for function and a minimum

important change of 21 for pain and 16 for function for improvement in WOMAC after total knee arthroplasty.[5] Although, it is planned to use the numerical rating scale (NRS) format of the questionnaire in this trial, it is known that VAS and NRS are highly correlated (r>0.93) and that VAS derived assumptions for sample size calculation are adequate and can be translated to a setting where NRS is used[6]. It is planned that the WOMAC scores (derived from NRS responses) will be transformed to a 0-100 range based on which the corresponding endpoints will be calculated.

In relation to expected treatment effects it was assumed that 20% of subjects discontinue permanently and 60% of these are retrieved at week 68. All subjects in the placebo arm are assumed to have same effect as subjects who complete the trial on placebo. Retrieved subjects in the semaglutide s.c. 2.4 mg once-weekly arm are assumed to have an effect corresponding to half the treatment difference (compared to placebo) of subjects who complete the trial on semaglutide s.c. 2.4 mg once-weekly. Non-retrieved subjects in the semaglutide s.c. 2.4 mg once-weekly arm are assumed to have an effect corresponding to placebo.

Under these assumptions and a 2:1 randomisation ratio, the desired power of at least 90% for change in WOMAC pain score is obtained with 375 subjects randomised to either receive semaglutide s.c. 2.4 mg once-weekly (250) or placebo (125).

Table 2-1 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number of 375 randomised subjects

Order	Endpoint	Assumed mean (±SD) or proportion for completers		Expected mean (±SD) or proportion	Expected difference or proportion ratio	Marginal power (%)	Two-sided significance level (%) *	Effective power (%)
		Semaglutide s.c. 2.4 mg once-weekly	Semaglutide placebo	Semaglutide s.c. 2.4 mg once-weekly				
1	% body weight change #	14.0 (±10)	3.0 (±10)	12.5 (±11)	9.5%-points	>99	1	99
1	WOMAC pain change #	11.0 (±20)	2.0 (±20)	9.7 (±21)	7.7 score-points	90	4	90
2	5% responders	82%	42%	76%	1.8	>99	5	90
3	10% responders	66%	24%	60%	2.5	>99	5	90
4	WOMAC function change #	15.0 (±19)	6.0 (±19)	13.7 (±20)	7.7 score-points	94	5	84
5	SF-36 physical functioning change	6.0 (±10)	2.0 (±10)	5.4 (±11)	3.4 score-points	80	5	67

SD: Standard deviation; WOMAC: Western Ontario McMasters Osteoarthritis Index ; SF-36: Short Form (36) Health Survey.

*Significance level for confirmatory secondary endpoints reflects local alpha if all superiority hypotheses for endpoints higher in the statistical hierarchy were rejected

Shown as a positive number

As currently there are no Novo Nordisk trials utilising WOMAC, see Table 2-2 for alternative power calculations to the main scenario assuming varying sample size, mean difference or standard deviation.

Table 2-2 Marginal power for WOMAC pain change (shown as a positive number) for alternative sample size, mean difference or standard deviation

Sample size	Expected mean for semaglutide placebo	Expected mean for semaglutide s.c. 2.4 mg once-weekly	Expected difference	Common SD	Marginal power (%)
Main scenario					
375	2	9.7	7.7	21	0.900
Varying sample size					
285	2	9.7	7.7	21	0.803
303	2	9.7	7.7	21	0.828
324	2	9.7	7.7	21	0.853
348	2	9.7	7.7	21	0.877
375	2	9.7	7.7	21	0.900
411	2	9.7	7.7	21	0.925
462	2	9.7	7.7	21	0.951
543	2	9.7	7.7	21	0.975
888	2	9.7	7.7	21	>.999
Varying mean difference					
375	2	5	**3**	21	0.226
375	2	6	**4**	21	0.375
375	2	7	**5**	21	0.545
375	2	8	**6**	21	0.708
375	2	9	**7**	21	0.837
375	2	10	**8**	21	0.921
375	2	11	**9**	21	0.968
375	2	12	**10**	21	0.989
375	2	13	**11**	21	0.997
375	2	14	**12**	21	>.999
375	2	15	**13**	21	>.999
Varying standard deviation					
375	2	9.7	7.7	**10**	>.999
375	2	9.7	7.7	**11**	>.999
375	2	9.7	7.7	**12**	>.999
375	2	9.7	7.7	**13**	>.999
375	2	9.7	7.7	**14**	0.998
375	2	9.7	7.7	**15**	0.996
375	2	9.7	7.7	**16**	0.990
375	2	9.7	7.7	**17**	0.981
375	2	9.7	7.7	**18**	0.967
375	2	9.7	7.7	**19**	0.949
375	2	9.7	7.7	**20**	0.927
375	2	9.7	7.7	**21**	0.900

375	2	9.7	7.7	**22**	0.871
375	2	9.7	7.7	**23**	0.840
375	2	9.7	7.7	**24**	0.807
375	2	9.7	7.7	**25**	0.773
375	2	9.7	7.7	**26**	0.740
375	2	9.7	7.7	**27**	0.706
375	2	9.7	7.7	**28**	0.673
375	2	9.7	7.7	**29**	0.642
375	2	9.7	7.7	**30**	0.611

SD: Standard deviation.

All above outlined sample size and power considerations are for the primary estimand for primary endpoints or the secondary estimand for confirmatory secondary endpoints (treatment policy strategy). It is assumed that up to 20% of subjects discontinue permanently and 60% of these are retrieved at week 68, which amounts to 8% expected missing data at week 68. Based on NN9536 STEP 1 trial 8.8% missing in-trial data was observed after 68 weeks for the primary estimand. Any superiority conclusions will be based on the primary or secondary estimand.

For the additional estimand (hypothetical strategy) however, data from retrieved subjects are not used. Hence, it is expected that up to 20% of data will be missing at week 68. Based on NN9536 STEP 1 trial 20.6% missing on-treatment data was observed after 68 weeks for the additional estimand. This included missing data not only due to treatment discontinuation, but also due to initiation of other anti-obesity therapies (<1%). For trial NN9536-4578 slightly higher missing on-treatment data is expected due to subjects initiating other knee OA interventions (<3%) and not complying with the washout period (<10%). In NN9536 STEP 1 trial it was seen that the treatment difference in mean changes for body weight was slightly higher and standard deviation was slightly lower for the additional estimand (using on-treatment data) than for the primary estimand (using in-trial data).

2.3 Definition of analysis sets

Two analysis sets are defined:

The *full analysis set (FAS)* includes all randomised subjects according to the intention-to-treat principle. The subjects in the *FAS* contribute to the evaluation as randomised.

The *safety analysis set (SAS)* includes all randomised subjects exposed to at least one dose of randomised treatment. The subjects in the *SAS* contribute to the evaluation as treated.

Any observation excluded from the analysis database will be documented before database lock with the reason for exclusion provided. Efficacy endpoints will be analysed using the FAS; safety endpoints will be analysed using the SAS.

Two observation periods are defined for each subject:

In-trial: The *in-trial period* is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site.

On-treatment (with trial product): A time-point is considered as "on-treatment" if any dose of trial product has been administered within the prior 2 weeks (14 days). The *on-treatment period* is defined as all times which are considered on-treatment.

In general, the *on-treatment period* will therefore be from the date of first trial product administration to date of last trial product administration excluding potential off-treatment time intervals triggered by at least two consecutive missed doses.

For the evaluation of AEs, the lag time for each on-treatment time interval is 7 weeks (49 days).

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

2.4 Statistical analyses

2.4.1 General considerations

The last available and eligible observation at or before randomisation is used as the baseline value. If no assessments are available, the mean value at randomisation across all subjects is used as the baseline value.

WOMAC scores considerations

The WOMAC raw pain score is derived as the sum of the 5 item scores in the pain domain. The WOMAC raw physical function score is derived as the sum of the 17 item scores in the physical function domain. The WOMAC raw stiffness score is derived as the sum of the 2 item scores in the stiffness domain. The WOMAC raw total score is derived as the sum of all 24 item scores.

All WOMAC raw scores (domain scores and total score) will be normalised and expressed on a 0-100 scale. This is done by dividing raw score by the highest possible value of the raw score for the domain (see Table 2-3) and multiplying by 100.

Handling partially missing responses

In the event of missing items the response for the domain can still be considered valid. The minimal numbers of available items required per domain for the score to be calculated from the data are presented in the Table 2-3. If the number of available items criterium for the domain score validity is not met, the raw score cannot be calculated and is considered missing. Otherwise the raw score is calculated as an average of the available items and multiplied by number of all items in the domain. The total score is calculated from the data only if all 3 domain scores are valid.

Table 2-3 WOMAC domain score validity and calculation with missing item scores overview.

Domain	Number of items	Maximum raw score value	Minimal required number of items answered	Derivation for the raw score with missing items*
Pain	5	50	4	Average of available pain items x 5
Stiffness	2	20	1	The value of the available stiffness item x 2
Physical Function	17	170	14	Average of available physical function items x 17
Total	24	240	All 3 domain scores must be regarded valid	Average of all available items x 24

*Raw score in the presence of missing items is calculated from the data only if minimal required number of items available within the domain is met. Otherwise the domain score is regarded as missing.

SF-36 scores considerations

The SF-36 composite scores used to calculate corresponding endpoints are norm based scores (NBS) and will be obtained from PRO-CoRE software by QualityMetric.

2.4.2 Primary endpoint*(s)*

The primary endpoints are change in body weight (%) and change in WOMAC pain score from baseline (week 0) to end of treatment (week 68) as listed in section 3 of the protocol. Regarding WOMAC, then the version used is the WOMAC 3.1 NRS version, an 11-point numeric rating scale with responses ranging from no symptom/difficulty (0) to extreme symptom/difficulty (10). The version has a 24-hour recall period.

Change from baseline to week 68 in body weight (%) is defined as

$$\%\ \text{body weight change} = \frac{(\text{body weight at week 68} - \text{body weight at baseline})}{\text{body weight at baseline}} \times 100.$$

Change from baseline to week 68 in WOMAC pain score is defined as

$$\text{WOMAC pain score change} = \text{WOMAC pain score at week 68} - \text{WOMAC pain score at baseline},$$

where the WOMAC pain score is the transformed raw score, that is, normalised and represented on a scale of 0-100, as described in 2.4.1.

All tests are tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo.

Let $\mu_{semaglutide}$ and $\mu_{semaglutide\ placebo}$ denote the true mean of % body weight change or WOMAC pain score change for semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo, respectively. The null and alternative hypotheses tested are

$$H_0: \mu_{semaglutide} \geq \mu_{semaglutide\ placebo}\ vs$$
$$H_A: \mu_{semaglutide} < \mu_{semaglutide\ placebo}.$$

The null hypotheses will be rejected and superiority claimed, if the obtained p-value is below the significance level on which the testing is performed and the direction of the estimated effect favours semaglutide.

Analyses addressing the primary estimand

The following statistical analyses and imputation methods are designed to address the primary estimand.

The analysis model for change in body weight (%) and change in WOMAC pain score will be a linear regression (ANCOVA) with randomised treatment as factor and either baseline body weight (kg) or baseline WOMAC pain score as covariate assuming equal variances. The estimated treatment difference between semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

Body weight measurements and WOMAC pain scores that are missing at week 68 will be imputed based on available data at week 68 and the endpoint will be derived from the imputed values, i.e. % body weight change and WOMAC pain score change.

Multiple imputation approach using retrieved subjects (RD-MI): The primary imputation approach for the primary estimand is a multiple imputation similar to the one described by McEvoy[1]. For subjects in the semaglutide s.c. 2.4 mg once-weekly and the semaglutide placebo arms, missing measurements at week 68 for non-retrieved subjects are imputed using all available week 68 assessments from retrieved subjects in each randomised treatment arm. This will be done according to the timing of last available observation during the on-treatment period (LAO-OT) as well as by taking sex, baseline BMI and baseline body weight / WOMAC pain score into account. Missing measurements at week 68 for subjects on randomised treatment (at week 68) are imputed by sampling from available measurements at week 68 from subjects on randomised treatment in the relevant randomised treatment arms. The multiple imputation approach is done in three steps:

- **Imputation:** Defines an imputation model using retrieved subjects from FAS and done within groups defined by randomised treatment and end of treatment status (on-drug/off-drug). The model will be a linear regression of body weight (kg) / WOMAC pain score at week 68 with sex (male/female), baseline BMI (kg/m^2) (in categories -<35, 35-<40, ≥40) and baseline body weight (kg) / WOMAC pain score, timing of last available observation during the on-treatment period (LAO-OT) and LAO-OT of body weight (kg) / WOMAC pain score as covariates. If no LAO-OT exists post-baseline then the LAO-OT will be the baseline body weight / WOMAC pain score and the timing will be 0. No interactions will be included. If the imputation model cannot be fit due to small group size, the model will be reduced until the model can be fit. Reduction will be done in a fixed order by first collapsing the two highest baseline BMI groups

into one (≥35), then removing baseline BMI group and finally removing sex. If the model still cannot be fit, the imputation will be done regardless of the randomised treatment arm. If no LAO-OT exists post-baseline then the LAO-OT will be the baseline body weight / WOMAC pain item score and the timing will be 0. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 68 body weight / WOMAC pain score values for each randomised treatment arm. This will be done 1,000 times and results in 1,000 complete data sets.

- **Analysis**: Analysis of each of the 1,000 complete data sets, using the analysis models (ANCOVA and logistic regression) results in 1,000 times 2 estimations.
- **Pooling**: Integrates the 1,000 times 2 estimation results into two final results using Rubin's formula.

Based on NN9536-4153 phase 2 results 1,000 copies should be sufficient to establish stable results. If 1,000 copies are insufficient, 10,000 copies will be used. The multiple imputations will be generated using Novo Nordisk trial number 95364578 as seed number. In addition to the seed number, it is specified that the dataset is sorted by subject ID.

Sensitivity analyses

Jump to reference multiple imputation approach (J2R-MI): Missing values of body weight / WOMAC pain score at week 68 for both the semaglutide 2.4 mg and semaglutide placebo group are imputed by sampling among all available assessments at week 68 in the semaglutide placebo group. This approach makes the assumption that subjects instantly after discontinuation lose any effect of randomised treatment beyond what can be expected from semaglutide placebo treatment as adjunct to reduced-calorie diet and increased physical activity[2]. The multiple imputation approach is done as above with the first step replaced by

- **Imputation**: Defines an imputation model using semaglutide placebo subjects from FAS with a week 68 measurement. The model will be a linear regression of body weight (kg) / WOMAC pain score at week 68 with sex (male/female), BMI (kg/m^2) (in categories -<35, 35-<40, ≥40 as factors and baseline body weight (kg) / WOMAC pain score as covariate. No interactions will be included. If the imputation model cannot be fit due to inadequate numbers of retrieved subjects in 1 or more groups, then the imputation model will be reduced until the model can be fit. Reduction will be done in a fixed order by first collapsing the two highest baseline BMI-groups into one (≥35), then removing baseline BMI-group and finally removing sex. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 68 body weight / WOMAC pain score values for each randomised treatment arm. This will be done 1,000 times and results in 1,000 complete data sets.

Tipping-point multiple imputation analysis (TP-MI): First, missing data are imputed according to the primary multiple imputation approach. Then, a penalty is added to the imputed values at week 68. The approach is to explore a range of penalties for both treatment groups, and the impact these would have on the study conclusions. The 2-dimensional space of penalties covering the range from -30% to 30% (for body weight change) / -50 to 50 (for WOMAC pain score) will be explored for both treatment groups. This sensitivity analysis evaluates the robustness of the superiority

conclusions to departures from the observed change in body weight / WOMAC pain score in both treatment groups.

ANCOVA for unequal variances: An alternative analysis model similar to the primary analysis model (ANCOVA), following the primary imputation approach (RD-MI), but assuming unequal variances instead of equal variances. The analysis model includes randomised treatment as factor and either baseline body weight (kg) or baseline WOMAC pain score as covariate. The estimated treatment difference between semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

ANCOVA addressing date/visit mismatch: This sensitivity analysis uses the same analysis model and imputation approach as the primary analysis, and aims to evaluate the robustness of the results for the primary endpoint of change in WOMAC pain score to potential data issues for 7 subjects (subject ids: [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted]) for whom there is a mismatch between the WOMAC assessment date and assigned visit that impacts the primary endpoint derivation at week 68. The assessments in question will be reassigned to the visit matching the assessment date.

Analyses addressing the additional estimand

The additional estimand for change in body weight (%) and change in WOMAC pain score will be assessed using a mixed model for repeated measurements (MMRM) approach.

Week 68 assessments for retrieved subjects are not used in this analysis. The MMRM will use assessments only from subjects who are taking the randomised treatment until end of treatment or until first discontinuation of randomised treatment. For subjects who experience other intercurrent events before completion or first discontinuing of randomised treatment, the date of initiating other anti-obesity therapies (weight management drugs or bariatric surgery) or other knee OA interventions (joint replacement or steroid injections) will be used as latest date for using assessments in this MMRM. Additionally, for the MMRM analysing change in WOMAC pain score, assessments not collected in compliance with the washout period for pain medication will not be used. The MMRM will be fitted using the change (% body weight change or change in WOMAC pain score) and the same factor and covariate as for the primary analysis all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

Table 2-4 Analysis and imputation methods to address the primary and additional estimands for primary endpoints

Endpoint title	Unit	Endpoint	Strategy	Analysis set	Statistical model	Imputation approach	Sensitivity analysis
Change in body weight	%	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	J2R-MI TP-MI Uneq.Var.
			Hypothetical	FAS	MMRM	-	-
Change in WOMAC pain score	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	J2R-MI TP-MI Uneq.Var.
			Hypothetical	FAS	MMRM	-	-

2.4.3 Secondary endpoints

2.4.3.1 Confirmatory secondary endpoints

Confirmatory secondary endpoints are listed in section 1.1.3.2. All tests are tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo.

Table 2-5 Analysis and imputation methods to address the secondary and additional estimands for confirmatory secondary endpoints

Endpoint title	Unit	Endpoint	Strategy	Analysis set	Statistical model	Imputation approach
Achieving body weight reduction ≥5% (yes/no)	Count of subject	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM
Achieving body weight reduction ≥10% (yes/no)	Count of subject	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM
Change in WOMAC physical function score	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-
Change in SF-36 physical functioning score	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-

Analyses addressing the secondary estimand

The confirmatory secondary endpoints addressing the secondary estimand will be analysed in a similar way as the primary endpoints addressing the primary estimand.

The statistical model for continuous confirmatory secondary endpoints will be the same linear regression as for the primary endpoints (ANCOVA) with treatment as a factor and the baseline value of the endpoint as covariate. The statistical model for confirmatory body weight responder endpoints is a logistic regression using randomised treatment as a factor and baseline body weight (kg) as covariate. The estimated odds ratio (OR) as well as risk differences between semaglutide s.c.

2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval and corresponding p-value.

The imputation approach is the same multiple imputation using retrieved subjects as described in section 2.4.2.

Analyses addressing the additional estimand

The confirmatory secondary endpoints change in WOMAC physical function score and change in SF-36 physical functioning score addressing the additional estimand will be analysed using the same MMRM as described for the primary endpoints addressing the additional estimand with randomised treatment as a factor and the baseline value of the endpoint as covariate. For these analyses assessments not collected in compliance with the washout period for pain medication will not be used.

The confirmatory body weight responder endpoints addressing the additional estimand will be analysed using the same MMRM described for the primary endpoint change in body weight (%) addressing the additional estimand except that body weight (kg) will be used as response variable in the model. For subjects with missing body weight at week 68, individual values for body weight will be predicted from the MMRM and used to classify each subject as 5% or 10% responder or not. This classification will then be analysed using a logistic regression model with randomised treatment as a factor and baseline body weight (kg) as covariate.

2.4.3.2 Supportive secondary endpoints

Supportive secondary endpoints are listed in section 1.1.3.3. All tests are tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo.

Analyses addressing the secondary estimand

The supportive secondary endpoints related to body weight, waist circumference, WOMAC and SF-36 addressing the secondary estimand will be analysed using the same imputation approach as used for the primary endpoints while supportive secondary endpoints related to pain intensity (NRS) will be analysed using the J2R-MI imputation approach as described for the sensitivity analysis of the primary endpoints. The statistical model for continuous endpoints will be the same linear regression as for the primary endpoints (ANCOVA) with treatment as a factor and the baseline value of the endpoint as covariate. The statistical model for responder endpoints is a logistic regression using treatment as a factor and baseline value of the endpoint as covariate. The estimated odds ratio (OR) as well as risk differences between semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval and corresponding p-value.

The baseline pain intensity (NRS) for each subject will be calculated as the mean of the available daily pain scores reported from 4 and up to 7 days prior to the randomisation visit. The means at each post-baseline visit until week 68 will be calculated in a similar way.

Analyses addressing the additional estimand

The supportive secondary endpoints related to body weight, waist circumference, WOMAC, SF-36, and pain intensity (NRS) addressing the additional estimand will be analysed using the same

MMRM as described for the primary endpoints addressing the additional estimand with randomised treatment as a factor and the baseline value of the endpoint as covariate. For the MMRM analysing endpoints related to WOMAC and SF-36, assessments not collected in compliance with the washout period for pain medication will not be used.

Responder endpoints (body weight, WOMAC pain or pain intensity (NRS)) addressing the additional estimand will be analysed using the same MMRM as described for the primary endpoint change in body weight (%) addressing the additional estimand except that the endpoint will be used as response variable in the model. For subjects with missing assessments at week 68, individual values will be predicted from the MMRM and used to classify each subject as a responder or not. This classification will then be analysed using a logistic regression model with randomised treatment as a factor and baseline value of the endpoint as covariate.

Other analyses

Use of pain medication and endpoints related to use of allowed rescue analgesics during washout period will be described using plots and descriptive statistics. Use of pain medication will be categorised into opioids, NSAIDs and acetaminophen. The summaries and plots will be done by these categories and will include overall time on medication, pain medication rates and prevalence plots. For opioids, time to event plot will be presented. The allowed rescue analgesics will be identified as acetaminophen reported in the pain medication diary 1, 2 or 3 days prior to WOMAC assessment and the individual amount of rescue analgesics at each visit will be calculated as a total dose reported taken on those days.

Responder analyses for WOMAC pain, WOMAC physical function and SF-36 physical functioning will be carried out with thresholds for clinically meaningful within-subject change derived prior to unblinding from NN9536-4578 data using anchor based methods (Patient Global Impression of Status and Patient Global Impression of Change items). The responder thresholds were derived by an external vendor based on the complete dataset prior to DBL. Responder analyses will be carried out on a range of responder thresholds including the final primary response definition values of clinically meaningful within-subject change for WOMAC pain, WOMAC physical function and SF-36 physical functioning based on one category improvement on the corresponding PGI-S items, plus the next lower/upper response value representing, respectively, no change and two category change on the PGI-S scale. The final thresholds are summarised in Table 2-6.

Table 2-6 Summary of the derived thresholds for meaningful within-subject change

PGI-S group	WOMAC pain score	WOMAC physical function score	SF-36 physical functioning score
No change	−17.8	-21.7	5.2
1-category improvement*	**−37.3**	**-41.2**	**11.4**
2-category improvement	−53.0	-49.8	16.4

*) The derived threshold value for final primary response value of clinically meaningful within-subject change

Table 2-7 Analysis and imputation methods to address the secondary and additional estimands for supportive secondary endpoints

Endpoint title	Unit	Endpoint	Strategy	Analysis set	Statistical model	Imputation approach
Change in waist circumference	cm	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-
Change in WOMAC stiffness score	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-
Change in WOMAC total score	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-
Change in SF-36 bodily pain score	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-
Change in SF-36 general health score	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-
Change in SF-36 physical component summary	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-
Change in SF-36 mental component summary	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-
Use of allowed rescue analgesics during wash out	Count of subjects	Binary	-	FAS	Descriptive statistics	-
Amount of allowed rescue analgesics used during wash out	Dose	Continuous	-	FAS	Descriptive statistics	-
Use of pain medication	Number of days	Continuous	-	FAS	Descriptive statistics	-
Change in pain intensity (NRS)	Score points	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI
			Hypothetical	FAS	MMRM	-
Achieving body weight reduction ≥15% (yes/no)	Count of subject	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM
Achieving body weight reduction ≥20% (yes/no)	Count of subject	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM
Achieving WOMAC pain reduction ≥30% (yes/no)	Count of subject	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM

Endpoint title	Unit	Endpoint	Strategy	Analysis set	Statistical model	Imputation approach
Achieving WOMAC pain reduction ≥50% (yes/no)	Count of subject	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM
Achieving threshold(s) for clinically meaningful within-subject change* in WOMAC pain score	Count of subject	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM
Achieving threshold(s) for clinically meaningful within-subject change* in WOMAC physical function score	Count of subject	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM
Achieving threshold(s) for clinically meaningful within-subject change* in SF-36 physical functioning score	Count of subject	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM
Achieving pain intensity (NRS) reduction ≥30% (yes/no)	Count of subject	Binary	Treatment policy	FAS	LR	J2R-MI
			Hypothetical	FAS	LR	MMRM
Achieving pain intensity (NRS) reduction ≥50% (yes/no)	Count of subject	Binary	Treatment policy	FAS	LR	J2R-MI
			Hypothetical	FAS	LR	MMRM

*) Thresholds for meaningful within-subject change are presented in Table 2-6

2.4.4 Exploratory endpoints

Exploratory endpoints are listed in section 1.1.3.4. All tests are tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo.

Analyses addressing the secondary estimand

The endpoints related to SF-36 addressing the secondary estimand will be analysed using the same imputation approach as used for the primary endpoints. The statistical model for continuous endpoints will be the same linear regression as for the primary endpoints (ANCOVA) with treatment as a factor and the baseline value of the endpoint as covariate.

Analyses addressing the additional estimand

The endpoints related to SF-36 addressing the additional estimand will be analysed using the same MMRM as described for the primary endpoints addressing the additional estimand with randomised treatment as a factor and the baseline value of the endpoint as covariate.

Other analyses

The endpoint change in 6 minutes walking distance from baseline to end of treatment will be summarised using descriptive statistics.

Table 2-8 Analysis and imputation methods to address the secondary and additional estimands for exploratory endpoints.

Endpoint title	Unit	Endpoint	Strategy	Analysis set	Statistical model	Imputation approach
Change in 6 minutes walking distance	Meters	Continuous	-	FAS	Descriptive statistics	-
Change in SF-36 role-physical score	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-
Change in SF-36 general health score	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-
Change in SF-36 vitality score	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-
Change in SF-36 social functioning score	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-
Change in SF-36 role-emotional score	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-
Change in SF-36 mental health score	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	-

Analysis of safety endpoints

Adverse events will be defined as “treatment-emergent” (TEAE), if the onset of the event occurs in the on-treatment period. TEAEs and SAEs will be summarised by descriptive statistics, such as frequencies and rates. No formal statistical inference will be carried out based on the number of TEAEs and SAEs. All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

3 References

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Harold Bays

Discloser Identifier: 814570

Disclosure Purpose: 24-03664

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
89Bio	Grant / Contract	Other - L-MARC Research Center
Recipient Name: L-MARC Research Center **Grant / Contract Description:** Harold Bays MD is a Principal Investigator at L-MARC Research Center **Additional Information:** **Recipient Type:** Institution **Grant / Contract Purpose:** Research		
89Bio	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Alon Medtech Epitomee	Grant / Contract	Other - Louisville Metabolic and Atherosclerosis Research Center
Recipient Name: Louisville Metabolic and Atherosclerosis Research Center **Grant / Contract Description:** Research **Additional Information:** **Recipient Type:** Institution **Grant / Contract Purpose:** Research		
Altimmune	Grant / Contract	Other - L-MARC Research Center
Recipient Name: Louisville Metabolic and Atherosclerosis Research Center **Grant / Contract Description:** Harold Bays MD is a Principal Investigator at L-MARC Research Center **Additional Information:** **Recipient Type:** Institution **Grant / Contract Purpose:** Research		
Altimmune	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Amgen	Grant / Contract	Other - LMARC Research Center
Recipient Name: Harold Bays MD **Grant / Contract Description:** Harold Bays MD is a Principal Investigator at L-MARC Research Center **Additional Information:** **Recipient Type:** Institution **Grant / Contract Purpose:** Research		
Amgen	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
BioAge Labs, Inc.	Grant / Contract	Other - L-MARC Research Center

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Recipient Name: L-MARC Research Center **Grant / Contract Description:** Harold Bays MD is a Principal Investigator at L-MARC Research Center **Additional Information:**		**Recipient Type:** Institution **Grant / Contract Purpose:** Research
Boehringer Ingelheim	Grant / Contract	Other - L-MARC Research Center
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Boehringer Ingelheim	Consultant	Self
Category: Consultant **Description:** Harold Bays MD **Additional Information:**		
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Eli LIlly	Grant / Contract	Other - L-MARC Research Center
Recipient Name: L-MARC Research Center **Grant / Contract Description:** **Additional Information:**		**Recipient Type:** Institution **Grant / Contract Purpose:** Research
Eli LIlly	Consultant	Self
Category: Consultant **Description:** Harold Bays MD **Additional Information:**		
Kallyope	Grant / Contract	Other - L-MARC Research Center
Recipient Name: L-MARC Research Center **Grant / Contract Description:** Harold Bays MD is a Principal Investigator at L-MARC Research Center **Additional Information:**		**Recipient Type:** Institution **Grant / Contract Purpose:** Research
Novartis	Grant / Contract	Other - L-MARC Research Center
Recipient Name: L-MARC Research Center **Grant / Contract Description:** Harold Bays MD is a Principal Investigator at L-MARC Research Center **Additional Information:**		**Recipient Type:** Institution **Grant / Contract Purpose:** Research
Novo Nordisk	Grant / Contract	Other - L-MARC Research Center
Recipient Name: L-MARC Research Center **Grant / Contract Description:** Harold Bays MD is a Principal Investigator at L-MARC Research Center **Additional Information:**		**Recipient Type:** Institution **Grant / Contract Purpose:** Research
Novo Nordisk	Consultant	Self
Category: Consultant **Description:** Harold Bays MD **Additional Information:**		

Entity	Type	Interest Held By
Pfizer Company	Grant / Contract	Other - LMARC Research Center
Recipient Name: L-MARC Research Center **Grant / Contract Description:** Harold Bays MD is a Principal Investigator at L-MARC Research Center **Additional Information:**		**Recipient Type:** Institution **Grant / Contract Purpose:** Research
Regeneron	Grant / Contract	Other - L-MARC Research Center
Recipient Name: L-MARC Research Center **Grant / Contract Description:** Harold Bays MD is a Principal Investigator at L-MARC Research Center **Additional Information:**		**Recipient Type:** Institution **Grant / Contract Purpose:** Research
Shionogi	Grant / Contract	Other - L-MARC Research Center
Recipient Name: L-MARC Research Center **Grant / Contract Description:** Harold Bays MD is a Principal Investigator at L-MARC Research Center **Additional Information:**		**Recipient Type:** Institution **Grant / Contract Purpose:** Research
Veru Inc	Grant / Contract	Other - L-MARC Research Center
Recipient Name: L-MARC Research Center **Grant / Contract Description:** Harold Bays MD is a Principal Investigator at L-MARC Research Center **Additional Information:**		**Recipient Type:** Institution **Grant / Contract Purpose:** Research
Viking	Grant / Contract	Other - L-MARC Research Center
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VIVUS, Inc.	Grant / Contract	Other - L-MARC Research Center
Recipient Name: L-MARC Research Center **Grant / Contract Description:** Harold Bays MD is a Principal Investigator at L-MARC Research Center **Additional Information:**		**Recipient Type:** Institution **Grant / Contract Purpose:** Research

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Semaglutide 2.4 mg in People with Obesity and Knee Osteoarthritis

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

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Henning Bliddal

Discloser Identifier: 713422

Disclosure Purpose: 24-03664

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
contura	Travel	Self
Location(s): Wien **Purpose:** Congress **Additional Information:**		
Novo Nordisk AS	Consultant	Self
Category: Consultant **Description:** Consultant for the STEP-9 **Additional Information:** 9 hours		
Novo Nordisk Fonden	Grant / Contract	Self
Recipient Name: Henning Bliddal **Grant / Contract Description:** Grant for the INKA trial, NCT05172843 **Additional Information:** NCT05172843	**Recipient Type:** Institution **Grant / Contract Purpose:** Research	

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Once-Weekly Semaglutide in People with Severe Obesity and Knee Osteoarthritis

3. **Are you the corresponding author?**

   Yes.

   a. **Please list the other authors' names here.**

      Harold Bays M.D.,2 Sébastien Czernichow M.D. Ph.D.,3 Joanna Udden Hemmingson M.D. Ph.D.,4 Jøran Hjelmesæth M.D. Ph.D.,5 Thomas Hoffmann Morville M.D. Ph.D.,6 Anna Koroleva M.D.,6 Jesper Skov Neergaard Ph.D,6 Patricia Vélez Sánchez M.D.,7 Sean Wharton M.D.,8 Alicja Wizert Ph.D,6 Lars Erik Kristensen M.D. PhD.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Sebastien Czernichow

Discloser Identifier: 789271

Disclosure Purpose: 24-03664

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Boehringer Ingelheim	Other	Self
Category: Other **Description:** SAB **Additional Information:**		
Bristol Myers Squibb Company	Other	Self
Category: Other **Description:** Speaker fees **Additional Information:**		
Eli LIlly	Other	Self
Category: Other **Description:** SAB **Additional Information:**		
Eli LIlly	Other	Other - Funding to my institution as a PI
Category: Other **Description:** Clinical Trial (Principal Investigator): SURMOUNT MMO **Additional Information:**		
Eli LIlly	Other	Self
Category: Other **Description:** Speaking Engagement **Additional Information:**		
Ipsen	Other	Self
Category: Other **Description:** speaker fees **Additional Information:**		
Janssen Cilag EMEA	Other	Self
Category: Other **Description:** speaker fees **Additional Information:**		
Novo Nordisk	Other	Other - funding to my institution as a PI
Category: Other **Description:** Clinical Trial (Principal Investigator): STEP 1 and STEP 9 trials **Additional Information:**		

Entity	Type	Interest Held By
Novo Nordisk	Other	Self
Category: Other **Description:** Scientific Advisory Board **Additional Information:** SAB or speaker fees since 2020		
Pfizer	Other	Self
Category: Other **Description:** SAB **Additional Information:**		
ViiV Healthcare	Other	Self
Category: Other **Description:** Speaker fees **Additional Information:**		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Semaglutide 2.4 mg in People with Obesity and Knee Osteoarthritis

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Jøran Hjelmesæth

Discloser Identifier: 432939

Disclosure Purpose: 24-03664

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Novo Nordisk AS	Other	Self

Category: Other
Description: Honoraria for lectures for health proffesionals
Additional Information:

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Semaglutide 2.4 mg in People with Obesity and Knee Osteoarthritis

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

ANNA KOROLEVA

Discloser Identifier: 1179353

Disclosure Purpose: 24-03664

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Novo Nordisk AS	Employment	Self

Title: Associate Global Medical Director
Position Description:
Additional Information:

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Once-weekly subcutaneous semaglutide 2.4 mg in people with obesity and knee osteoarthritis

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Lars Kristensen

Discloser Identifier: 856955

Disclosure Purpose: 24-03664

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
AbbVie	Consultant	Self
Category: Consultant **Description:** Has recieved fees for consultancy and speaking **Additional Information:** Fairmarket value reimbursement		
Amgen	Consultant	Self
Category: Consultant **Description:** Has recieved fees for speaking/lecturing **Additional Information:** Fairmarket value reimbursement		
Biogen Idec	Consultant	Self
Category: Consultant **Description:** Has recieved fees for speaking and consultancy **Additional Information:** Fairmarket value reimbursement		
Bristol-Myers Squibb	Consultant	Self
Category: Consultant **Description:** Has recieved fees for speaking and consultancy **Additional Information:** Fairmarket value reimbursement		
Celgene	Consultant	Self
Category: Consultant **Description:** Has recieved fees for speaking and consultancy **Additional Information:** Fair market value reimbursement		
Eli LIlly	Grant / Contract	Other - IIT funded the PArker Institute conducting the study (IPA)
Recipient Name: Lars Erik KRistensen **Grant / Contract Description:** IIT grant for doing translational science project in psoriatic arthritis **Additional Information:**	**Recipient Type:** Institution **Grant / Contract Purpose:** Research	
Eli LIlly	Consultant	Self
Category: Consultant **Description:** Has recieved fees for speaking and consultancy **Additional Information:** Fairmarket value reimbursement		
Eli LIlly	Stock	Self
Additional Information: Part of retirement fund administered by bank		

Entity	Type	Interest Held By
Janssen Biotech	Consultant	Self
Category: Consultant **Description:** Has recieved fees for speaking and consultancy **Additional Information:** Fairmarket value reimbursement		
Merck	Stock	Self
Additional Information: PArt of retirement fund administered by bank		
Merck & Co., Inc.	Consultant	Self
Category: Consultant **Description:** Has recieved fees for speaking and consultancy **Additional Information:** Fair market value reimbursement		
Novartis	Consultant	Self
Category: Consultant **Description:** Has recieved fees for consultancy and speaking **Additional Information:** Fair market value reimbursement		
Novartis	Stock	Self
Additional Information: Part of retirement fund administered by bank		
Novo Nordisk AS	Stock	Self
Additional Information: Part of retirement portfolio adminstered by Bank		
Pfizer	Consultant	Self
Category: Consultant **Description:** Has recieved fees for speaking and consultancy from Pfizer **Additional Information:** Fair market value reimbursement		
Sanofi	Consultant	Self
Category: Consultant **Description:** Has recieved fees for speaking and consultancy **Additional Information:** Fairmarket value reimbursement		
UCB	Consultant	Self
Category: Consultant **Description:** Has recieved fees for speaking and consultancy **Additional Information:** Fairmarket value reimbursement		
UCB	Stock	Self
Additional Information: Part of retirement fund administered by Bank		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Once-weekly subcutaneous semaglutide 2.4 mg in people with obesity and knee osteoarthritis

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

May 16, 2024 03:54:50 EDT
New England Journal of Medicine

Thomas Morville

Discloser Identifier: 1179352

Disclosure Purpose: 24-03664

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Novo Nordisk AS	Employment	Self

Title: Senior International Medical Manager
Position Description: Medical specialist in Medical & Science Obesity
Additional Information:

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Once-weekly subcutaneous semaglutide 2.4 mg in people with obesity and knee osteoarthritis

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Jesper Neergaard

Discloser Identifier: 1179356

Disclosure Purpose: 24-03664

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Novo Nordisk AS	Employment	Self
Title: Department Manager **Position Description:** Manage a team of safety surveillance **Additional Information:** Above is my current position which was started Jan 2024. At the time of the study reported in the publication I was working as a Senior Clinical Outcome Assessment Manager.		
Novo Nordisk AS	Stock	Self
Additional Information:		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Semaglutide 2.4 mg in People with Obesity and Knee Osteoarthritis

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Joanna Josefine Udden Hemmingsson

Discloser Identifier: 1179351

Disclosure Purpose: 24-03664

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Abbott Pharmaceuticals	Consultant	Self
Category: Consultant **Description:** I´ve held lectures. **Additional Information:**		
AstraZeneca AB	Consultant	Self
Category: Consultant **Description:** Lectures. I´ve also been co-Investigator in one clinical trial **Additional Information:**		
F. Hoffmann-La Roche	Consultant	Self
Category: Consultant **Description:** I´ve held lectures. I´ve also been co-Investigator in clinical trials **Additional Information:**		
Medtronic	Grant / Contract	Self
Recipient Name: Joanna Uddén Hemmingsson **Recipient Type:** Institution **Grant / Contract Description:** Unrestricted research grant in Obesity and Diabetes reserach **Grant / Contract Purpose:** Research **Additional Information:**		
Navamedic	Consultant	Self
Category: Consultant **Description:** Lectures and Advisory Board **Additional Information:**		
Novo Nordisk	Consultant	Self
Category: Consultant **Description:** Lectures and participation in Advisory Boards. I´ve also been Primary Investigator and Swedish National Coordinator in several clinical trials **Additional Information:**		
Sanofi Pharmaceuticals	Consultant	Self
Category: Consultant **Description:** Lectures **Additional Information:**		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Semaglutide 2.4 mg in People with Obesity and Knee Osteoarthritis

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

patricia velez

Discloser Identifier: 1179357

Disclosure Purpose: 24-03664

Summary of Interests

I do not have any interests to disclose at this time.

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Once-Weekly Semaglutide in People with Obesity and Knee Osteoarthritis

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

sean wharton

Discloser Identifier: 1053775

Disclosure Purpose: 24-03664

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Amgen Canada	Other	Self
Category: Other **Description:** Speaking engagement **Additional Information:**		
AstraZeneca	Other	Self
Category: Other **Description:** Academic speaking engagement **Additional Information:** Advisory Boards involvement		
Bausch and Lomb	Other	Self
Category: Other **Description:** Academic speaking engagements **Additional Information:** Honoraria for academic speaking engagements		
Biohaven Pharmaceuticals, Inc.	Other	Self
Category: Other **Description:** Scientific Advisory Board **Additional Information:** Academic advisory board		
Boehringer Ingelheim	Other	Self
Category: Other **Description:** Scientific Advisory Board **Additional Information:**		
Eli Lilly and Company	Other	Self
Category: Other **Description:** Speaking Engagement, Advisory Board **Additional Information:**		
Novo Nordisk	Grant / Contract	Self
Recipient Name: Sean Wharton **Grant / Contract Description:** Academic research **Additional Information:**	**Recipient Type:** Individual **Grant / Contract Purpose:** Research	
Novo Nordisk	Other	Self
Category: Other **Description:** Academic speaking engagements **Additional Information:** Honoraria for academic talks to colleagues		

Entity	Type	Interest Held By
Novo Nordisk	Other	Self

Category: Other
Description: Scientific Advisory Board, Academic Speaking Engagement
Additional Information: Academic Advisory Board

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Semaglutide 2.4 mg in People with Obesity and Knee Osteoarthritis" to the New England Journal of Medicine.

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Alicja Wizert

Discloser Identifier: 1179358

Disclosure Purpose: 24-03664

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Novo Nordisk AS	Employment	Self

Title: Statistical Specialist
Additional Information:

Position Description:

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Semaglutide 2.4 mg in People with Obesity and Knee Osteoarthritis

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Data Sharing Statement

Bliddal H, Bays H, Czernichow S, et al. Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis. N Engl J Med. DOI: 10.1056/NEJMoa2403664.

Question	Authors' Response
Will the data collected for your study be made available to others?	Yes
Would you like to offer context for your decision?	—
Which data?	Complete deidentified patient data set. Other (e.g., partial data sets) — please describe.
Additional information about data	Deidentified participant data are available for this article on a specialized SAS data platform. The study protocol and redacted clinical study report will be made available according to Novo Nordisk data sharing commitments. Access to data can be made through a request proposal form and the access criteria can be found online. Data will be shared with bona fide researchers submitting a research proposal requesting access to data. Data use is subject to approval by the independent review board according to the IRB Charter (see novonordisk-trials.com).
How or where can the data be obtained?	Deidentified participant data are available for this article on a specialized SAS data platform. Access to data can be made through a request proposal form and the access criteria can be found online. Data will be shared with bona fide researchers submitting a research proposal requesting access to data. Data use is subject to approval by the independent review board according to the IRB Charter (see novonordisk-trials.com).
When will data availability begin?	Data sets from Novo Nordisk will be available permanently after research completion and approval of product and product use in both the EU and USA.
When will data availability end?	—
Will any supporting documents be available?	—
Which supporting documents?	—
Additional information about supporting documents	—
How or where can supporting documents be obtained?	—
When will supporting documents availability begin?	—
When will supporting documents availability end?	—
To whom will data be available?	—
For what type of analysis or purpose?	—
By what mechanism?	—
Any other restrictions?	—
Additional information	—

This statement was posted on October 31, 2024, at NEJM.org.