Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05064735
Sponsor trial ID:	NN9536-4578
Official title of study:	Effect of subcutaneous semaglutide 2.4 mg once-weekly compared to placebo in subjects with obesity and knee osteoarthritis
Document date*:	21 April 2021

*Document date refers to the date on which the document was most recently updated.
Note: The date in the header from Page 2 and 94 is the date of compilation of the documents and not of an update to content.

9.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

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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
Original protocol version 1.0	24 July 2020	CA, CO, DK, FR, NO, RU, SA, ZA, ES, SE, US

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.

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Protocol attachment I Global list of key staff and relevant departments and suppliers

Protocol attachment II Country list of key staff and relevant departments.

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

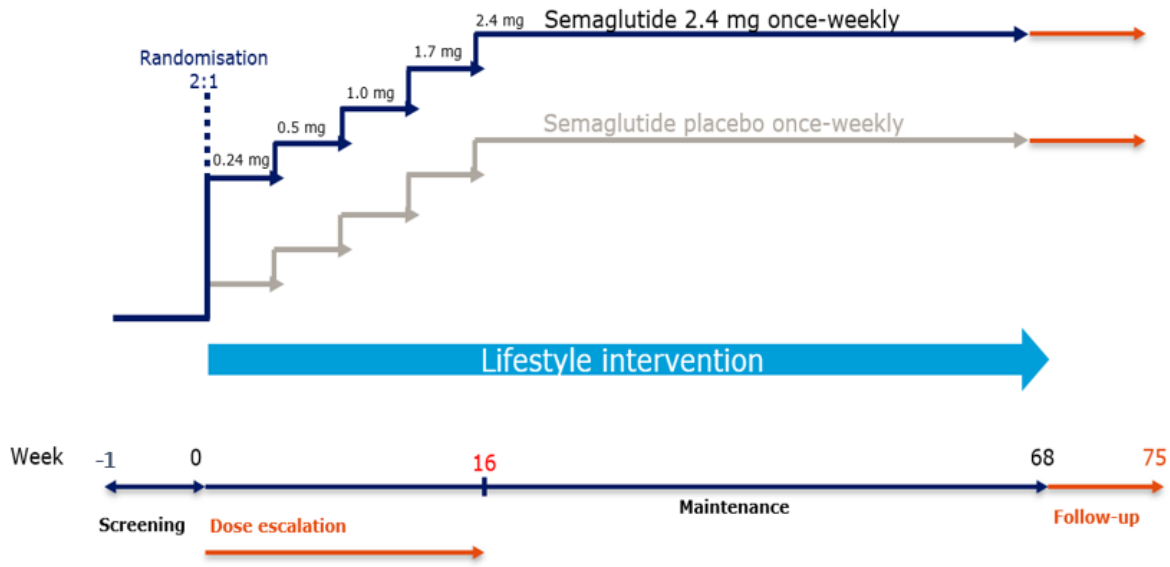
This trial is designed to evaluate weight loss and knee OA-related outcomes and will apply a targeted approach to collection of safety data focusing on serious adverse events (SAEs), adverse events (AEs) leading to discontinuation of trial product and other selected AEs. An adequate characterisation 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.

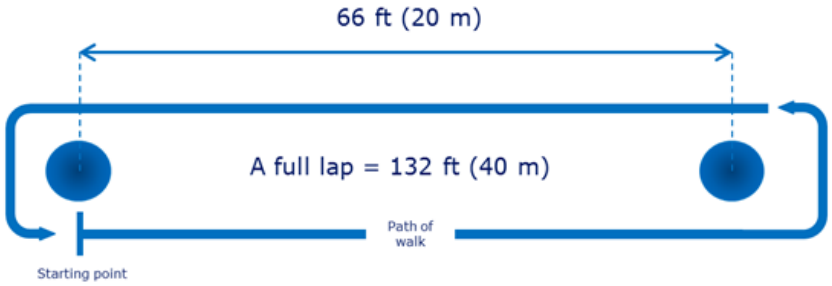


Figure 8-1 Walkway marking for the six-minute walk text

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

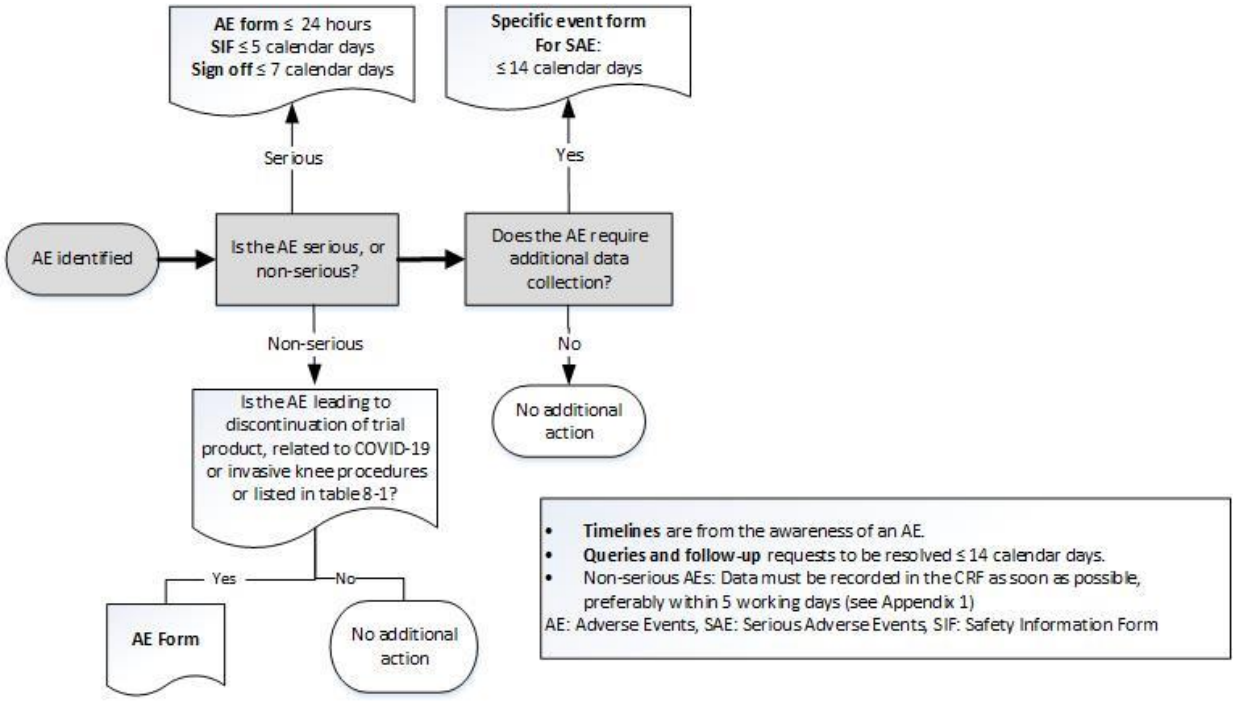


Figure 10-1 Decision tree for determining the event type and the respective forms to complete with associated timelines

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.

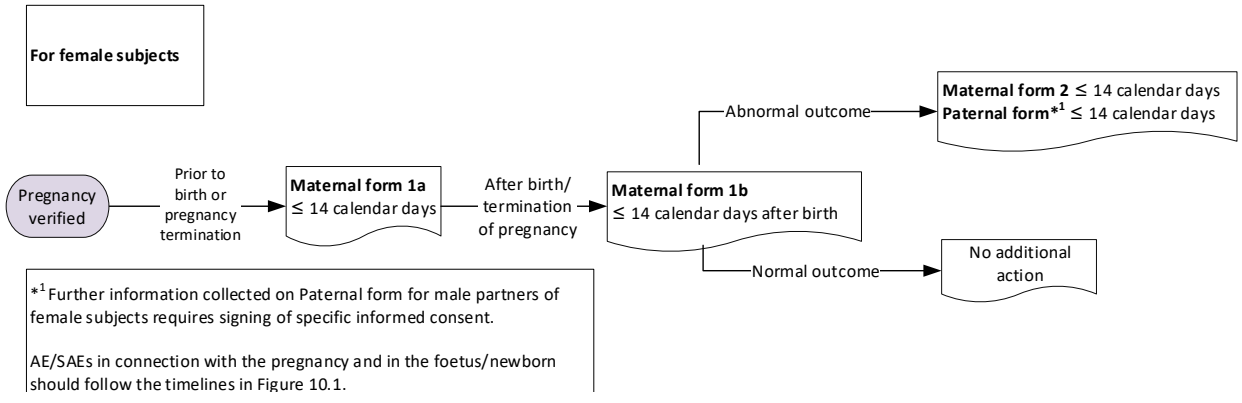


Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy

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.

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Signature Page for VV-TMF-4175464 v2.0

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 27-Apr-2021 07:23:59 GMT+0000

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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.