# Cover Page for Protocol

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| Sponsor name: | Novo Nordisk A/S |
| NCT number | NCT05040971 |
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| Official title of study: | Efficacy and safety of subcutaneous semaglutide 2.4 mg once-weekly in subjects with obesity and prediabetes |
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### 9.1.1 Protocol and protocol amendments

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# Protocol

**Protocol title: Efficacy and safety of subcutaneous semaglutide 2.4 mg once-weekly in subjects with obesity and prediabetes**

**Substance name: semaglutide**

**Universal Trial Number: U1111-1253-1956**

**EudraCT Number: 2020-002939-29**

**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 4.0 | 24 February 2023 | Global |
| Protocol version 3.0 | 08 February 2022 | Global |
| Protocol version 2.0 | 13 July 2021 | Global |
| Original protocol version 1.0 | 02 March 2021 | Final protocol |

### Protocol version 4.0 (24 February 2023)

This amendment is considered to be non-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, because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.[1]

### Overall rationale for preparing protocol version 4.0

This version of the protocol was prepared to remove data base lock (DBL) and interim clinical trial report (CTR) after 'safety visit' (week 57) and plan only one DBL after completion of the 'end of trial visit' (week 80) and one CTR will be prepared including the main and the extension phase of the trial.

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 9.7 (Reporting of the main part of the trial) | Deletion of the DBL and CTR after 'Safety visit, P13' (week 57) of the main phase of the trial. | On re-evaluation it was concluded to simplify operational set-up of the trial, as DBL and CTR is not needed until the end of the extension phase. |

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# 1 Protocol summary

## 1.1 Synopsis

### Rationale:

The prevalence of obesity has reached epidemic proportions in most countries around the world and it is continuing to increase at an alarming rate. The medical and societal impacts are extensive, and obesity is one of the most significant public health challenges worldwide.[3-9]

Obesity is associated with a higher risk of a variety of comorbidities, including prediabetes, and the risk of obesity-related comorbidities increases with increasing body mass index (BMI).[10] Individuals with both obesity and prediabetes are at increased risk of type 2 diabetes (T2D) as well as other weight-related comorbidities associated with an increased risk of mortality, and are likely to benefit from weight reduction.[11]

The present 52-week trial will compare the effect of semaglutide subcutaneous (s.c.) 2.4 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity on body weight and on reversal to normoglycaemia in subjects with BMI ≥ 30.0 kg/m$^2$ and prediabetes, defined as $HbA_{1c}$ between 6.0 and 6.4% (both inclusive) and/or fasting plasma glucose (FPG) between 5.5 and 6.9 mmol/L (both inclusive) at baseline.[12]

### Objectives and endpoints:

### Primary objective (week 0 to week 52)

To confirm the superiority of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo, both as adjuncts to a reduced-calorie diet and increased physical activity in subjects with obesity and prediabetes, on body weight and reversal to normoglycaemia.

### Secondary objectives (week 0 to week 52)

To compare the efficacy of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo on:

- glucose metabolism
- cardiovascular risk factors
- other factors related to body weight

### Primary estimand

The primary clinical question of interest is: what is the average treatment effect of semaglutide s.c. 2.4 mg once-weekly as an adjunct to a reduced-calorie diet and increased physical activity, in subjects with obesity and prediabetes, measured by change from baseline to week 52 in body weight and reversal to normoglycaemia, regardless of discontinuation or dose reduction of randomised treatment and regardless of initiating other glucose-lowering medication or anti-obesity therapies (weight management drugs or bariatric surgery) (“treatment policy” strategy).

## Primary endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in body weight | From randomisation (week 0) to end of treatment (week 52) | % |
| Change to normoglycemia* | From randomisation (week 0) to end of treatment (week 52) | Count of subjects |

*Normoglycemia is defined as having both HbA1c < 6.0% (< 42 mmol/mol) and FPG < 5.5 mmol/L (< 99 mg/dL)

## Overall design:

### Main phase

This is a 52-week, randomised, two-arm, double-blinded, parallel-group, multi-centre, multinational clinical trial comparing semaglutide s.c. 2.4 mg once-weekly with semaglutide placebo once-weekly as an adjunct to a reduced-calorie diet and increased physical activity in subjects with obesity (BMI ≥30.0 kg/m$^2$) and prediabetes, defined as $HbA_{1c}$ between 6.0 and 6.4% (both inclusive) and/or FPG between 5.5 and 6.9 mmol/L (both inclusive) at baseline.[12] A safety visit (phone visit) will take place 5 weeks after end of treatment (week 57).

### Extension phase

The extension phase is a 28-week off-treatment period after the last visit in the main phase (visit 12), including standard diet and physical activity counselling according to local guidelines. Two visits are planned at week 66 and week 80 for assessment of body weight, and glycaemic and cardiovascular parameters. Total trial duration (main phase and extension phase) for each subject is approximately 82 weeks.

Eligible subjects will be randomised in a 2:1 manner to receive either semaglutide s.c. 2.4 mg once-weekly or placebo. Randomisation will take place 1-2 weeks after screening.

## Key inclusion criteria

- Male or female aged ≥18 years at the time of signing informed consent.
- BMI ≥30.0 kg/m$^2$
- Prediabetes defined as at least one of the following:[12]
  - HbA1c between 6.0 and 6.4 % (42 and 47 mmol/mol) (both inclusive) as measured by central laboratory at screening.
  - FPG between 5.5 and 6.9 mmol/L (99 and 125 mg/dL) (both inclusive) as measured by central laboratory at screening.

## Key exclusion criteria

- History of type 1 or type 2 diabetes.
- Treatment with glucose-lowering agent(s) within 90 days before screening.
- HbA1c ≥6.5 % (≥48 mmol/mol) as measured by central laboratory at screening.
- FPG ≥ 7.0mmol/L (126 mg/dL) as measured by central laboratory at screening.
- A self-reported change in body weight >5 kg (11 lbs) within 90 days before screening irrespective of medical records.

- Treatment with any medication for the indication of obesity within the past 90 days before screening.

**Number of subjects:**

Approximately 201 subjects will be randomly assigned to trial product.

**Treatment groups and duration:**

The total trial duration (main phase and extension phase) for the individual subject will be approximately 82 weeks. The trial includes 2 screening visits (weeks -2 and -1) followed by randomisation (week 0) and visits every 4$^{th}$ week during dose escalation. From week 20, visits will take place every 8$^{th}$ week for the remaining maintenance period until end of treatment (week 52). In the off-treatment extension phase, there will be a phone visit at week 57, and 2 visits with 14 weeks apart (week 66 and week 80).

The following trial products will be supplied by Novo Nordisk A/S for the duration of the trial:

- Semaglutide D 0.5 mg/mL, solution for injection, DV3396 0.5 mL pen-injector
- Semaglutide D 1.0 mg/mL, solution for injection, DV3396 0.5 mL pen-injector
- Semaglutide D 2.0 mg/mL, solution for injection, DV3396 0.5 mL pen-injector
- Semaglutide D 2.27 mg/mL, solution for injection, DV3396 0.75 mL pen-injector
- Semaglutide D 3.2 mg/mL, solution for injection, DV3396 0.75 mL pen-injector
- Semaglutide placebo Ia, solution for injection, 0.5mL pen-injector
- Semaglutide placebo Ib, solution for injection, 0.75 mL pen-injector

**Data monitoring committee:** No

## 1.2 Flowchart

| | Screening 1 | Screening 2 | Randomisation | Dose escalation period | | | | Treatment period | | | | End of treatment | Safety visit | Extension phase | End of trial |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | P13 | V14ext | V15ext |
| Timing of Visit (Weeks) | -2 | -1 | 0 | 4 | 8 | 12 | 16 | 20 | 28 | 36 | 44 | 52 | 57 | 66 | 80 |
| Visit Window (Days) | ±6 | -6 to 0 | ±0 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | 0 to+5 | ±5 | ±5 |
| Informed Consent and Demography [a] (10.1.3) | X | | | | | | | | | | | | | | |
| Eligibility Criteria (5.1 and 5.2) | X | X | X | | | | | | | | | | | | |
| Medical History/Concomitant Illness (8.2) | X | | | | | | | | | | | | | | |
| Physical Examination( 8.2.1) | X | | | | | | | | | | | | | | |
| Childbearing Potential [b] (10.4) | X | | | | | | | | | | | | | | |
| Randomisation (6.3) | | | X | | | | | | | | | | | | |
| Concomitant Medication (6.5) | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tobacco Use (5.3.2) | X | | | | | | | | | | | | | | |
| Evaluation of Glycaemic Status (8) | | | | | | | | X | X | | | X | | X | X |
| Evaluation of Antihypertensive and lipid-lowering treatment (8) | | | | | | | | | | | | X | | | X |
| Occupation (8.11) | | | X | | | | | | | | | | | | |
| Body Weight (8.1.1) | X | | X | X | X | X | X | X | X | X | X | X | | X | X |
| Height / BMI (8.1.1) | X | | | | | | | | | | | | | | |
| Waist Circumference (8.1.1) | | | X | | | | | | X | | | X | | X | X |
| Pregnancy Test [b] (10.4) | X | | X | | X | | X | X | X | X | X | X | X | | |
| Laboratory Assessments (10.2) | X | X | X | | X | | | X | X | | | X | | X | X |
| Attend Visit Fasting (5.3.1) | | X | X | | X | | | X | X | | | X | | X | X |
| Biosamples for Future Analysis[c] (8.10 and 10.6) | | | X | | X | | | X | X | | | X | | X | X |
| Vital signs (8.2.2) | X | | X | | X | | | X | X | | | X | | X | X |

| | Screening 1 | Screening 2 | Randomisation | Dose escalation period | | | | Treatment period | | | | End of treatment | Safety visit | Extension phase | End of trial |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | P13 | V14ext | V15ext |
| Timing of Visit (Weeks) | -2 | -1 | 0 | 4 | 8 | 12 | 16 | 20 | 28 | 36 | 44 | 52 | 57 | 66 | 80 |
| Visit Window (Days) | ±6 | -6 to 0 | ±0 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | 0 to+5 | ±5 | ±5 |
| Adverse Event (8.3 and 10.3) | | X | X | X | X | X | X | X | X | X | X | X | X | X[d] | X[d] |
| Barriers and Motivation Interview (8) | X | | | | | | | | | | | | | | |
| Employment and time missed from work (8.11) | | | X | X | X | X | X | X | X | X | X | X | | X | X |
| Clinical Outcome Assessments (8.1.2) | | | X | | | | | X | | | | X | | | |
| Diet and Physical Activity Counselling (6.1.2) | | | X | X | X | X | X | X | X | X | X | | | | |
| Hand out direction for use (6.1.1) | | | X | | | | | | | | | | | | |
| Drug Dispensing (6.2) | | | X | X | X | X | X | X | X | X | X | | | | |
| Training in Devices (6.1.1) | | | X | X | X | X | X | X | X | X | X | | | | |

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

[b] Only for female subjects of childbearing potential

[c] Subjects must sign and date a separate informed consent form before samples are collected

[d] Only serious adverse events

# 2 Introduction

## 2.1 Trial rationale

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.[3-9] Obesity is associated with an increased risk of a variety of comorbidities including hyperglycaemia, T2D, hypertension, dyslipidaemia, obstructive sleep apnoea, atherosclerosis, osteoarthritis, urinary incontinence, non-alcoholic steatohepatitis, cardiovascular disease, certain types of cancers, and risk of early death.[13-27] Moreover, obesity adversely affects physical and mental health and reduces health-related quality of life.[28, 29]

Even a body weight loss of > 5% has been shown to have significant health benefits on many obesity-related comorbidities as well as physical symptoms and health-related quality of life[30] and studies suggest a beneficial impact of weight loss on cardiovascular risk and mortality in individuals with obesity.[31-33]

Lifestyle intervention in the form of diet and exercise is first line treatment for obesity, but most individuals with obesity struggle to achieve and maintain their weight loss.[34-42] Surgical interventions for weight loss offer an effective alternative for some individuals with severe obesity, but surgery carries a risk in connection with the procedure and may not be without complications.[43, 44] Furthermore, surgery is limited in terms of the number of individuals it can be offered to compared with the number of individuals requiring intervention to treat obesity.[34, 37, 38, 43-47] Therefore, pharmacotherapy may serve as a valuable adjunct to lifestyle intervention for individuals with obesity in order to achieve and maintain a clinically relevant weight loss, to improve comorbid conditions and to facilitate a healthier lifestyle.

The risk of obesity-related comorbidities increases with increasing BMI[10], and individuals with both obesity and prediabetes are at significant risk of T2D, other weight-related comorbidities and mortality and are likely to benefit from weight reduction and improvement in glycaemic status.

The present trial will compare the effect on reversal to normoglycaemia of 52 weeks of treatment with semaglutide s.c. 2.4 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with obesity (BMI ≥ 30.0) and prediabetes, defined as $HbA_{1c}$ between 6.0 and 6.4% (both inclusive) and/or FPG between 5.5 and 6.9 mmol/L (both inclusive).[12] Furthermore, the trial will compare the effect on body weight of semaglutide s.c. 2.4 mg once-weekly versus placebo. An off-treatment extension phase from week 52 to week 80 is included to obtain a better understanding of how glucose metabolism, body weight, and cardiovascular risk factors develop after completed pharmacotherapy intervention in people living with obesity and prediabetes. The extension phase of this trial mimics a real-world setting and can thereby provide better guidance to health care professionals, as well as to patients, in the future management of obesity and prediabetes.

## 2.2 Background

### 2.2.1 Semaglutide

Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA), approved for the treatment of T2D in adults (Ozempic®), which is currently under development by Novo Nordisk for the treatment of weight management at higher doses. Semaglutide has a half-life of approximately 160 hours, making it suitable for once-weekly dosing.[48]

GLP-1 is a physiological regulator of appetite and postprandial GLP-1 response is present in several areas of the brain involved in appetite regulation.[49] In line with this, clinical[50-55] and non-clinical data[56] indicate that the body weight-reducing effect of semaglutide is mainly mediated by a reduced energy intake.

A global phase 3a clinical development programme with semaglutide s.c. 2.4 mg once-weekly has been completed (STEP programme), having enrolled approximately 4,500 adults with overweight or obesity. The programme consists of four trials (NN9536-4373, NN9536-4374, NN9536-4375 and NN9536-4376). The 68-week phase 3a weight management trial STEP 1 (NN9536-4373) demonstrated clinically significant weight loss with semaglutide s.c. 2.4 mg once-weekly: a total of 1,961 subjects with overweight or obesity were included, and at week 68, subjects in the semaglutide s.c. 2.4 mg 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)[57] and any updates hereof.

### 2.2.2 Trial population

The trial population will consist of subjects with BMI ≥30.0 kg/m$^2$ and prediabetes, defined as $HbA_{1c}$ between 6.0 and 6.4% (both inclusive) and/or FPG between 5.5 and 6.9 mmol/L (both inclusive) at baseline.[12] These subjects are at significant risk for weight-related comorbidities and mortality and are likely to benefit from weight reduction and improvement in glycaemic status (reversal to normoglycaemia).

## 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 (AEs) of semaglutide can be found in the IB[57] and any updates hereof.

### 2.3.1 Risk assessment

| Potential risk of clinical significance | Summary of data/rationale for risk | Mitigation strategy |
|---|---|---|
| **Trial treatment** | | |
| Gastrointestinal (GI) AE | Consistent with findings with other GLP-1 RAs, the most frequently reported AEs 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.<br><br>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. | Clinical trials have shown that a low starting dose and gradual dose escalation mitigates the risk of developing gastrointestinal symptoms.<br><br>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 should be informed of the characteristic symptoms of acute pancreatitis and if pancreatitis is suspected, semaglutide should be discontinued. If confirmed, semaglutide should not be restarted. |
| Medullary thyroid cancer (MTC) (based on non-clinical data) | Thyroid C-cell tumours were seen in the mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. No hyperplasia was observed in monkeys after 52 weeks exposure up to 13-fold above the clinical plasma exposure at 2.4 mg/week.<br>The GLP-1 receptor is not expressed in the normal human thyroid, and therefore the clinical relevance of the findings is considered to be low. | To mitigate this risk, subjects with a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2) are excluded from clinical trials with semaglutide. |
| 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. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies. | 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 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.<br><br>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 neoplasms, however since long term exposure is still limited monitoring of neoplasms continues. | 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 trial treatment | Available data do not suggest an increased risk of infection or a more severe progression of infection when treated with semaglutide s.c. | Detailed information about the known risks for s.c. semaglutide can be found in the investigator's brochure and summary of product characteristics. |
| **Trial procedures** | | |
| Venous laboratory samples drawn at screening and selected visits may be associated with slight discomfort and complicated by bruising in the region. | | |
| Risk of COVID-19 infection in relation to trial participation | Subjects 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. | To minimize the risk as much as possible, local guidelines must be followed. |

| 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. Women of childbearing potential are required to use highly effective contraceptive methods when participating in this trial (Appendix 4, Table 10-3). If a subject wish to become pregnant, or pregnancy occurs, semaglutide should be discontinued (please refer to protocol section7.1 for further guidance). The effect of semaglutide on fertility in humans is unknown. |

### 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 had a safe and well-tolerated profile, consistent with previous findings.

In addition, it is expected that all 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. 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 to minimise the risks and inconveniences of participation in the trial. The safety profile for semaglutide generated from the clinical and non-clinical development programme has not revealed any safety issues that would prohibit administration of semaglutide s.c. 2.4 mg once-weekly. The results of the phase 3a trials (NN9536-4373, NN9536-4374, NN9536-4375 and NN9536-4376) indicate that semaglutide will 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 s.c. 2.4 mg once-weekly are justified by the anticipated benefits that may be afforded to subjects with obesity.

# 3 Objectives and endpoints

## 3.1 Primary, secondary and exploratory objectives and estimands

**Primary objective (week 0 to week 52)**

To confirm the superiority of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo, both as adjuncts to a reduced-calorie diet and increased physical activity in subjects with obesity and prediabetes, on body weight and reversal to normoglycemia.

### Secondary objectives (week 0 to week 52)

To compare the efficacy of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo on:

- glucose metabolism
- cardiovascular risk factors
- other factors related to body weight

### Secondary safety objective (week 0 to week 57)

To compare the safety and tolerability of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo.

### Exploratory objectives

**Main phase (week 0 to week 52)**
To compare the efficacy of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo on physical functioning, vitality, work productivity, and progression to T2D.

**Main and extension phase (week 0 to week 80)**
To explore the change in body weight, reversal to normoglycemia, glucose metabolism, cardiovascular risk factors, other factors related to body weight, and progression to T2D in subjects after treatment with semaglutide s.c. 2.4 mg once-weekly or semaglutide placebo followed by an off-treatment period.

### Primary estimand

The primary clinical question of interest is: what is the average treatment effect of semaglutide s.c. 2.4 once-weekly as an adjunct to a reduced-calorie diet and increased physical activity, in subjects with obesity and prediabetes, measured by relative change from baseline to week 52 in body weight and reversal to normoglycaemia, regardless of discontinuation or dose reduction of randomised treatment and regardless of initiating other glucose-lowering medication or anti-obesity therapies (weight management drugs or bariatric surgery) ("treatment policy" strategy).

The estimand is described by the following attributes (according to International Council for Harmonisation (ICH) E9(R1)[58]):

- Treatment condition: The randomised treatment regardless of discontinuation or dose reduction of randomised treatment or initiation of other glucose-lowering medication or anti-obesity therapies (as defined above)
- Other intercurrent events: none
- Population: Subjects with obesity and prediabetes
- Endpoints: The two primary endpoints relative change in body weight and reversal to normoglycaemia, both from baseline to week 52
- Population-level summary: For change in body weight, the treatment effect will be quantified by the difference in mean changes between treatment conditions. For reversal to normoglycaemia, the treatment effect will be quantified by the odds ratio between treatment conditions.

A similar estimand applies to all supportive secondary endpoints, which is called the secondary estimand.

Rationale for estimand: The primary (and secondary) estimand 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 as an adjunct to a reduced-calorie diet and increased physical activity, in subjects with obesity and prediabetes, measured by relative change from baseline to week 52 in body weight and reversal to normoglycaemia, had they remained on their randomised treatment for the entire planned duration of the trial and not initiated other glucose-lowering medication or anti-obesity therapies (weight management drugs or bariatric surgery) ("hypothetical" strategy).

The estimand is described by the following attributes (according to ICH E9(R1)[58]):

- Treatment condition: The randomised treatment if subjects had adhered for the entire duration of the trial and not initiated other glucose-lowering medication or anti-obesity therapies (as defined above)
- Other intercurrent events: none
- Population: Subjects with obesity and prediabetes
- Endpoints: The primary endpoints relative change in body weight and reversal to normoglycaemia, both from baseline to week 52
- Population-level summary: For relative change in body weight, the treatment effect will be quantified by the difference in mean changes between treatment conditions. For reversal to normoglycaemia, the treatment effect will be quantified by the odds ratio between treatment conditions.

Rationale for estimand: The additional estimand aims at reflecting the treatment effect in the absence of intercurrent events.

## 3.2 Primary, secondary and exploratory endpoints

### 3.2.1 Primary endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in body weight | From randomisation (week 0) to end of treatment (week 52) | % |
| Change to normoglycemia* | From randomisation (week 0) to end of treatment (week 52) | Count of subjects |

* Normoglycemia is defined as having both $HbA_{1c}$ < 6.0% (< 42 mmol/mol) and FPG < 5.5 mmol/L (< 99 mg/dL)

### 3.2.2 Secondary endpoints

#### 3.2.2.1 Confirmatory secondary endpoints

Not applicable for this trial

### 3.2.2.2 Supportive secondary endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in $HbA_{1c}$ | From randomisation (week 0) to end of treatment (week 52) | %-points |
| Change in FPG | From randomisation (week 0) to end of treatment (week 52) | mmol/L |
| Change in waist circumference | From randomisation (week 0) to end of treatment (week 52) | cm |
| Change in systolic blood pressure | From randomisation (week 0) to end of treatment (week 52) | mmHg |
| Change in lipids<br>• Triglycerides<br>• Total cholesterol<br>• High density lipoprotein (HDL) cholesterol<br>• Low density lipoprotein (LDL) cholesterol<br>• Very low density lipoprotein (VLDL) cholesterol | From randomisation (week 0) to end of treatment (week 52) | % |

## 3.2.3 Exploratory endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in EuroQol five dimensions three level (EQ-5D-3L) index score | From randomisation (week 0) to end of treatment (week 52) | Score points |
| Change in EQ-5D-3L visual analogue scale (VAS) score | From randomisation (week 0) to end of treatment (week 52) | Score points |
| Change in Work Limitations Questionnaire 25-item version (WLQ-25) Six-item Physical Demands scale | From randomisation (week 0) to end of treatment (week 52) | Score points |
| Change in WLQ-25 total score | From randomisation (week 0) to end of treatment (week 52) | Score points |
| Change to normoglycemia* | From randomisation (week 0) to end of extension phase (week 80) | Count of subjects |
| Change in body weight | From randomisation (week 0) to end of extension phase (week 80) | % |
| Change in $HbA_{1c}$ | From randomisation (week 0) to end of extension phase (week 80) | %-points |
| Change in FPG | From randomisation (week 0) to end of extension phase (week 80) | mmol/L |
| Change in waist circumference | From randomisation (week 0) to end of extension phase (week 80) | cm |
| Change in systolic blood pressure | From randomisation (week 0) to end of extension phase (week 80) | mmHg |
| Change in lipids<br>• Triglycerides<br>• Total cholesterol<br>• High-density lipoprotein (HDL) cholesterol<br>• Low-density lipoprotein (LDL) cholesterol | From randomisation (week 0) to end of extension phase (week 80) | % |

| | | |
|---|---|---|
| • Very low-density lipoprotein (VLDL) cholesterol | | |
| Progression to T2D** | From randomisation (week 0) to end of treatment (week 52) | Count of subjects |
| Progression to T2D** | From randomisation (week 0) to end of extension phase (week 80) | Count of subjects |

* Normoglycemia is defined as having both HbA1c < 6.0% (< 42 mmol/mol) and FPG < 5.5 mmol/L (< 99 mg/dL)
**Diagnosis of T2D is defined as HbA1c ≥6.5% (≥ 48 mmol/mol) and/or FPG ≥ 7.0 mmol/L (≥ 126 mg/dL) verified with a repeated blood sample within 4 weeks.

# 4 Trial design

## 4.1 Overall design

**Main phase**
This is a 52-week, randomised, two-arm, double-blinded, parallel-group, multi-centre, multinational clinical trial comparing semaglutide s.c. 2.4 mg once-weekly with semaglutide placebo once-weekly on body weight and reversal to normoglycaemia in subjects with obesity (BMI ≥ 30.0 kg/m$^2$) and prediabetes ($HbA_{1c}$ between 6.0 and 6.4%, both inclusive and/or FPG between 5.5 and 6.9 mmol/L, both inclusive[12]) at baseline.

The trial includes 2 screening visits (week -2 and week -1) to assess the subject's eligibility followed by randomisation (week 0) and visits every 4$^{th}$ week during dose escalation. From week 20, visits will take place every 8$^{th}$ week for the remaining maintenance period until end of treatment at week 52. A safety visit (phone visit) will take place 5 weeks after end of treatment (week 57).

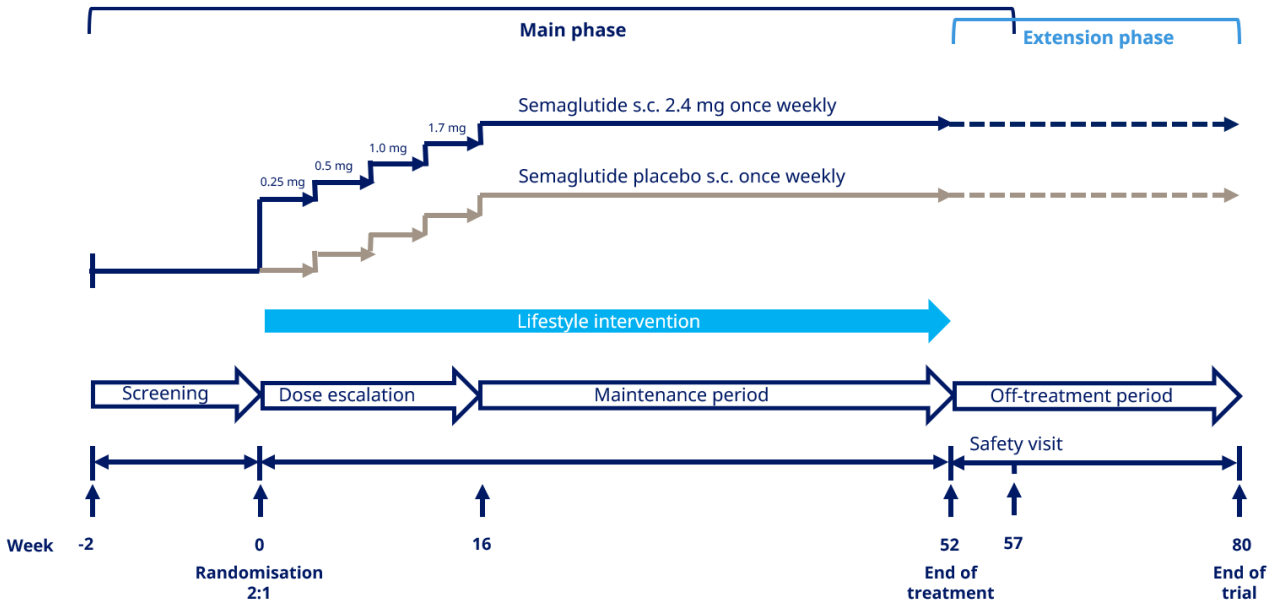
**Extension phase**
All subjects will continue in the 28-week off-treatment extension phase after the last visit in the main phase (visit 12). Two visits with 14 weeks apart will take place (week 66 and week 80) for assessment of body weight, and glycaemic and cardiovascular parameters.

The total trial duration (main phase and extension phase) for each subject is approximately 82 weeks (up to 2 weeks screening, 52 weeks treatment and 28 weeks off treatment).

Approximately 201 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 an adjunct to a reduced-calorie diet and increased physical activity.

The trial design is outlined in Figure 4-1.

**Figure 4-1 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 prediabetes, defined as $HbA_{1c}$ between 6.0 and 6.4% (both inclusive) and/or FPG between 5.5 and 6.9 mmol/L (both inclusive) at baseline.[12] These subjects are likely to benefit from weight reduction and improvement in glycaemic status (reversal to normoglycaemia).

The treatment duration is 52 weeks which is the same as the length of the phase 2 trial (NN9536-4153) where the mean weight loss was 13.8% with the highest dose of semaglutide (0.4 mg once-daily) compared to 2.3% with placebo[59]. Also, mean weight loss at 52 weeks was very near the maximum reached in the phase 3a programme. Thus, a 52-week treatment period (including 36 weeks on target dose) is considered sufficient to realise the weight loss potential of the intervention. A safety visit (phone visit) will take place 5 weeks after end of treatment (week 57) to account for the exposure and the long half-life of semaglutide. A 28-week off-treatment period is included to explore how body weight, cardiovascular risk factors and glucose metabolism develop after completed pharmacotherapy in subjects with obesity and prediabetes.

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.

## 4.3 Justification for dose

A maintenance dose of semaglutide s.c. 2.4 mg once-weekly has been chosen for the phase 3 weight management development programme. The 68-week phase 3a weight management trial STEP 1 (NN9536-4373) demonstrated clinically significant weight loss with semaglutide s.c. 2.4 mg once-weekly. In STEP 1, 1,961 subjects with overweight or obesity were included. 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. In the STEP 1 trial, semaglutide s.c. 2.4 mg once-weekly had a safe and well-tolerated profile, consistent with previous findings.

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 STEP 1–4 trials, a fixed-dose escalation regimen is selected, with dose escalation every 4 weeks until the target dose is reached. Treatment will be initiated at a once-weekly dose of 0.25 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.

### 4.4 End of trial definition

A subject is considered to have completed the trial if he/she has completed all phases of the trial including the last visit ('end of trial' according to the flowchart).

The end of the trial is defined as the date of the 'end of trial' 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 aged ≥ 18 years at the time of signing informed consent.
3. BMI ≥ 30.0 kg/m$^2$
4. Prediabetes defined as at least one of the following:[12]
    a. HbA1c between 6.0 and 6.4 % (42 and 47 mmol/mol) (both inclusive) as measured by central laboratory at screening.
    b. FPG between 5.5 and 6.9 mmol/L (99 and 125 mg/dL) (both inclusive) as measured by central laboratory at screening.

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

### 5.2 Exclusion criteria

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

1. History of type 1 or type 2 diabetes.
2. Treatment with glucose-lowering agent(s) within 90 days before screening.
3. HbA1c ≥ 6.5 % (≥ 48 mmol/mol) as measured by central laboratory at screening.
4. FPG ≥ 7.0 mmol/L (126 mg/dL) as measured by central laboratory at screening.
5. A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records.
6. Treatment with any medication for the indication of obesity within the past 90 days before screening.
7. Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following are allowed: (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.

8. Uncontrolled thyroid disease.
9. Known or suspected hypersensitivity to trial product or related products.
10. Previous participation in this trial. Participation is defined as signed informed consent.
11. 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).
12. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening*
13. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.
14. History of chronic pancreatitis or acute pancreatitis within 180 days prior to screening
15. End-stage renal disease or chronic or intermittent haemodialysis or peritoneal dialysis.
16. Presence or history of malignant neoplasms (other than basal and squamous cell skin cancer, *in situ* carcinomas of the cervix, or *in situ* prostate cancer) within 5 years before screening.
17. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 60 days prior to the day of screening.
18. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.
19. Other subject(s) from the same household participating in any semaglutide trial.
20. Presence or history of severe psychiatric disorders (e.g., schizophrenia, bipolar disorder, major depressive disorder or anxiety), as judged by the investigator.
21. Known or suspected abuse of alcohol or recreational drugs.
22. Surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator.
23. Any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

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

*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.

**Denmark, Finland, Spain and United Kingdom**: see local requirements in Appendix 7 (Section 10.7).

## 5.3 Lifestyle considerations

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

### 5.3.1 Meals and dietary restrictions

Subjects must attend the visits fasting according to the flowchart.

Fasting is defined as at least 8 hours before the visit, without food or liquids, except for water. Trial product and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood samples have been obtained.

If the subject is not fasting as required, the subject should be called in for a new visit within the visit window to have the fasting procedures done. Procedures requiring subject to fast include blood sampling of FPG.

### 5.3.2 Caffeine and tobacco

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

Tobacco use is defined as smoking at least one cigarette or equivalent daily.

## 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 serious adverse event (SAE). 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 laboratory parameters, re-sampling is not allowed. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

## 5.5 Run-in criteria, randomisation criteria and dosing day criteria

Not applicable for this trial.

# 6 Treatments

## 6.1 Treatments administered

### Investigational medicinal products (IMP)

All trial products listed in Table 6-1 are considered investigational medicinal products (IMP).

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

| Trial product name | Dose | Dosage form | Route of administration | Dosing instructions | Delivery device |
|---|---|---|---|---|---|
| Semaglutide D 0.5 mg/mL DV3396 | 0.25 mg | Solution for injection | s.c. | Once-weekly | 0.5 mL single-dose pen-injector |

| | | | | | |
|---|---|---|---|---|---|
| Semaglutide D 1.0 mg/mL DV3396 | 0.5 mg | Solution for injection | s.c. | Once-weekly | 0.5 mL single-dose pen-injector |
| Semaglutide D 2.0 mg/mL DV3396 | 1.0 mg | Solution for injection | s.c. | Once-weekly | 0.5 mL single-dose pen-injector |
| Semaglutide placebo Ia | N/A | Solution for injection | s.c. | Once-weekly | 0.5 mL single-dose pen-injector |
| Semaglutide D 2.27 mg/mL DV3396 | 1.7 mg | Solution for injection | s.c. | Once-weekly | 0.75 mL single-dose pen-injector |
| Semaglutide D 3.2 mg/mL DV3396 | 2.4 mg | Solution for injection | s.c. | Once-weekly | 0.75 mL single-dose pen-injector |
| Semaglutide placebo Ib | N/A | Solution for injection | s.c. | Once-weekly | 0.75 mL DV3396 single-dose 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 semaglutide 2.4 mg once weekly or 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 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 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.
- A dose reminder card will be handed out to the subjects at each site visit during the escalation period. 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 /semaglutide placebo**

| Trial product name | Dose | Delivery device | Duration |
|---|---|---|---|
| **Dose escalation period** | | | |
| Semaglutide D 0.5 mg/mL DV3396/ semaglutide placebo Ia | 0.25 mg | 0.5 mL single-dose pen-injector | 4 weeks |
| Semaglutide D 1.0 mg/mL DV3396/ semaglutide placebo Ia | 0.5 mg | 0.5 mL single-dose pen-injector | 4 weeks |
| Semaglutide D 2.0 mg/mL DV3396/ semaglutide placebo Ia | 1.0 mg | 0.5 mL single-dose pen-injector | 4 weeks |
| Semaglutide D 2.27 mg/mL DV3396/ semaglutide placebo Ib | 1.7 mg | 0.75 mL single-dose pen-injector | 4 weeks |
| **Maintenance period** | | | |
| Semaglutide D 3.2 mg/mL DV3396/ semaglutide placebo Ib | 2.4 mg | 0.75 mL single-dose pen-injector | 36 weeks |

- 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 re-commence 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 starting 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 medical experts.

**Auxiliary supplies**

Direction for use (DFU) for DV3396 pen-injector will be provided in accordance with the trial materials manual (TMM). The DV3396 pen-injector comes with an integrated and hidden needle, therefor no needles are required.

### 6.1.1 Medical devices

Information about the DV3396 pen-injector may be found in the IB[57] and any updates hereof. Information about the use of the drug-device combination products can be found in the DFU.

**Training in the DV3396 pen-injector**

Site staff will train subjects according to the flowchart (Section 1.2). Novo Nordisk will train the site staff and only trained site staff can be allocated the task to train and supervise subjects. All training must be documented.

The following should be emphasised during training of subjects:

- use of the pen-injector (according to instruction guidelines given in the DFU)
- long-term and in-use storage conditions of the pen-injector (as specified on the label and in the TMM).

The investigator must document that directions for use are given to the subject verbally and in writing as a DFU document at the first dispensing visit (as specified in the flowchart (Section 1.2)) and that subjects are trained. Training must be repeated as specified in the flowchart and, if needed, during the trial at regular intervals in order to ensure correct use of the pen-injector and correct injection technique. Training is the responsibility of the investigator or a delegate.

The first dose of trial product must be taken on the day of randomisation (V3) at the clinical site by self-administration under supervision by trained site staff.

### 6.1.2 Diet and physical activity counselling

At every visit in the first 52-week period the subject should be offered individual counselling with regards to diet and physical activity by a dietician or a similar qualified healthcare professional. During the 28-week off-treatment extension period, subjects should be offered healthy lifestyle counselling as per normal clinical practise and according to local guidelines.

## 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.

- Acceptable temperature ranges and conditions for storage and handling of each trial product when not in use and when in use are described in the TMM.
- Each site will be supplied with enough trial products for the trial on an ongoing basis controlled by the IWRS. 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 must be performed in the IWRS by registering pen-injectors as used, unused or lost.

- The subject must return all 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.
- Destruction of trial products must be documented in the IWRS.
- 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 subjects' homes" document. This 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 subject. 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 subjects 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

All subjects will be screened and centrally 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.

Semaglutide once-weekly and semaglutide placebo will be double blinded. The active drug and placebo are visually identical for the following trial products:

- Semaglutide D 0.5 mg/mL, Semaglutide D 1.0 mg/mL, Semaglutide D 2.0 mg/mL DV3396 and Semaglutide placebo Ia
- Semaglutide D 2.27 mg/mL, Semaglutide D 3.2 mg/mL and Semaglutide placebo Ib

The specific treatment for a subject will be assigned using an IWRS. The site will access the IWRS before the start of trial product administration for each subject.

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 I. Treatment with trial product can be resumed if there are no safety concerns at the discretion of the investigator.

## 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 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. Compliance can be assessed by cross checking the following sources and comparing these to the expected use:

- Drug accountability information; visual inspection of pen-injectors
- Questioning of subjects about current treatment dose and missed doses at every visit. Information on current treatment dose and information on periods > 14 days without treatment will be recorded in the electronic case report form (eCRF).

Treatment start and stop dates must be recorded in the eCRF.

## 6.5 Concomitant medication

Any medication (including over-the-counter or prescription medicines) 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

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.

Treatment and monitoring of T2D developed in subjects during the trial is the responsibility of and at the discretion of the investigator, but treatment should preferably be weight-neutral, and GLP-1 RAs must be avoided.

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

### 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 treated 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.

Temporary or permanent discontinuation of treatment with trial product will not lead to withdrawal 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 (V12) containing the final data collection of primary endpoints.
- The 'safety visit' (P13) is scheduled approximately 5 weeks after end of treatment to ensure the safety of the subject. If the subject has discontinued trial product >5 weeks prior to the 'end of treatment' visit, and the requirements for the follow-up period prior to the 'safety visit' is fulfilled, then the 'safety visit 'can be omitted.
- If the subject refuses to attend the 'end of treatment' visit 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 investigational medicinal product in another clinical trial*

*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 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[60] are not fulfilled at the investigators discretion and thus, the suspicion of acute pancreatitis is not confirmed. 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 eCRF, and final drug accountability must be performed. A 'treatment status session' must be made in the IWRS to discontinue 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).

A treatment status session must be made in the IWRS when a subject pauses treatment or resumes treatment.

In case of suspicion of acute pancreatitis, the trial product must promptly be discontinued; however, 'treatment status session' should not be made in IWRS before diagnosis of acute pancreatitis is confirmed. If acute pancreatitis is confirmed, treatment with trial product must not be restarted, and a 'treatment status session' should be made in IWRS.

## 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 or the 'end of trial' visit, depending on the timing of the withdrawal the consent. See the flowchart (Section 1.2) for data to be collected.

Final drug accountability must be performed even if the subject is not able to come to the site. The investigator must make a 'treatment status session' in IWRS to discontinue 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 eCRF.

### 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.
- Screening visits 1 and 2 must not be combined.
- 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. The suggested order of the assessments:
    1. Vital signs (see Section 8.2.2) and body measurements (see Section 8.1.1)
    2. Blood samples

3. Patient-reported outcomes (PROs) (see Section 8.1.2)
4. Other assessments

- The Barriers and Motivation Interview identify barriers to and motivation for lifestyle change and compliance with the protocol. The interview can 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 can ensure that any minor barriers are addressed during lifestyle counselling.
  - The results of the interview will not be entered into the eCRF. It will be at the investigator's discretion to evaluate the motivation of the subject and related eligibility.
- Review of laboratory reports must be documented either on the documents or in the subject's source documents.
- Repeat laboratory samples may be taken for technical issues and must be taken in the event of HbA1c ≥ 6.5% (≥ 48 mmol/mol) or FPG ≥ 126 mg/dL (7.0 mmol/L) any time during the trial. Please refer to Appendix 2 (Section 10.2) for further details on laboratory samples.
- Results of pregnancy testing must be documented in the subject's medical records.
- For subjects receiving antihypertensive or lipid-lowering treatment, the investigator should evaluate changes in the subjects' treatment intensity within each therapeutic area. The evaluation should be based on whether an overall change from randomisation to end of treatment (V12) and from end of treatment (V12) to end of trial (V15ext) has occurred (i.e., either increase, decrease or no change) after reviewing all available relevant information e.g., changes in drug dose, drug class, number of drugs or a combination of these.
- The investigator will evaluate the subject's glycaemic status during the trial as detailed in the flowchart based on all available relevant information e.g. medical records, concomitant medication, blood glucose parameters ($HbA_{1c}$, FPG) and AEs. The subject's glycaemic status will be categorised as normoglycaemia, prediabetes or diagnosed with T2D according to local guidelines.

## 8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart (Section 1.2).

### 8.1.1 Body measurements

**Body weight** should be measured at all site visits without shoes, with an empty bladder and only wearing light clothing. Body weight 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 according to manufacturer's recommendation or local requirements – the strictest requirement must be followed.

**Height** is measured without shoes in centimetres or inches (one decimal). BMI will be calculated in the eCRF from screening data.

**Waist circumference** is defined as abdominal circumference located midway between the lower rib margin and the iliac crest. Measures must be obtained in standing position with a non-stretchable measuring tape and recorded 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.

### 8.1.2 Clinical outcome assessments

Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. The subject must transcribe directly into a site-pad/web-solution. Each questionnaire takes approximately 10 minutes to complete.

The following PRO questionnaires will be used:

**The WLQ-25 version 2.0**

The WLQ-25 evaluates at-work disability and productivity loss. It contains 25 items arranged under four subscales addressing four dimensions of job demands: time demands, physical demands, mental/interpersonal demands, and output demands.

**The EQ-5D-3L questionnaire – Digital Self-Complete Tablet**

The EQ-5D-3L questionnaire evaluates general health status. It consists of the EQ-5D-3L descriptive system and the EQ VAS. The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The EQ VAS records the subject's self-rated health on a vertical VAS where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'.

### 8.1.3 Clinical laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (section 10.2), must be conducted in accordance with the flowchart and the laboratory manual.

## 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. Special attention should be made on recording comorbidities related to obesity such as hypertension, dyslipidaemia, obstructive sleep apnoea, knee and hip osteoarthritis, non-alcoholic fatty liver disease and steatohepatitis, cardiovascular disease, asthma, chronic obstructive pulmonary disease, polycystic ovary syndrome, and kidney disease.

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.

As part of the medical history, information on the following will be collected:

- Weight history (incl. previous weight, debut time of overweight, previous weight loss attempts, previous use of prescription medication for obesity, considerations regarding bariatric surgery, and family history of overweight/obesity)
- History of weight disorder
- History of breast neoplasm
- History of cardiovascular disorder and procedure
- History of dyslipidaemia
- History of gallbladder disease and procedure
- History of gastrointestinal disorder and neoplasm
- History of genitourinary tract disorder
- History of kidney disease
- History of liver disease
- History of musculoskeletal system disorder
- History of pancreatic disease
- History of psychiatric disorder
- History of respiratory disorder
- History of skin cancer and skin disorder
- Other relevant concomitant illness/medical history (also including COVID-19 and malignant neoplasms not covered by the above categories)

### 8.2.1 Physical examinations

A physical examination will include assessments of:

- general appearance
- skin
- head, ears, eyes, nose, throat and neck
- thyroid gland
- cardiovascular and respiratory systems
- abdomen
- musculoskeletal system

Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 8.2.2 Vital signs

Pulse rate, as well as systolic and diastolic blood pressure will be assessed.

The method for measuring pulse rate, systolic and diastolic blood pressure needs to follow the standard clinical practice at site.
However, as a minimum:

- Blood pressure (diastolic and systolic) and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. television, cell phones).

- Blood pressure and pulse rate measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

## 8.3 Adverse events and serious adverse events

**Main phase**
The trial will employ selective safety data collection. The investigator is responsible for detecting, documenting, recording and following up on all the events listed below:

- Serious AEs (SAEs)
- Following AEs irrespective of seriousness:
  - AEs leading to premature discontinuation of trial product
  - Selected types of AEs (SAEs and non-SAEs) requiring additional data collection (Table 8-1)
  - Pregnancies and pregnancy related AEs
  - AEs of COVID-19, irrespective of seriousness*

  *Note: 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 should, if they take place, be reported on an AE form 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.

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

| Event type | AE requiring additional data collection |
|---|---|
| Medication error | X |
| Misuse and abuse | X |
| Acute pancreatitis | X |

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

In the main phase of the trial, 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, and including, P13 at time points specified in the flowchart (Section 1.2). In the extension phase (including V14ext and V15ext, see flowchart in Section 1.2), only SAEs will be collected.

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 an 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, institutional review board (IRB)/independent ethics committee (IEC), and investigators. This also includes suspected unexpected serious adverse reactions (SUSARs).

An investigator who receives an investigator safety report describing an 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 first exposure to trial product 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 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 multiple doses 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, considering 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[57] and any updates hereof.

## 8.5 Pharmacokinetics

Not applicable for this trial.

## 8.6 Pharmacodynamics

Not applicable for this trial.

## 8.7 Genetics

Genetic samples are collected for future research. Refer to Section 8.10 (Human biosamples for future research) and to Appendix 6 (Section 10.6) for retention. **For Finland**, see country-specific requirements in Appendix 7 (Section 10.7).

### 8.8 Biomarkers

Biosamples are collected for future biomarker research. Refer to Section 8.10 (Human biosamples for future research) and to Appendix 6 (Section 10.6) for retention. **For Finland**, see country-specific requirements in Appendix 7 (Section 10.7).

### 8.9 Immunogenicity assessments

Not applicable for this trial.

### 8.10 Human biosamples for future research

Collection of biosamples for future analysis is a component of this trial. The samples will be stored in a biobank and allow for future analyses when new knowledge or improved testing technologies may have become available during or after the trial. Participation is optional and participants must sign a separate informed consent to indicate their participation in the biobank component of the trial. Participants who do not wish to participate in the biobank component may still participate in the trial. Blood samples will be collected according to Appendix 6 (Section 10.6) and stored for use. **For Finland**, see country-specific requirements in Appendix 7 (Section 10.7).

Genetic analyses may include analysis of selected genes or genetic markers throughout the genome with the purpose of understanding and predicting response to semaglutide as well as to understand obesity, prediabetes or other related conditions.

Analyses of circulating biomarkers will measure hormones, metabolites or other serum entity with the purpose of understanding and predicting response to semaglutide as well as understanding obesity, prediabetes or other related conditions.

The human biosamples for future research will be stored for up to 15 years and after end of trial in a central laboratory or appropriate storage facility (see Appendix 6 (Section 10.5.2)).

### 8.11 Health economics

Health economics data, associated with occupation, current employment status and time missed from work due to feeling unwell, will be collected in the eCRF by the investigator and site staff for all subjects throughout the trial. The data collected may be used to conduct exploratory economic analyses.

## 9 Statistical considerations

### 9.1 Statistical hypotheses

The tests of superiority of semaglutide 2.4 mg to semaglutide placebo for the primary endpoints are performed using the fixed-sequence statistical strategy and will be based only on analyses addressing the primary estimand. This strategy tests the endpoints using a predefined hierarchical order, all at the significance level of 5%, moving to test the next endpoint only after a statistically significant superiority result (p-value < 5%) on the previous endpoint. The test hierarchy is given in Table 9-1 with underlying assumptions, marginal power and effective power. The effective power is calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively.

## 9.2 Sample size determination

The sample size and thereby the power for this trial is primarily defined to ensure both that sufficient efficacy data are available from each of the participating countries, and that a sufficient number of subjects complete the end of trial visit at week 80. However, no formal statistical testing is planned either by country, or based on endpoints collected at week 80. Given the trial sample size, the power of statistical tests for the primary endpoints is described below.

The trial is designed with an effective power of > 99% to detect differences on the primary endpoints. 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 power calculations are presented in Table 9-1 and are based on findings from NN9536-4373.

Due to less frequent in-person visits than in the NN9536 global Phase 3a trials, it is conservatively assumed that 30% of subjects will discontinue permanently and 50% of these are retrieved at week 52. All subjects in the semaglutide placebo arm are assumed to have same effect as subjects who complete the trial on semaglutide 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 semaglutide 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 semaglutide placebo. Based on data from the NN9536 global Phase 3a trials, it is expected that <1% of subjects will initiate other glucose-lowering medication or anti-obesity therapies, so the impact of this intercurrent event is expected to be negligible.

Under these assumptions and a 2:1 randomisation ratio, a sample size of 201 subjects randomised to either receive semaglutide s.c. 2.4 mg once-weekly (134 subjects) or semaglutide placebo (67 subjects) yields an effective power of >99% for both primary endpoints.

**Table 9-1 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number of 201 randomised subjects**

| Order | Endpoint | Assumed mean (±SD) or proportion for completers | | Expected mean (±SD) or proportion | Expected difference or proportion ratio | Marginal power (%) | Effective power (%) |
|---|---|---|---|---|---|---|---|
| | | Semaglutide s.c. 2.4 mg once-weekly | Semaglutide placebo | Semaglutide s.c. 2.4 mg once-weekly | | | |
| 1 | % body weight change | 15.8 (±10) | 3.0 (±10) | 12.9 (±11) | 9.9%-points | >99 | >99 |
| 2 | Reversal to normoglycaemia | 91.2% | 39.9% | 79.7% | 2.0 | >99 | >99 |

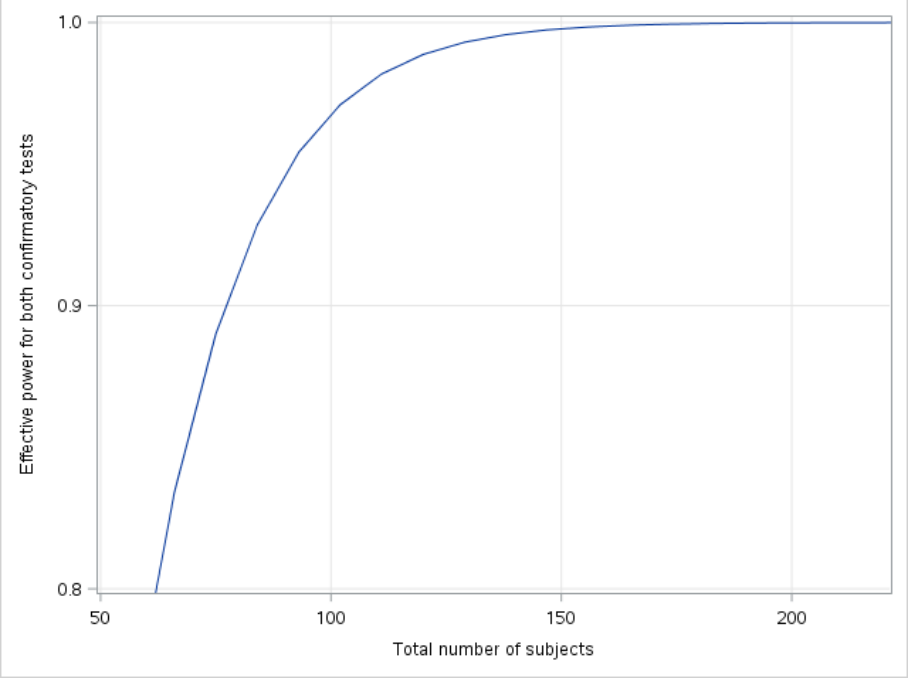
Table 9-2 shows how sensitive the power is to deviations from the design assumptions in terms of responder proportions.

**Table 9-2 Power by proportions reversing to normoglycaemia with a sample size of 201 subjects**

| Proportion reversing to normoglycaemia | | |
|---|---|---|
| **Semaglutide s.c. 2.4 mg** | **Semaglutide placebo** | **Power** |
| 79.7% | 39.9% | >99% |
| 79.7% | 50.0% | 99.0% |
| 75.0% | 39.9% | >99% |
| 75.0% | 50.0% | 94.1% |
| 70.0% | 39.9% | 98.6% |
| 70.0% | 45.0% | 93.1% |
| 70.0% | 50.0% | 79.0% |

The effective power versus total number of subjects randomised is shown in Figure 9-1, indicating that the power remains above 90% even for large reductions of the sample size.

**Figure 9-1 Effective power including all confirmatory tests versus total number of subjects randomised**




All above outlined sample size and power considerations are for the primary estimand (treatment policy strategy). It is assumed that up to 30% of subjects discontinue permanently and 50% of these are retrieved at week 52, which amounts to 15% expected missing data at week 52. This is higher than observed on NN9536-4373, in which 10.8% missing in-trial FPG data were observed after

68 weeks for the primary estimand. Any superiority conclusions will be based on the primary estimand.

For the additional estimand (hypothetical strategy) however, data from retrieved subjects are not used. Hence, it is expected that up to 30% of data will be missing at week 52. Based on NN9536-4373, 21.6% missing on-treatment data were 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 NN9536-4734 slightly higher missing on-treatment data is expected due to subjects initiating glucose-lowering medication (<1%). In NN9536-4373 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).

Finally, based on the extension phase of NN9536-4373 it is expected that 76% of subjects attending the end of treatment visit at week 52 will also attend the end of trial visit at week 80. Therefore, a sample size of 201 randomised subjects is expected to give 130 subjects attending the end of trial visit at week 80.

## 9.3 Populations for analyses

The following populations and observation periods are defined:

| Population | Description |
|---|---|
| Full analysis set | Full analysis set (FAS): All subjects randomised. Exclusion of data from analyses should be used restrictively, and normally no data should be excluded from the FAS. Subjects will be analysed according to the randomised treatment |
| Safety analysis set | All subjects randomly assigned to trial treatment and who take at least 1 dose of trial product. Subjects are analysed according to the treatment they actually received. |

| Observation period | Description |
|---|---|
| In-trial | The time period where the subject is assessed in the trial. The in-trial observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive):<br>• 'End of trial' visit<br>• withdrawal of consent<br>• last contact with subject (for subjects lost to follow-up)<br>• death |
| In-trial (main phase) | The time period where the subject is assessed in the main phase of the trial. The in-trial (main phase) observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive):<br>• safety visit<br>• withdrawal of consent<br>• last contact with subject (for subjects lost to follow-up)<br>• death |
| On-treatment | The time period where subjects are treated 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.<br><br>For the evaluation of AEs and potential pregnancies, the lag time for each on-treatment time interval is 5 weeks (35 days). |

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 safety analysis set (SAS).

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. The in-trial (main phase) period defines the patient years of observation (PYO) during the main phase of the trial as the total time duration in the period.

## 9.4 Statistical analyses

### 9.4.1 General considerations

The statistical analysis plan (SAP) will be finalised prior to breaking the blind to treatment assignment, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and confirmatory secondary endpoints.

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 endpoints

The primary endpoints are change in body weight (%) and reversal to normoglycaemia, both from baseline (week 0) to end of treatment (week 52) as listed in Section 3.2.1.

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

**Analyses addressing the primary estimand**

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

The analysis model for change in body weight (%) will be a linear regression (ANCOVA), assuming unequal variances with randomised treatment as factor and baseline body weight (kg) 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.

The statistical model for the reversal to normoglycaemia endpoint is a logistic regression using randomised treatment as factor and baseline $HbA_{1c}$ (%) and FPG (mmol/L) as covariates. 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.

All available data at week 52 are used and missing values at week 52 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.[61] For subjects in the semaglutide s.c. 2.4 mg once-weekly and the semaglutide placebo groups, missing measurements at week 52 for non-retrieved subjects are imputed using assessments from retrieved subjects in each treatment group. The timing of last available observation during the on-treatment period (LAO-OT) will be included in the imputation model as a continuous covariate. Missing measurements at week 52 for subjects on randomised treatment (at week 52) are imputed by sampling from available measurements at week 52 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 (%) will be assessed using a mixed model for repeated measurements (MMRM) approach. Week 52 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 or initiation of glucose-lowering medication or other anti-obesity therapies (weight management drugs or bariatric surgery). The MMRM will be fitted using change and the same factors 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.

The additional estimand for the reversal to normoglycaemia endpoint will be analysed according to the following procedure:

1) $HbA_{1c}$ (%) will be analysed in an MMRM using assessments only from subjects who are taking the randomised treatment until end of treatment or until first discontinuation of randomised treatment or initiation of glucose-lowering medication or other anti-obesity therapies (weight management drugs or bariatric surgery). The MMRM will be fitted using randomised treatment as factor and baseline $HbA_{1c}$ (%) as covariate nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

2) FPG (mmol/L) will be analysed in the same MMRM as for $HbA_{1c}$ (%), but with FPG (mmol/L) as outcome and baseline FPG (mmol/L) as covariate.

3) For subjects with missing $HbA_{1c}$ (%) and/or FPG (mmol/L) at week 52, individual values will be predicted from the MMRM analyses and used to classify each subject as normoglycaemic or not. This classification will then be analysed using a logistic regression model with randomised treatment as factor and baseline $HbA_{1c}$ (%) and FPG (mmol/L) as covariates.

### 9.4.3 Secondary endpoints

#### 9.4.3.1 Confirmatory secondary endpoint

Not applicable for this trial.

#### 9.4.3.2 Supportive secondary endpoints

For details on analyses of additional supportive secondary endpoints, please refer to the SAP.

### 9.4.4 Exploratory endpoints

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

### 9.4.5 Other safety analyses

All safety analyses will be made on the safety analysis set. For further description of other safety analyses, please refer to the SAP.

## 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

A database lock is planned after completion of the ‘end of trial visit’ (week 80) of the extension phase. One (1) clinical trial report (CTR) will be prepared including the main and the extension phase of the 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[62] and applicable ICH Good Clinical Practice (GCP) Guideline[63]
- Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (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 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.

### 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.
- 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[63], Declaration of Helsinki[62] 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 forms during their participation in the trial.
- A copy of the informed consent forms 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.

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.

### 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.

**United Kingdom**: see local requirements in Appendix 7 (Section 10.7).

### 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.

### 10.1.7 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)[64], the Food and Drug Administration Amendment Act (FDAAA)[65], European Commission Requirements[1, 66, 67] and other relevant recommendations or regulations. If a subject request 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 (PCD) is the last assessment of the primary endpoint and is for this trial last subject first treatment (LSFT) + 52 weeks corresponding to 'end of treatment' visit (visit 12). 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 eCRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data and electronic PROs). 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
- The following will be provided as paper CRFs to be used when access to the eCRF is revoked or the eCRF 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 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 the WLQ-25 and EQ-5D-3L, data will be recorded directly into a tablet and will be 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 reported on the paper CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

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

### 10.1.10 Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, 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.

**Canada and Spain**: see local requirements in Appendix 7 (Section 10.7).

### 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 accepts liability in accordance with 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 CTRs for this trial.

One investigator will be appointed by Novo Nordisk to review and sign the CTRs (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.[68]

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 central laboratory with the exception of urine human chorionic gonadotropin (hCG) pregnancy test.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.
- The central laboratory will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their lab SOPs. These data will not be transferred to the trial database. The investigator should review such values for AEs and report these according to this protocol.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- Laboratory samples will be destroyed no later than at finalisation of the CTR except for the biosamples for future research.

### Table 10-1 Protocol-required laboratory assessments

| Laboratory assessments | Parameters |
|---|---|
| Glucose metabolism<br>Visit 1, 3, 5, 8, 9, 12, 14, 15<br>Visit 2, 3, 5, 8, 9, 12, 14, 15 | • $HbA_{1c}$<br>• Fasting plasma glucose (FPG) |
| Lipids<br>Visit 3, 9, 12, 15 | • Triglycerides<br>• Total cholesterol<br>• High density lipoprotein (HDL) cholesterol<br>• Low density lipoprotein (LDL) cholesterol<br>• Very low density lipoprotein (VLDL) cholesterol |
| Pregnancy Testing<br>Visit 1, 3, 5, 7, 8, 9, 10, 11, 12, P13 | • Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[1] |
| Biosamples for future research[2]<br>Visit: 3<br>Visit: 3, 5, 8, 12, 15<br>Visit: 3, 5, 8, 9, 12, 14, 15 | • Whole blood (DNA)<br>• Plasma<br>• Serum, Plasma, whole blood (RNA) |
| Notes:<br>[1]Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.<br>[2]Subjects must sign and date a separate informed consent form before samples are collected | |

### Table 10-2 Outliers

| |
|---|
| In the event of HbA1c ≥ 6.5% (≥48 mmol/mol) or FPG ≥ 126 mg/dL (7.0 mmol/L) any time during the trial a repeated measurement must be taken within four weeks at central laboratory in order to diagnose diabetes. |

## 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 investigational medicinal product (IMP), whether or not considered related to the IMP.<br>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<br>• Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected<br>• Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition<br>• Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction<br>• Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent<br><br>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.<br>Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.<br>• Medical or surgical procedures (e.g. endoscopy, appendectomy). The condition that leads to the procedure is the AE.<br>• 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 AEs). |

### 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**<br>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**<br>• 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.<br>• 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.<br>Note:<br>• Hospitalisations for administrative, trial-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs.<br>• 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**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• 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:**<br>• 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.<br>• The following adverse events must always be reported as SAEs using the important medical event criterion if no other seriousness criteria are applicable:<br>• Suspicion of transmission of infectious agents via the IMP<br>• 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)** |
|---|
| **Acute pancreatitis**<br>The diagnosis of acute pancreatitis requires two of the following three features:<br>(1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)<br>(2) serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal<br>(3) characteristic findings of acute pancreatitis on imaging.<br><br>**Medication error**<br>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**

- 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:<br>• **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.<br>• **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.<br>• **Severe**: An event that prevents normal everyday activities.<br>Note: An AE that is assessed as severe should not be confused with an 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.<br>• Relationship between an AE/SAE and the relevant IMP(s) should be assessed as:<br>  • Probable - Good reason and sufficient documentation to assume a causal relationship.<br>  • Possible - A causal relationship is conceivable and cannot be dismissed.<br>  • Unlikely - The event is most likely related to aetiology other than the IMP.<br>• 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.<br>• The investigator should use the investigator's brochure for the 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.<br>• 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 assesses causality for every event before the initial transmission of the SAE data.**<br>• The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.<br>• The causality assessment is one of the criteria used when determining regulatory reporting requirements. |
| **Final outcome** |
| The investigator will select the most appropriate outcome:<br>• **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented<br>• **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).<br>Note: For SAEs, this term is only applicable if the subject has completed the follow-up period and is expected to recover.<br>• **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.<br>• **Not recovered/not resolved:** The condition of the subject has not improved, and the symptoms are unchanged, or the outcome is not known.<br>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 die 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

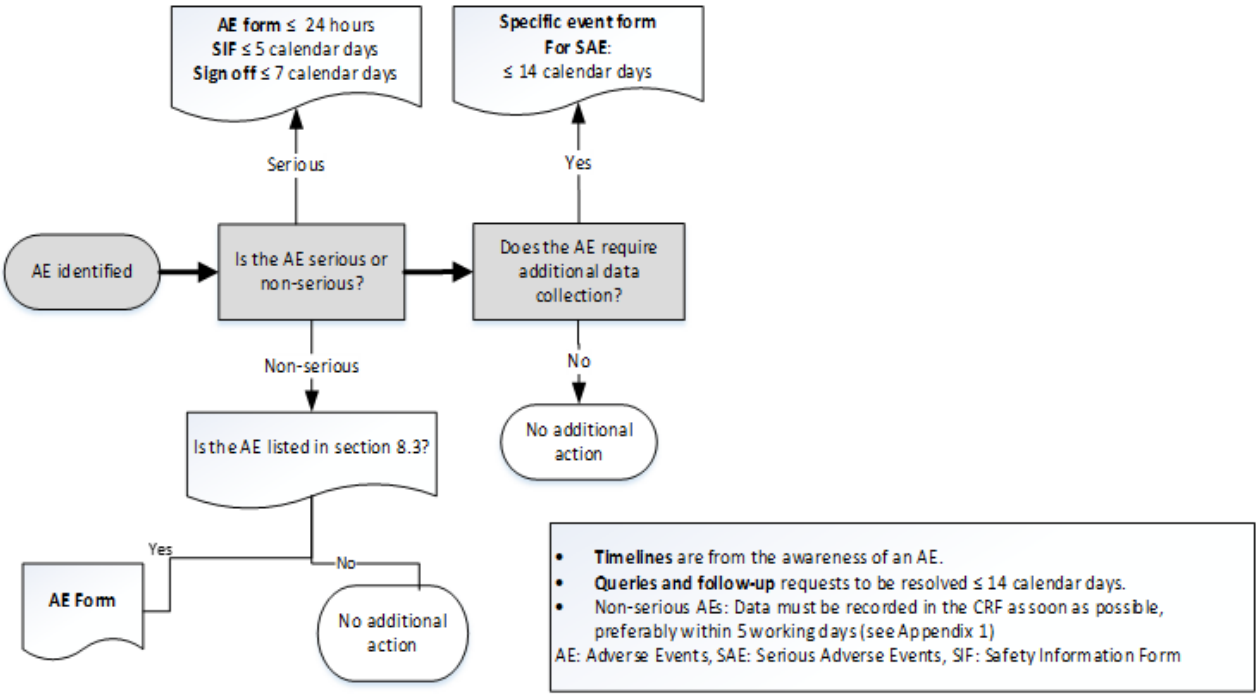
**SAE reporting via electronic CRF**

- Relevant forms (AE form, safety information form and specific event form) must be completed in the eCRF.
- For reporting and sign-off timelines, see Figure 10-1 below.
- If the eCRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the eCRF 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 eCRF as soon as it becomes available.
- After the trial is completed, the trial database will be locked, and the eCRF 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 eCRF 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 10-3 Highly effective contraceptive methods

**CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:**

- **Highly effective methods[b, c] that have low user dependency** (Failure rate of <1% per year when used consistently and correctly):
  - Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)[b]
  - Bilateral tubal occlusion
  - Vasectomized partner
    Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.

- **Highly effective methods[b,c] that are user dependent** (Failure rate of <1% per year when used consistently and correctly):
  - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[d]
    - 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) Contraception should be utilised during the treatment period and for at least 35 days (corresponding to time needed to eliminate trial product) after the last dose of trial product.
d) 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.

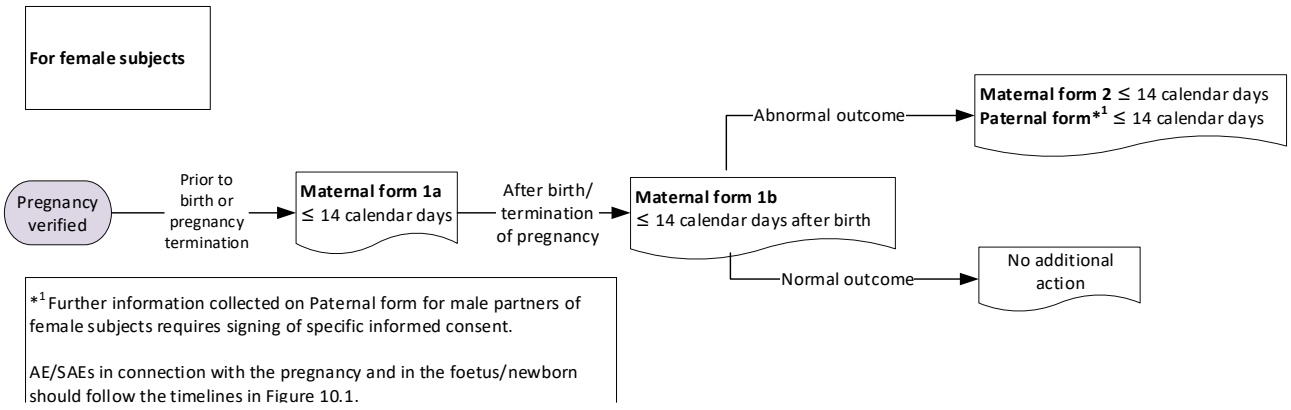
**Pregnancy testing**

- 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.
- Additional pregnancy testing should be performed during the treatment period, if required locally (Appendix 7 [Section 10.7]).

**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.<br><br>Technical complaints must be reported on a separate technical complaint form:<br>1. One technical complaint form must be completed for each affected DUN.<br>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:<br>• 24 hours if related to an SAE<br>• 5 days calendar for all other technical complaints<br><br>If the eCRF 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 eCRF 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.<br>Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product. |

## 10.6 Appendix 6: Retention of human biosamples for future research

In countries where applicable, the study will involve collection of human biosamples for future research to be stored in a central laboratory facility.

Human biosamples (also in some cases known as human biospecimen or human biological materials) are samples that have been taken from the human body during life. It includes:

- Primary cells containing fluids of human origin (whole blood)
- Cell free fluids of primary human origin (serum and plasma)
- Extracts or derivatives of the above, when derived by purification (DNA, RNA, proteins, membranes, microsomes and other cellular substructures).

### Table 10-4 Samples to be collected

| Sample | Visit | Tubes/aliquots per visit |
|---|---|---|
| Whole blood (DNA) | 3 | 1 tube |
| Whole blood (RNA) | 3, 5, 8, 9, 12, 14, 15 | 1 tube |
| Serum | 3, 5, 8, 9, 12, 14, 15 | 5 aliquots |
| Plasma, | 3, 5, 8, 9, 12, 14, 15 | 5 aliquots |
| Plasma | 3, 5, 8, 12, 15 | 1 tube |

The biosamples will be stored at a central laboratory, at a central storage facility or an analysing laboratory contracted by Novo Nordisk for up to 15 years after end of trial. Only relevant Novo Nordisk employees, consultants, auditors, research organisations or laboratories working for or collaborating with Novo Nordisk as well as storage facility employees will be able to access the stored biosamples and associated data. The biosamples may be transferred to other countries for analysis and will be destroyed at the latest 15 years after end of trial.

The analyses of the biosamples for future research are not intended to identify participant-specific findings, but to understand and predict response to semaglutide as well as understanding obesity, prediabetes and related conditions on a population level. Analysis will be done on the biosamples and associated data (data relating to the test results or results from the main study).

Novo Nordisk will ensure that third party collaborators live up the regulations on data protection, see Appendix 1 (Section 10.1).

The participant may request the stored biosamples for future research to be destroyed by withdrawing the designated informed consent at any timepoint during and after the trial. For samples that have already been analysed, the results can still be used for scientific research and will not be removed from the datafile.

## 10.7 Appendix 7: Country-specific requirements

**For Denmark:**

**Section 5.2 Exclusion criterion no. 11**

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) is not considered a 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 Spain:**

**Appendix 1 Section 10.1.10 Retention of clinical trial documentation**

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

**Section 5.2 Exclusion criterion no. 11**

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) is not considered a highly effective birth control.

## For Finland

### Section 5.2 Exclusion criterion no. 11

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) is not considered a highly effective birth control.

Collection of human biosamples for future research (Section 8.10) will not be performed for subjects from Finland.

## For United Kingdom

### Section 5.2 Exclusion criterion no. 11

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) is not considered a highly effective birth control.

### Section 5.2 Exclusion criterion no. 12 and Section 7.1 Discontinuation of trial treatment

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 not allowed.

## Appendix 1 Section 10.1.5 Data protection

Protocol text: “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.” In the UK the IRB/IEC do not have access to the patients’ medical records.

## 10.8 Appendix 8: Abbreviations

| | |
|---|---|
| ADA | American Diabetes Association |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| BMI | body mass index |
| CI | confidence interval |
| CRF | case report form |
| CTFG | Clinical Trial Facilitation Group |
| CTR | clinical trial report |
| DFU | directions for use |
| DUN | dispensing unit number |
| EASD | The European Association for the Study of Diabetes |
| eCRF | electronic case report form |
| EQ-5D-3L | EuroQol five dimensions three level |
| FAS | full analysis set |
| FDA | U.S. Food and Drug Administration |
| FDAAA | U.S. Food and Drug Administration Amendments Act |
| FPG | fasting plasma glucose |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GLP-1 | glucagon-like peptide-1 |
| $HbA_{1c}$ | glycated haemoglobin |
| hCG | human chorionic gonadotropin |
| HDL | high density lipoproteins |
| HRT | hormone replacement therapy |
| IB | investigator's brochure |
| ICH | International Council for Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | independent ethics committee |
| IMP | investigational medicinal product |
| IRB | institutional review board |
| IUD | intrauterine device |
| IUS | intrauterine hormone-releasing system |
| IWRS | interactive web response system |
| LAO-OT | last available observation during the on-treatment period |
| LDL | low density lipoprotein |
| LSFT | last subject first treatment |
| MEN2 | multiple endocrine neoplasia type 2 |
| MMRM | mixed model for repeated measurements |
| MTC | medullary thyroid cancer |
| NYHA | New York Heart Association |
| OR | odds ratio |
| PCD | primary completion date |
| PRO | patient-reported outcome |
| PYE | patient years of exposure |
| PYO | patient years of observation |
| RA | receptor agonist |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | safety analysis set |
| s.c. | subcutaneous |

| | |
|---|---|
| SD | standard deviation |
| SOP | standard operating procedure |
| SUSAR | suspected unexpected serious adverse reaction |
| T2D | type 2 diabetes |
| TMM | trial materials manual |
| UNL | upper normal limit |
| VAS | visual analogue scale |
| VLDL | Very low-density lipoprotein |
| WLQ-25 | Work Limitations Questionnaire 25-item version |
| WOCBP | woman of childbearing potential |

## 10.9 Appendix 9: Protocol amendment history

### Protocol version 2.0 (13 July 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]

### Overall rationale for preparing protocol version 2.0

This version of the protocol was prepared to include a clarification in Section 8.3 of reporting of serious adverse events in the extension phase of the trial. Furthermore, a clarification of the time-period for evaluation of subjects' treatment intensity regarding lipid-lowering and antihypertensive medication has been included (Section 8). A specification of the primary analysis of change in body weight has been included. An overview of all updates is presented in the table below:

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| 1.2 Flowchart<br>Section 8.3 (Adverse events and serious adverse events) | Reporting of SAEs in the extension phase | To comply with EU guideline[2] |
| Section 8 (Trial assessments and procedures) | Update of time frame for evaluation of treatment intensity of antihypertensive and lipid-lowering medication | For clarification. |
| Section 9 (statistical considerations) | Inclusion of assumption on unequal variances in the primary analysis of change in body weight | Based on recommendation from FDA |
| Section 10.7 (Country-specific requirements) | Specification that human biosamples for future research will not be collected from subjects from Finland | Country-specific requirement from Finland |

### Protocol version 3.0 (08 February 2022)

This amendment is considered to be non-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]

### Overall rationale for preparing protocol version 3.0

This version of the protocol was prepared to delete a requirement for recording date of T2D onset in the CRF as presented in the table below:

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 10.2 (Clinical laboratory tests) | Deletion of the requirement to record the date of T2D onset in the CRF | This information is not needed for the purpose of the exploratory endpoints on progression to T2D |

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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.