Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04074161
Sponsor trial ID:	NN9536-4576
Official title of study:	Effect and safety of subcutaneous semaglutide 2.4 mg once weekly compared to liraglutide 3.0 mg once daily on weight management in subjects with overweight or obesity
Document date*:	25 November 2020

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

16.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

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[redacted] [redacted]

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Protocol

Protocol title:

Effect and safety of subcutaneous semaglutide 2.4 mg once weekly compared to liraglutide 3.0 mg once daily on weight management in subjects with overweight or obesity

Substance names: semaglutide and liraglutide

Universal Trial Number: U1111-1233-0977

EUdraCT Number: N/A

Trial phase: 3b

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
Protocol version 4.0	25 November 2020	US
Protocol version 3.0	15 April 2020	US
Protocol version 2.0	17 March 2020	US
Original protocol version 1.0	08 July 2019	US

Protocol version 4.0 (01 December 2020)

This amendment is considered to be substantial.

Overall rationale for preparing protocol, version 4.0:

Co-participation in other clinical trials is generally not allowed while participating in a Novo Nordisk trial. However, given the large societal impact of the COVID-19 pandemic, Novo Nordisk will allow for co-participation in trials with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions. For the current trial it has been evaluated that the safety profiles of liraglutide and semaglutide are well established and based on current knowledge it is expected that co-participation in COVID-19 trials will not lead to unreasonable unforeseen risks for trial subjects. Discontinuation criterion 6 regarding simultaneous participation in other trials has thus been amended.

Section # and name	**Description of change**	**Brief rationale**
Section 8.1	Amending the discontinuation criterion 6, so that subjects are allowed to continue in the trial, while also participating in a COVID-19 trial.	To allow for simultaneous participation in current trial and a COVID-19 trial.

Overall rationale for preparing protocol, version 2.0 and 3.0:

To improve ease of use and convenience for subjects, Novo Nordisk is developing a single dose pen-injector with an integrated prefilled syringe for semaglutide s.c. referred to as DV3396 pen-injector. In order to generate clinical trial data with the DV3396 pen-injector, all

semaglutide/semaglutide placebo subjects will switch device from PDS290 to DV3396 at week 44 (visit 18).

Further, a new questionnaire (Injection Device Experience and Acceptance (IDEA) Questionnaire) will be introduced for subjects switching device. The questionnaire has a total of 21 questions and will be completed one time at the end of treatment visit (week 68).

In Protocol version 2.0 there was a mistake in the summary of changes table, which is updated and therefore version 3.0.

Section # and name	Description of change	Brief rationale
Section 1 Synopsis	Adding information about the different doses provide in DV3396 pen-injector.	Adding new device.
Section 2 Flowchart	Adding information about trial product handling regarding DV3396 pen-injector, IDEA questionnaire and Injection Device Experience and Acceptance Questionnaire.	To ensure correct handling of trial product and correct collection of data.
Section 3 Introduction. Section 3.3.2 Risk and precautions	Adding information about rationale and risk of the DV3396.	To clarify the reason for the new device in this protocol.
Section 7	Adding information about the new device DV3396.	To explain the new device, doses, trial product handling and ensure alignment.
Section 9 Trial assessment and procedures	Adding information about the new device, total drug accountability for the PDS290 pen-injectors and questionnaire to site staff about training of subjects in the DV3396. Adding new section 9.10: Pen-injector use error for DV3396 pen-injector. Adding missing information about how to evaluate subject's glycaemic status and ADA guidance.	To ensure alignment if definitions and provide guidance.
Section 9.3 Treatment of overdose	Adding safety information about liraglutide and hypoglycaemia.	Adding new information on liraglutide.

References added:

- Novo Nordisk A/S. Investigator's Brochure, Semaglutide subcutaneous administration, Project NN9536 and NN9931, (edition 5). 20 Sep 2019.

- Standards of Medical Care in Diabetes-2017: Summary of Revisions. Diabetes Care. 2017;40(Suppl 1):S4-S5

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Attachment I Global list of key staff and relevant departments and suppliers

Attachment II Country list of key staff and relevant departments, if applicable for the individual country

1 Synopsis

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[1-7]. The medical and societal impacts are extensive, and obesity is one of the most significant public health challenges worldwide[1-7].

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

The risk of obesity-related comorbidities increases with increasing body mass index (BMI), and even a body weight loss of 5–10% has been shown to have significant health benefits on many obesity related comorbidities as well as physical symptoms and quality of life[23].

Lifestyle intervention in the form of diet and exercise is first line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss[24-32].

The present trial will compare the effect on body weight and safety of semaglutide s.c. 2.4 mg once weekly versus liraglutide s.c. 3.0 mg once daily as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity. The 68 weeks duration of the trial ensures a treatment period of 52 weeks at the maintenance dose of semaglutide. This will make it possible to compare the effect and safety of once weekly semaglutide for weight management after 52 weeks of maintenance dose with the already marketed anti-obesity medication liraglutide s.c. 3.0 mg once daily.

Objectives and endpoints

Primary objective

To show the superiority of semaglutide s.c. 2.4 mg once weekly versus liraglutide 3.0 mg once daily both as adjuncts to a reduced-calorie diet and increased physical activity in subjects with obesity or with overweight and at least one weight related comorbidity on body weight.

Secondary objectives

To compare the safety and tolerability of semaglutide s.c. 2.4 mg once weekly versus liraglutide 3.0 mg once daily both as adjuncts to reduced-calorie diet and increased physical activity in subjects with obesity or with overweight and at least one weight related comorbidity.

To compare the effect of semaglutide s.c. 2.4 mg once weekly versus liraglutide 3.0 mg once daily both as adjuncts to a reduced-calorie diet and increased physical activity in subjects with obesity or

with overweight and at least one weight related comorbidity on cardiovascular risk factors and glucose metabolism.

To show the superiority of semaglutide s.c. 2.4 mg once weekly versus placebo both as adjuncts to a reduced-calorie diet and increased physical activity in subjects with obesity or with overweight and at least one weight related comorbidity on body weight.

To show the superiority of liraglutide s.c. 3.0 mg once daily versus placebo both as adjuncts to a reduced-calorie diet and increased physical activity in subjects with obesity or with overweight and at least one weight related comorbidity on body weight.

Primary estimand

The estimand will quantify the average treatment effect of semaglutide relative to liraglutide after 68 weeks, as adjuncts to a reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment and regardless of starting rescue interventions (weight management drugs or bariatric surgery) ("treatment policy" estimand). The estimand will cover all effect-related objectives.

The following expansion of the primary estimand will cover objectives related to weight. The estimand will quantify the average treatment effect of semaglutide s.c. 2.4 mg relative to placebo after 68 weeks, as an adjunct to reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment and regardless of starting rescue interventions.

The following expansion of the primary estimand will cover objectives related to weight. The estimand will quantify the average treatment effect of liraglutide s.c. 3.0 mg relative to placebo after 68 weeks, as an adjunct to reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment and regardless of starting rescue interventions.

Secondary estimand

The estimand will quantify the average treatment effect of semaglutide relative to liraglutide after 68 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects had they remained on their randomised treatment for the entire planned duration of the trial and not started any rescue intervention (weight management drugs or bariatric surgery) ("hypothetical" estimand). The estimand will cover the primary objective.

Primary endpoint

- Change from baseline (week 0) to week 68 in body weight (%)

Confirmatory secondary endpoints

- Subject who from baseline (week 0) to week 68 achieve (yes/no):

- Body weight reduction ≥10%
- Body weight reduction ≥15%
- Body weight reduction ≥20%

Overall design:

This is a 68-week, randomised, open label, pairwise placebo-controlled, multi-centre, US only clinical trial comparing semaglutide s.c. 2.4 mg once weekly with liraglutide s.c. 3.0 mg once daily in subjects with overweight or obesity. Semaglutide once weekly vs liraglutide once daily treatment will be open label, but each of the two active treatment arms will be double blinded against placebo administered at the same dosing frequency.

Key Inclusion criteria

1. Male or female, age ≥ 18 years at the time of signing informed consent
2. Body mass index (BMI) ≥ 30.0 kg/m^2 or ≥ 27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease
3. History of at least one self-reported unsuccessful dietary effort to lose body weight

Key exclusion criteria

1. HbA1c ≥ 48 mmol/mol (6.5%) as measured by the central laboratory at screening
2. History of type 1 or type 2 diabetes mellitus
3. A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records

Number of subjects:

Approximately 396 subjects will be screened to achieve 336 subjects randomly assigned to trial product.

Treatment groups and duration:

Eligible subjects will be randomised in a 3:1:3:1 manner to receive either semaglutide s.c. 2.4 mg once weekly, semaglutide placebo, liraglutide s.c. 3.0 mg once daily or liraglutide placebo.

The total trial duration for the individual subject will be approximately 76 weeks, including a one week screening period to assess the subject´s eligibility, a 68 week treatment period, and a follow up period of 7 weeks. The treatment period will include 16 weeks of dose escalation in the semaglutide/semaglutide placebo arms, and 4 weeks of dose escalation in the liraglutide/liraglutide placebo arms. The follow up period of 7 weeks is included to account for the long half-life of semaglutide.

The following trial products will be supplied by Novo Nordisk A/S:

- Semaglutide B 3.0 mg/mL PDS290 and semaglutide placebo, solution for injection, 3 mL PDS290 pre-filled pen-injector.

- Liraglutide 6.0 mg/mL PDS290 and liraglutide placebo, solution for injection, 3 mL PDS290 pre-filled pen-injector.

At week 44 (visit 18) all subjects treated with semaglutide/semaglutide placebo will switch from the PDS290 pen-injector to DV3396 pen-injector.

From week 44:

- Semaglutide D 0.5 mg/mL DV3396 or semaglutide placebo Ia, solution for injection, 0.5 mL DV3396 pen-injector.

- Semaglutide D 1.0 mg/mL DV3396 or semaglutide placebo Ia, solution for injection, 0.5 mL DV3396 pen-injector.

- Semaglutide D 2.0 mg/mL DV3396 or semaglutide placebo Ia, solution for injection, 0.5 mL DV3396 pen-injector.

- Semaglutide D 2.27 mg/mL DV3396 or semaglutide placebo Ia, solution for injection, 0.75 mL DV3396 pen-injector.

- Semaglutide D 3.2 mg/mL DV3396 or semaglutide placebo Ib, solution for injection, 0.75 mL DV3396 pen-injector.

2 Flowchart

	Screening	Randomisation	Treatment period																			End of treatment	End of trial
Visit	V1	V2	V3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	V19	V20	V21	V22	V23
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	50	56	62	68	75
Visit Window (Days)	-7 to 0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Informed consent and Demography[a]	X																						
Inclusion and exclusion criteria (6.1 and 6.2)	X	X																					
C-SSRS and PHQ-9 (9.4.1)	X																					X	
Barriers and motivation interview (9)	X																						
Injection Device Experience and Acceptance Questionnaire [b] (7.9)																						X	
Medical History/Concomitant Illness (9.4)	X																						
Weight history (9)		X																					
Tobacco Use[c]	X																						
Concomitant medication (7.9)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial product compliance (7.1) (7.8)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body measurements (9.1.1)																							
Body Weight	X	X	X	X		X		X		X		X		X		X		X	X	X	X	X	X
Height	X																						
Waist Circumference	X	X		X		X		X		X		X		X		X		X		X		X	
Attend visit fasting (6.3.1)		X										X								X		X	
Laboratory Assessment (Appendix B)	X	X										X								X		X	
Vital Signs (9.4.3)	X	X		X		X		X		X		X		X		X		X		X		X	X
Physical examination (9.4.2)	X																					X	
Pregnancy test (9.4.5) (Appendix E)	X	X		X		X		X		X		X		X		X		X		X		X	X

	Screening	Randomisation	Treatment period																			End of treatment	End of trial
Visit	V1	V2	V3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	V19	V20	V21	V22	V23
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	50	56	62	68	75
Visit Window (Days)	-7 to 0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Pen-injector use error (9.10)																		X	X	X	X	X	
ECG (9.4.4)		X										X								X		X	
Adverse event (9.2) (Appendix D)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation of lipid-lowering treatment (9)													X									X	
Evaluation of antihypertensive treatment (9)													X									X	
Evaluation of glycaemic status (9)		X											X									X	
Breast Neoplasms Follow-up 9.4)																						X	X
Colon Neoplasms Follow-up (9.4)																						X	X
Drug dispensing (7)		X				X				X		X		X		X		X	X	X	X	X	
Diet and physical activity counselling (7.2.1)		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	
Training in devices (7.1)		X		X		X		X		X		X		X		X		X	X	X	X		

[a] Demography consists of date of birth, sex, ethnicity and race.

[b] Applies only for subjects receiving semaglutide/semaglutide placebo.

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

3 Introduction

3.1 Background

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

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

The risk of obesity-related comorbidities increases with increasing body mass index (BMI), and even a body weight loss of 5–10% has been shown to have significant health benefits on many obesity related comorbidities as well as physical symptoms and quality of life[23].

Lifestyle intervention in the form of diet and exercise is first line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss[24-32].

Glucagon-like-peptide (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[33].

Semaglutide is the next generation GLP-1 receptor agonist (RA) currently under development by Novo Nordisk for the treatment of weight management. Semaglutide has a half-life of approximately 160 hours, making it suitable for once-weekly dosing[34].

Clinical[35] and non-clinical[36] data indicate that the body weight reducing effect of semaglutide is mainly mediated by a reduced energy intake.

The GLP-1 receptor agonist liraglutide 3.0 mg is approved for weight management with once daily dosing and is launched under the brand name Saxenda®. In the development programme, treatment with liraglutide 3.0 mg as adjunct to diet and exercise resulted in significantly greater weight loss than diet and exercise alone in subjects with obesity or overweight with at least one weight-related comorbidity[37].

A 52-week phase 2 dose-finding trial in weight management with semaglutide (NN9536-4153) has been completed. A total of 957 randomised subjects with obesity (without diabetes) were exposed to semaglutide (n=718), liraglutide 3.0 mg (n=103) or placebo (n=136). An overall dose-dependent weight loss was observed across the 5 semaglutide doses tested (0.05 to 0.4 mg once-daily). The estimated weight loss at week 52 was 13.8 % at the highest dose tested (0.4 mg once-daily)

compared to the weight loss of 7.8% with liraglutide and of 2.3% achieved by diet, exercise and placebo alone[38].

No unexpected safety findings were identified, and the tolerability and the safety profile were overall consistent with previous findings in the T2D development programme for semaglutide and with the GLP-1 RA class in general[38].

The phase 3a programme for semaglutide for weight management is currently ongoing.

A comprehensive review of results from the non-clinical and clinical studies of semaglutide and liraglutide can be found in the current edition of the investigator's brochures (IB)[39, 40] and any updates hereof.

3.2 Trial rationale

In the phase 2 trial with semaglutide for weight management, semaglutide was administered once daily, while the dose for semaglutide in the phase 3 programme is 2.4 mg once weekly. The decision to dose once weekly in phase 3a and in this trial is that the pharmacokinetic properties and the efficacy and tolerability data obtained with semaglutide allow patients to get the benefit of more convenient once weekly injections.

The phase 2 trial had a total duration of 52 weeks, and the mean weight loss with the highest dose of semaglutide appeared to continue at week 52[41].

The present trial will compare the effect on body weight and safety of semaglutide s.c. 2.4 mg once weekly versus liraglutide s.c. 3.0 mg once daily as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity. The duration of the trial is 68 weeks which ensures a treatment period of 52 weeks at the maintenance dose of semaglutide s.c. of 2.4 mg.

To further improve ease of use and convenience for subjects, Novo Nordisk is developing a single dose pen-injector with an integrated prefilled syringe for semaglutide s.c. referred to as DV3396 pen-injector. In order to generate clinical trial data with the DV3396 pen-injector, this pen-injector will be included in the trial from week 44 (visit 18). The DV3396 pen-injector will be similar for all doses, however, with a dose volume of 0.5 mL for the three lower doses (0.25 mg, 0.5 mg and 1 mg) and 0.75 mL for the two higher doses (1.7 mg and 2.4 mg). In order to administer the five doses with the DV3396 pen-injector, the semaglutide drug product (semaglutide D) will be available in five concentrations: 0.5 mg/mL, 1.0 mg/mL, 2.0 mg/mL, 2.27 mg/mL and 3.2 mg/mL. The drug product formulation (semaglutide D) is similar to the current phase 3a drug product formulation for semaglutide 1.0 mg/mL and 3.0 mg/mL solution for injection (semaglutide B); except that the solutions do not contain phenol (preservative), as the DV3396 pen-injector is intended for single use.

Data obtained in this study will allow direct comparison of the effect and safety of once weekly semaglutide for weight management after 52 weeks of maintenance dose with the already marketed anti-obesity medication liraglutide s.c. 3.0 mg once daily.

The trial population will consist of subjects with obesity (BMI ≥ 30.0 kg/m^2) or overweight (BMI ≥ 27.0 kg/m^2) and at least one weight-related comorbidity. These subjects represent a clinically relevant population for pharmacotherapeutic weight management as they are at significant risk for weight related morbidities and mortality and are likely to benefit from weight reduction. Information about weight-related comorbidities, including hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease, will be collected systematically at screening by the investigators as part of the medical history.

Subjects with T2D are excluded from the trial. Treatment with semaglutide for weight management in subjects with overweight or obesity and T2D is being addressed in a dedicated phase 3a trial (NN9536-4374).

First line treatment in weight management should always be lifestyle modification through a reduced-calorie diet and increased physical activity. Only subjects who have tried but failed a dietary weight loss intervention will be included in this trial in accordance with regulatory guidelines[42, 43].

3.3 Benefit-risk assessment

3.3.1 Benefits

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

Results from the phase 2 trial (NN9536-4153) demonstrated that semaglutide once-daily as an adjunct to a reduced calorie diet and increased physical activity was effective for weight loss in subjects with obesity, while displaying a satisfactory tolerability profile[41].

Results from the clinical development programme for liraglutide for weight loss demonstrated that liraglutide 3.0 mg, as an adjunct to a reduced calorie diet and increased physical activity, was effective for weight loss in subjects with overweight or obesity while displaying a satisfactory tolerability profile[44].

Weight loss with either semaglutide or liraglutide in clinical trials was accompanied by a consistent improvement in the weight-related comorbidities, indicated by cardiovascular risk factors, lipid profile and glycaemic factors, as well as improvements in clinical outcome assessments[41, 44].

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.

3.3.2 Risks and precautions

The sections below describe identified and potential risks and precautions associated with semaglutide and liraglutide treatment. For classification and further details, please refer to the current version of the IBs or any updates hereof[39, 40]. The identified/potential risks are based on findings in non-clinical studies and clinical trials with semaglutide, liraglutide as well as other GLP-1 RAs. For each of these risks and precautions, mitigating actions have been implemented to minimise the risks for subjects enrolled in this trial.

Semaglutide

When used in accordance with the directions for use, the risk associated with the semaglutide formulations to be used in the DV3396 pen-injector are considered to be similar to the risk associated with the semaglutide formulation used in the PDS290 pen-injector. Local reactions at the injection site may be seen; these include pain, redness, warmth, hives, swelling, itching and bruising and are usually of short duration.

Gastrointestinal adverse events

- Consistent with findings with other GLP-1 RAs, the most frequently reported adverse events (AE) in clinical trials with semaglutide were gastrointestinal AEs. A low starting dose and dose escalation steps will be implemented in the trial to mitigate the risk of gastrointestinal AEs.

Cholelithiasis

- Events of cholelithiasis were the most frequently reported gallbladder events in the phase 2 weight management trial (NN9536-4153) and were in a few instances co-reported with the event adjudication committee (EAC) confirmed acute pancreatitis. As a precaution, 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. As a precaution, subjects with a history of chronic pancreatitis or recent acute pancreatitis will not be enrolled in the trial. In addition, trial product should be discontinued in case of suspicion of acute pancreatitis in accordance to section 8.1.

Medullary thyroid cancer (MTC) (based on non-clinical data)

- Expected proliferative thyroid C-cell changes were seen in the mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. No hyperplasia was observed in monkeys after 52 weeks exposure up to 13-fold above the clinical plasma exposure at 2.4 mg/week. In clinical trials with semaglutide, there have been no clinically relevant changes in calcitonin levels. The C-cell changes in rodents are mediated by the GLP-1 receptor, which is not expressed in the normal human thyroid. Accordingly, the risk of GLP-1 receptor-mediated C-cell changes in humans is considered to be low. However, as a precaution, exclusion and discontinuation criteria related to medical history of multiple endocrine neoplasia type 2 (MEN2) or MTC and elevated plasma levels of calcitonin (biomarker for MTC) have been implemented in the trial.

Pancreatic cancer

- There is currently no support from non-clinical studies, clinical trials or post-marketing data that GLP-1 RA based therapies increase the risk of pancreatic cancer, but pancreatic cancer has been classified as a potential class risk of GLP-1 RAs by European Medicines Agency. As a precaution, subjects with a history of malignant neoplasms within the past 5 years prior to screening will be excluded from the trial.

Allergic reactions

- As is the case with all protein-based pharmaceuticals, subjects treated with semaglutide are at risk of developing immunogenic and allergic reactions. As a precaution, subjects with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this trial.

Pregnancy and fertility (based on non-clinical data)

- Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. Exclusion and discontinuation criteria related to pregnancy have been implemented in the trial.

Liraglutide

Liraglutide shares the same risks as presented for semaglutide. In addition to the above, the following risks have also been associated with liraglutide treatment.

Altered renal function

- During post-marketing surveillance of spontaneous reports from marketed use of liraglutide for T2D (Victoza®), Novo Nordisk A/S identified reports of acute renal failure. These events mainly occurred in relation to dehydration as the result of gastrointestinal adverse events, and the majority were reported in patients with pre-existing renal impairment. Patients should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Acute gallstone disease

- Events of acute gallstone disease including cholelithiasis and cholecystitis were reported more commonly in subjects treated with liraglutide 3.0 mg compared to placebo during the development programme for liraglutide for weight management. From literature it is well known that obesity carries an increased risk of cholelithiasis and that an association between rapid and marked weight loss and the development of cholelithiasis is present. Both cholelithiasis and cholecystitis have possible clinical implications for the patients as the events might lead to hospitalization and cholecystectomy.

Neoplasms (including melanoma)

- Patients with overweight or obesity have an increased risk of certain types of cancer. In the liraglutide weight management programme, the reporting rate of neoplasm events confirmed by event adjudication was similar with liraglutide and placebo. A limited number of reports in the weight management programme identified a numerical imbalance in events of malignant melanoma, breast neoplasms in females and colorectal adenomas in males.

3.3.3 Conclusion on benefit-risk profile

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 profiles for semaglutide and liraglutide generated from the clinical and non-clinical development programmes have not revealed any safety issues that would prohibit administration of semaglutide s.c. 2.4 mg once-weekly or liraglutide 3.0 mg once-daily, and both products can provide a clinically meaningful weight loss.

In conclusion, the potential risk to the subjects in this trial is considered low and outweighed by the anticipated benefits that would be provided to subjects included in the trial.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of semaglutide and liraglutide may be found in the investigator´s brochures[39, 40].

4 Objectives and endpoints

4.1 Primary and secondary objectives

Primary objective

To show the superiority of semaglutide s.c. 2.4 mg once weekly versus liraglutide 3.0 mg once daily both as adjuncts to a reduced-calorie diet and increased physical activity in subjects with obesity or with overweight and at least one weight related comorbidity on body weight.

Secondary objectives

To compare the safety and tolerability of semaglutide s.c. 2.4 mg once weekly versus liraglutide 3.0 mg once daily both as adjuncts to reduced-calorie diet and increased physical activity in subjects with obesity or with overweight and at least one weight related comorbidity.

To compare the effect of semaglutide s.c. 2.4 mg once weekly versus liraglutide 3.0 mg once daily both as adjuncts to a reduced-calorie diet and increased physical activity in subjects with obesity or with overweight and at least one weight related comorbidity on cardiovascular risk factors and glucose metabolism

To show the superiority of semaglutide s.c. 2.4 mg once weekly versus placebo both as adjuncts to a reduced-calorie diet and increased physical activity in subjects with obesity or with overweight and at least one weight related comorbidity on body weight.

To show the superiority of liraglutide s.c. 3.0 mg once daily versus placebo both as adjuncts to a reduced-calorie diet and increased physical activity in subjects with obesity or with overweight and at least one weight related comorbidity on body weight.

Primary estimand

The estimand will quantify the average treatment effect of semaglutide relative to liraglutide after 68 weeks, as adjuncts to a reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment and regardless of starting rescue interventions (weight management drugs or bariatric surgery) ("treatment policy" estimand). The estimand will cover all effect-related objectives.

The following expansion of the primary estimand will cover objectives related to weight. The estimand will quantify the average treatment effect of semaglutide s.c. 2.4 mg relative to placebo after 68 weeks, as an adjunct to reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment and regardless of starting rescue interventions.

The following expansion of the primary estimand will cover objectives related to weight. The estimand will quantify the average treatment effect of liraglutide s.c. 3.0 mg relative to placebo after 68 weeks, as an adjunct to reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment and regardless of starting rescue interventions.

Secondary estimand

The estimand will quantify the average treatment effect of semaglutide relative to liraglutide after 68 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects had they remained on their randomised treatment for the entire planned duration of the trial and not started any rescue intervention (weight management drugs or bariatric surgery) ("hypothetical" estimand). The estimand will cover the primary objective.

The handling of intercurrent events with respect to data collection and analysis is specified in Table 4-1 for the primary endpoint. Apart from the listed intercurrent events, missing data will occur due to death, or if subjects withdraw consent, become lost to follow-up, or continue to be followed without being ascertained for the endpoint.

Table 4-1 Handling of intercurrent events for the primary endpoint

Intercurrent event	Data collection	Data analysis
Premature treatment discontinuation	Subjects will be followed and data collected after intercurrent events	**Primary estimand:** data collected after intercurrent events used in analysis in line with a treatment-policy strategy **Secondary estimand:** data collected after intercurrent events treated as missing in line with a hypothetical strategy
Initiation of other weight management drugs or bariatric surgery		

4.2 Primary and secondary endpoints

4.2.1 Primary endpoint

- Change from baseline (week 0) to week 68 in body weight (%)

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

- Subject who from baseline (week 0) to week 68 achieve (yes/no):
  - Body weight reduction ≥10%
  - Body weight reduction ≥15%
  - Body weight reduction ≥20%

4.2.2.2 Supportive secondary endpoints

The supportive secondary endpoints are used to compare the effect of semaglutide s.c. 2.4 mg once-weekly versus liraglutide 3.0 mg once-daily unless otherwise stated:

- Change from baseline (week 0) to week 68 in waist circumference (cm)
- Change from baseline (week 0) to week 68 in body weight (%) (semaglutide s.c. 2.4 mg once-weekly versus placebo and liraglutide s.c. 3.0 mg once-daily versus placebo)
- Change from baseline (week 0) to week 68 in:
  - systolic blood pressure (mmHg)
  - lipids (mg/dL)
    - Total cholesterol
    - High density lipoprotein (HDL) cholesterol
    - Low density lipoprotein (LDL) cholesterol

- Very low density lipoprotein (VLDL) cholesterol
- Free fatty acids (FFA)
- Triglycerides

- hsCRP (mg/L)
- HbA1c (%)
- fasting plasma glucose (mg/dL)
- glycaemic category (normo-glycaemia, pre-diabetes, T2D)

- Subjects who from baseline (week 0) to week 68 have permanently discontinued randomised trial product (yes/no)
- Number of treatment emergent adverse events (TEAEs) from baseline (week 0) to week 75
- Number of serious adverse events (SAEs) from baseline (week 0) to week 75

5 Trial design

5.1 Overall design

This is a 68-week, randomised, open label, pairwise placebo-controlled, multi-centre, US only clinical trial comparing semaglutide s.c. 2.4 mg once weekly with liraglutide s.c. 3.0 mg once daily in subjects with overweight or obesity. Semaglutide once weekly vs liraglutide once daily treatment will be open label, but each of the two active treatment arms will be double blinded against placebo administered at the same dosing frequency.

The trial includes a screening visit to assess the subject's eligibility followed by visits/phone contacts every 2nd week until week 20. From week 20, visits/phone contacts will take place every 4th week until week 44 and then every 6 weeks until end of treatment (week 68). A follow-up visit ('End of trial') for safety assessments is scheduled 7 weeks after end of treatment to account for the long half-life of semaglutide.

Eligible subjects will be randomised in a 3:1:3:1 manner to receive either semaglutide s.c. 2.4 mg once weekly or semaglutide placebo once weekly or liraglutide s.c. 3.0 mg once daily or liraglutide placebo once daily as an adjunct to a reduced-calorie diet and increased physical activity.

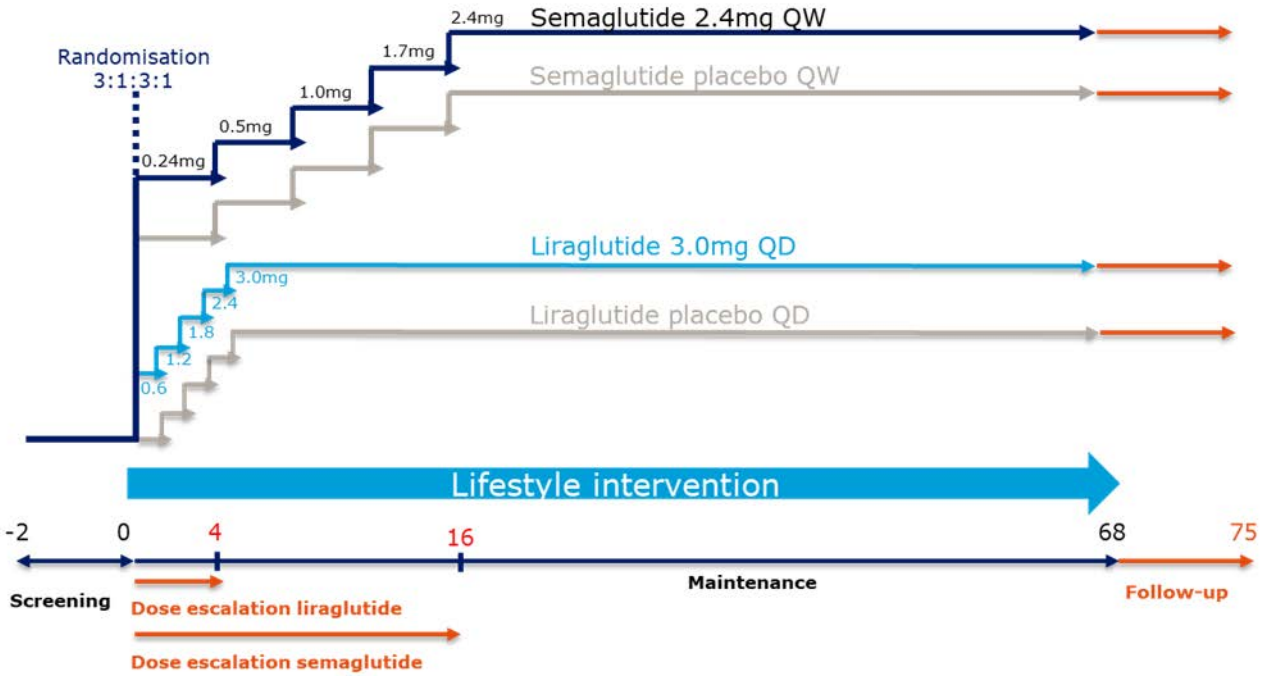


Figure 5-1 A schematic diagram of the trial design

5.2 Subject and trial completion

Approximately 396 subjects will be screened to achieve 336 subjects randomly assigned to trial product.

Trial period completion for a subject:
Trial period completion is defined as when the randomised subject has completed the final scheduled visit ('end of trial' according to the flowchart).
'Date of trial completion' is the date the subject completed the final scheduled visit.

Treatment period completion for a subject:
Treatment period completion is defined as when the randomised subject attended the 'end of treatment' visit according to the flowchart.

5.3 End of trial definition

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

5.4 Scientific rationale for trial design

The trial population will consist of subjects with obesity (BMI ≥ 30.0 kg/m^2) or with overweight (BMI ≥ 27.0 kg/m^2) and at least one weight-related comorbidity. These subjects represent a clinically relevant population for pharmacotherapeutic weight management as they are at significant risk for weight related comorbidities and mortality and are likely to benefit from weight reduction.

The treatment length will be 68 weeks to allow for 52 weeks at maintenance dose of semaglutide after 16 weeks of dose escalation.

The follow up period of 7 weeks is included to account for the long half-life of semaglutide.

To mitigate potential bias, the trial is randomised and both active treatment arms are controlled against placebo in a double blinded design.

We know that some patients treated with placebo and lifestyle intervention have a considerate weight loss. We include a double blinded placebo arm matching each of the active treatment arms so that both the investigator and the subjects will be unaware if they are on active treatment or not.

The comparison between semaglutide s.c. once weekly vs liraglutide s.c. once daily is open label due to the differences in the length of the titration periods and differences in the treatment policies.

The treatment of subjects who do not tolerate the maximum dose of trial product is different in the two arms, as it for semaglutide is aligned with the method used in the 3a programme for semaglutide for the treatment of obesity, while it is aligned with the approved label for Saxenda in the liraglutide arm.

5.5 Justification for dose

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

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

It is well known that to mitigate gastrointestinal side effects with GLP-1 RA treatment, dose escalation to the target dose is required.

For semaglutide, based on experience from the semaglutide T2D development programme, a fixed-dose escalation regimen was selected, with dose escalation every 4 weeks until the target dose is reached.

For liraglutide, clinical trials in adults with or without obesity and with or without T2D have demonstrated that liraglutide should be initiated at a daily dose of 0.6 mg, with subsequent dose

escalation in 0.6 mg weekly increments until reaching the maintenance dose. The dose of liraglutide s.c. 3.0 mg once daily has been tested in the clinical development programme for liraglutide for weight management.

Please refer to section 7 for more details on treatment doses.

6 Trial population

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

6.1 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male or female, age ≥ 18 years at the time of signing informed consent
3. Body mass index (BMI) ≥ 30.0 kg/m^2 or ≥ 27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnea or cardiovascular disease
4. History of at least one self-reported unsuccessful dietary effort to lose body weight

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

6.2 Exclusion criteria

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

Glyceamia related:
1. HbA1c ≥ 48 mmol/mol (6.5%) as measured by the central laboratory at screening
2. History of type 1 or type 2 diabetes mellitus
3. Treatment with glucose-lowering agent(s) within 90 days before screening

Obesity related:
4. A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records
5. Treatment with any medication for the indication of obesity within the past 90 days before screening
6. 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

7. Uncontrolled thyroid disease, defined as thyroid stimulating hormone (TSH) > 6.0 mIU/L or < 0.35 mIU/L as measured by the central laboratory at screening

Mental health:

8. History of major depressive disorder within 2 years before screening
9. Diagnosis of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder)
10. A Patient Health Questionnaire-9 (PHQ-9) score ≥ 15 at screening
11. A lifetime history of suicidal attempt
12. Suicidal behaviour within 30 days before screening
13. Suicidal ideation corresponding to type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the past 30 days before screening

General Safety:

14. Presence of acute pancreatitis within the past 180 days prior to the day of screening
15. History or presence of chronic pancreatitis
16. Calcitonin ≥ 100 ng/L as measured by the central laboratory at screening
17. Personal or first-degree relative history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
18. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR <15 ml/min/1.73 m^2 as defined by KDIGO 2012[45] by the central laboratory at screening
19. History of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed
20. Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina or transient ischaemic attack within the past 60 days prior to screening.
21. Subject presently classified as being in New York Heart Association (NYHA) Class IV
22. Surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator
23. Known or suspected abuse of alcohol or recreational drugs
24. Known or suspected hypersensitivity to trial product(s) or related products.
25. Previous participation in this trial. Participation is defined as signed informed consent.
26. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.
27. Other subject(s) from the same household participating in any semaglutide or liraglutide trial
28. 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

29. Any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the subject's safety or compliance with the protocol

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

6.3 Lifestyle restrictions

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

6.3.1 Meals and dietary restrictions

- Subjects must attend 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 the subject to fast include blood sampling of FPG, fasting serum insulin and free fatty acids.

6.3.2 Caffeine and tobacco

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

6.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to in/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 date of informed consent, date of visit, 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. Re-sampling is not allowed if the subject has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

7 Treatments

7.1 Treatments administered

- All trial products listed in Table 7-1 and Table 7-2 are considered investigational medicinal products (IMP).
- Total drug accountability for the PDS290 pen-injectors for semaglutide/semaglutide placebo must be performed at visit 18.
- The investigator must document that directions for use are given to the subject orally and in writing at the first dispensing visit as specified in the flowchart.
- 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. This is to remind the subjects of the dose to be taken until next site visit and provide a conversion of the dose to value shown in the dose counter. Once the target dose has been reached, the dose reminder card is only handed out as needed.

Table 7-1 Trial products provided by Novo Nordisk A/S

Trial product name:	Liraglutide 6.0 mg/mL or Liraglutide placebo	Semaglutide B 3.0 mg/mL or Semaglutide placebo
Dosage form:	Solution for injection	Solution for injection
Route of administration:	Subcutaneous	Subcutaneous
Dosing instructions:	Once-daily	Once-weekly
Delivery device	3 mL PDS290 pre-filled pen-injector	3 mL PDS290 pre-filled pen-injector

At visit 18 (week 44) all semaglutide/semaglutide placebo subjects will switch from the PDS290 pen-injector to the DV3396 pen-injector.

Table 7-2 Semaglitide/semaglutide placebo trial products from visit 18/week 44

Trial product name	**Dose**	**Dosage form**	**Route**	**Dosage instructions**	**Delivery device**
Semaglutide D 0.5 mg/mL DV3396	0.25 mg	Solution for injection	s.c.	Once-weekly	0.5 mL DV3396 pen-injector
Semaglutide D 1.0 mg/mL DV3396	0.5 mg	Solution for injection	s.c.	Once-weekly	0.5 mL DV3396 pen-injector
Semaglutide D 2.0 mg/mL DV3396	1.0 mg	Solution for injection	s.c.	Once-weekly	0.5 mL DV3396 pen-injector

Semaglutide placebo Ia	NA	Solution for injection	s.c	Once-weekly	0.5 mL DV3396 pen-injector
Semaglutide D 2.27 mg/mL DV3396	1.7 mg	Solution for injection	s.c.	Once-weekly	0.75 mL DV3396 pen-injector
Semaglutide D 3.2 mg/mL DV3396	2.4 mg	Solution for injection	s.c.	Once-weekly	0.75 mL DV3396 pen-injector
Semaglutide placebo Ib	NA	Solution for injection	s.c.	Once-weekly	0.75 mL DV3396 pen-injector

7.1.1 Semaglutide

- Dose escalation of semaglutide/semaglutide placebo should take place during the first 16 weeks after randomisation as described in Table 7-3. All subjects should aim at reaching the recommended target dose of semaglutide 2.4 mg once-weekly or the corresponding volume of semaglutide placebo.

Table 7-3 Dose escalation and maintenance of semaglutide 2.4 mg once-weekly/semaglutide placebo

Trial product name	Dose	Value shown in dose counter	Duration
Dose escalation period			
Semaglutide B 3.0 mg/mL PDS290/ semaglutide placebo	0.24 mg	8	4 weeks
Semaglutide B 3.0 mg/mL PDS290/ semaglutide placebo	0.5 mg	17	4 weeks
Semaglutide B 3.0 mg/mL PDS290/ semaglutide placebo	1.0 mg	34	4 weeks
Semaglutide B 3.0 mg/mL PDS290/ semaglutide placebo	1.7 mg	57	4 weeks
Maintenance period			
Semaglutide B 3.0 mg/mL PDS290/ semaglutide placebo	2.4 mg	80	28 weeks

Table 7-4 Maintenance of semaglutide /semaglutide placebo Ib from V18 to V22 (DV3396)

Trial product name	Dose	Volume	Duration
Maintenance period			
Semaglutide D 3.2 mg/mL DV3396 or semaglutide placebo Ib	2.4 mg*	0.75 mL	24 weeks

*applicable for subjects who are on the maintenance dose of 2.4 mg once-weekly at V18. For subjects on a different dose level, please contact Novo Nordisk for further guidance.

- 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 8).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.
- If a subject does not tolerate the recommended target dose of 2.4 mg once-weekly, the subject may stay at the 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 on 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.

7.1.2 Liraglutide

- Dose escalation of liraglutide/liraglutide placebo should take place during the first 4 weeks after randomisation as described in Table 7-5. If the subject does not tolerate an increased dose during the dose escalation window, the investigator can delay the dose escalation by maintaining the subject at the current dosage step for approximately one additional week. After reaching the maintenance dose (3.0 mg), the dose and dosing frequency should not be changed.

Table 7-5 Dose escalation and maintenance of liraglutide 3.0 once-daily/liraglutide placebo

Trial product name	Dose	Duration
Dose escalation period		
Liraglutide 6.0 mg/mL PDS290/ liraglutide placebo	0.6 mg	1 week
liraglutide 6.0 mg/mL PDS290/ Liraglutide placebo	1.2 mg	1 week
Liraglutide 6.0 mg/mL PDS290/ liraglutide placebo	1.8 mg	1 week
Liraglutide 6.0 mg/mL PDS290/ liraglutide placebo	2.4 mg	1 week
Maintenance period		
Liraglutide 6.0 mg/mL PDS290/ liraglutide placebo	3.0 mg	64 weeks

- Injections may be administrated in the abdomen, thigh, or upper arm, at any time of day, irrespective of timing of meals.
- The injection site and timing can be changed without dose adjustment.
- If a single dose is missed, the once-daily regimen should be resumed as prescribed at the next scheduled dose.
- If more than 3 consecutive days have elapsed since the last dose, subject should reinitiate dose escalation, (e.g. restart the dosing at 0.6 mg and follow the dose escalation schedule again) if considered safe as per the investigator's discretion and if the subject does not meet any of the discontinuation criteria. In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk medical experts.
- If a subject cannot tolerate the 3.0 mg dose, or if any of the other treatment discontinuation criteria are met, then treatment with trial product must be discontinued. In case this happens, it is acceptable to restart trial product (at the discretion of investigator); the dose must be escalated according to the algorithm above.

7.1.3 Auxiliary supplies

Auxiliary supplies will be provided in accordance with the trial materials manual (TMM) and Table 7-6.

Table 7-6 Auxiliary supplies provided by Novo Nordisk A/S

Auxiliary supply	Details
Needles	Needles for pre-filled pen system. Details provided in the TMM.

Auxiliary supply	Details
	Only needles provided and approved by Novo Nordisk must be used for administration of trial product. The DV3396 pen-injector comes with an integrated and hidden needle of 6 mm in length (29G), therefore no needles are required to be used with this pen-injector
Direction for use (DFU)	DFUs for 3 mL PDS290 pre-filled pen-injectors Not included in the dispensing unit and to be handed out separately. DFU for DV3396 pen-injector Not included in the dispensing unit and is to be handed out separately

7.2 Medical devices

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

Information about the DV3396 pen-injector can be found in the investigator's brochure (IB) edition 5[46] and any updates hereof. Information about the use of the DV3396 pen-injector can be found in the DFU.

Information about the use of the pre-filled PDS290 pen-injector for liraglutide 6.0 mg/mL liraglutide placebo can be found in the DFU.

7.2.1 Diet and physical activity counselling

All subjects will receive counselling with regards to diet (500 kcal deficit per day relative to the estimated total daily energy expenditure (TEE) calculated once at randomisation) and physical activity (minimum 150 min of physical activity per week is encouraged, e.g. walking or use the stairs). Counselling should be done by a dietician or a similar qualified healthcare professional every 4th to 6th week via visits/phone contacts.

Calculation of estimated TEE

The TEE is calculated by multiplying the estimated Basal Metabolic Rate (BMR) (Table 7-7 with a Physical Activity Level value of 1.3[47].

$$TEE = BMR \times 1.3$$

Table 7-7 Equation for estimated BMR

Sex	Age	BMR (kcal/day)
Men	18-30 years 31-60 years > 60 years	15.057 × weight at randomisation in kg + 692.2 11.472 × weight at randomisation in kg + 873.1 11.711 × weight at randomisation in kg + 587.7
Women	18-30 years 31-60 years > 60 years	14.818 × weight at randomisation in kg + 486.6 8.126 × weight at randomisation in kg + 845.6 9.082 × weight at randomisation in kg + 658.5

If a BMI ≤ 22.5 kg/m^2 is reached, the recommended energy intake should be recalculated with no kcal deficit (maintenance diet) for the remainder of the trial. If deemed necessary, the investigator could consult Novo Nordisk to discuss when maintenance diet can be initiated.

7.3 Dose modification

Not applicable for this trial. Please refer to 7.1.1 and 7.1.2 for description of missed dose(s).

7.4 Method of treatment assignment

All subjects will be centrally randomised using 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.

7.5 Shipment of trial product to subject's home

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 subject's 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.

7.6 Blinding

Semaglutide once weekly vs liraglutide once daily treatment will be open label, but each of the two active treatment arms will be double blinded against placebo.

The active drugs and placebo are shown in Table 7-1 For the semaglutide/semaglutide placebo trial products from week 44/visit 18, please refer to Table 7-2.

- The active drug and matching placebo are visually identical.
- 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 instructions. The blind may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Novo Nordisk will be notified immediately after breaking the blind. The date when and reason why the blind was broken must be recorded in the subject's medical record.

Whenever the blind is broken, the person breaking the blind must print the "code break confirmation" notification generated by the IWRS, and sign and date the document.

When the blind is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IWRS is not accessible at the time of blind break, the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

7.7 Preparation/Handling/Storage/Accountability

Only subjects enrolled in the trial may receive trial product and only authorised site staff may supply or administer trial product.

Storage- and in-use conditions will be available on the trial product label and in the TMM.

- Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to screening and randomisation.
- The investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and 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 authorised site staff.

- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the TMM.
- Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk.
- Subjects must return all used, partly used and unused trial products as instructed by the investigator.
- The investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- Drug accountability must be performed in the IWRS by registering pen-injectors as used/partly used, unused or lost.
- 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, expired or damaged trial products (for technical complaint samples see Appendix F) 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 trial site.

7.8 Treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant the investigator will remind the subject of the importance of following the instructions given, including taking the trial products as prescribed.

Treatment compliance of trial product will be assessed by asking the subject about missed doses and current treatment dose at every visit. Information on treatment dose and periods >14 days without treatment will be recorded in the CRF.

7.9 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
- Dose (only to be recorded for anti-hypertensive and lipid-lowering medication)

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.

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE, then this must be reported according to section 9.2.

7.10 Treatment after the end of the trial

After the end of the trial, the subject should be treated at the discretion of the investigator.

8 Discontinuation/Withdrawal criteria

The 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 the 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.

8.1 Discontinuation of trial treatment

- Discontinuation of trial product can be decided by either the investigator or 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 efforts should be made to have the subject attend at least the ‘end of treatment’ clinic visit containing the final data collection of primary and confirmatory secondary efficacy endpoints, and the ‘end of trial’ visit.
- The ‘end of trial’ visit is scheduled approximately 7 weeks after the final data collection, to ensure the safety of the subject. If the subject has discontinued trial product >7 weeks prior to the ‘end of treatment’ visit, and the requirements for the follow-up period prior to the ‘end of trial’ visit is fulfilled, then the ‘end of trial’ visit can be performed in combination with ‘end of treatment’ visit.
    - If the subject refuses to attend the ‘end of treatment’ and/or ‘end of trial’ visit, information about the attempts to follow up with the subject must be documented in the subject’s medical record.

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

1. Safety concern as judged by the investigator
2. Calcitonin ≥ 100 ng/L (Appendix G)
3. Suspicion of pancreatitis
4. Pregnancy
5. Intention of becoming pregnant
6. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product[a].

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

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

Subjects meeting discontinuation of trial product criterion no. 3 can resume trial product if the Atlanta criteria[48] are not fulfilled 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, 4 and 5 are allowed to resume trial product, if the criteria are no longer met (8.1.1).

The primary reason for discontinuation of trial product must be specified in the source data at the time of discontinuation, and the subject should continue to follow the visit and assessment schedule. A change in 'treatment status' must be made in the IWRS to discontinue trial product. If the subject is not allowed to resume trial product, then the reason for discontinuation will be recorded in the 'end of treatment' form in the CRF, and final drug accountability must be performed.

8.1.1 Temporary discontinuation of trial treatment

If a subject has discontinued trial product due to a temporary safety concern and can resume, the subject should follow the guide for missed doses (7.1). Similarly, subjects who discontinue trial product on their own initiative should be encouraged to resume trial product (7.1).

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

8.2 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. Refer to the flowchart for data to be collected.

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

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.

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

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

8.2.1 Replacement of subjects

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

8.3 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 trial site.

The following actions must be taken if a subject fails to return to the trial 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 the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator 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 at the 'end of treatment' visit, he/she will be considered to have withdrawn from the trial with a primary reason of lost to 'follow-up'.

9 Trial assessments and procedures

- Trial procedures and their timing are summarised in the flowchart.
- Informed consent must be obtained before any trial related activity (Appendix C).

- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- 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. Electrocardiogram (ECGs) and vital signs
  2. Blood samples
  3. Mental health assessment instruments (9.4)
  4. Other assessments
- Source data of clinical assessments performed and recorded in the CRF must be available and will usually be the subject's medical records. Additional recording to be considered source data includes, but is not limited to laboratory reports, ECG and Mental Health assessments.
- The barriers and motivation interview identify barriers to and motivation for lifestyle change and compliance with the protocol. The interview must be conducted at screening to assist in identifying subjects who are unable or unwilling to comply with protocol procedures as per the exclusion criteria. In addition, the interview will ensure that any minor barriers are addressed during lifestyle counselling.
    - The results of the interview will not be entered in the CRF. It will be at the investigator's discretion to evaluate the motivation of the subject and related eligibility.
- After the final injection, semaglutide/semaglutide placebo subjects will rate ease-of-use and user experience using an instrument Injection Device Experience and Acceptance (IDEA) developed by Novo Nordisk.
    - The results of the questionnaire must be entered in the CRF.
- After training the semaglutide/semaglutide placebo subject in the new DV3396, there will be a questionnaire to site staff: "How difficult or easy was it for site staff to train the subject?", answered on a 5-point scale (very difficult-very easy).
- The results must be entered in the CRF.Subject's weight history must be recorded in the subject's medical record.
- Review of mental health assessment instruments, ECG and 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. Please refer to Appendix B for further details on laboratory samples.

- 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 until the time of the evaluation 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.
- Investigator will evaluate the subject's glycaemic status periodically during the trial as detailed in the flowchart based on all available relevant information e.g. medical records, concomitant medication, blood glucose parameters (HbA1c, FPG) and AEs. The subject's glycaemic status will be categorised as normo-glycaemia, prediabetes or diagnosed with type 2 diabetes accordingly to the American Diabetes Association's definitions[49].
- If a pen-injector use error (see Section 9.10) occurs subject is instructed to contact the trial site or report it at the next scheduled visit. The pen-injector use error form must be completed by the site staff

9.1 Efficacy assessments

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

9.1.1 Body measurements

Body weight should be measured at all site visits without shoes, on an empty bladder and only wearing light clothing. It should be measured on a digital scale and recorded in kilograms or pounds (one decimal) using the same scale throughout the trial. The scale must be calibrated yearly as a minimum.

Height is measured without shoes in centimetres or inches (one decimal). BMI will be calculated from screening data and must agree with inclusion criterion no. 3.

Waist circumference is defined as abdominal circumference located midway between the lower rib margin and the iliac crest. Measures must be obtained in standing position with a non-stretchable measuring tape and to the nearest cm or inch. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally. The same measuring tape should be used throughout the trial. The measuring tape will be provided by Novo Nordisk to ensure standardisation.

9.1.2 Clinical efficacy laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix B, must be conducted in accordance with the flowchart and the laboratory manual.

9.2 Adverse events

The definitions of AEs and SAEs can be found in Appendix D.

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE.

9.2.1 Time period and frequency for collecting AE and SAE information

All AEs will be collected from the first trial-related activity after obtaining informed consent and until the end of trial visit, at the time points specified in the flowchart.

All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours, as indicated in Appendix D. 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 investigational trial product or trial participation, the investigator must promptly notify Novo Nordisk.

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 D.

Timelines for reporting of AEs are listed in Figure 9-1.

Some AEs require additional data collection via a specific event form. This includes medication errors observed during the trial. The relevant specific events are listed in Table 9-1 and the reporting timelines in Figure 9-1.

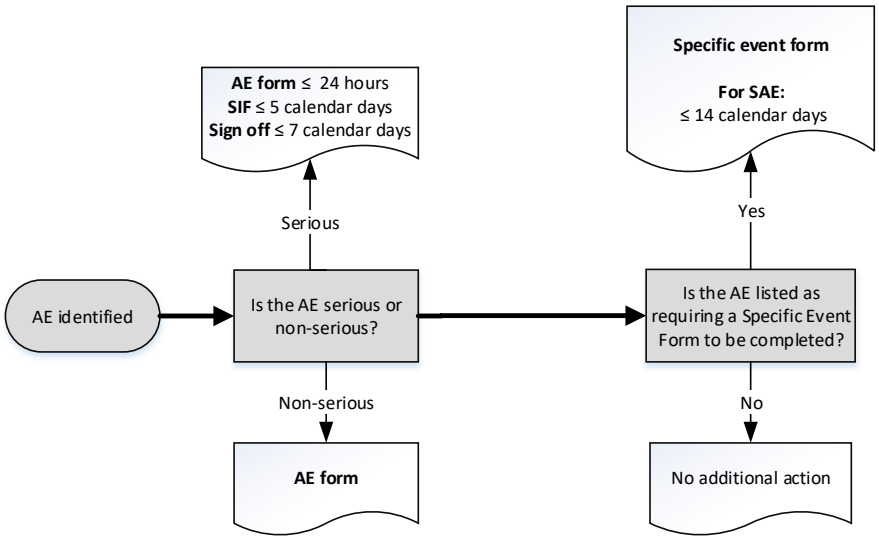


Figure 9-1 Decision tree for determining the event type and the respective forms to complete with associated timelines

Table 9-1 AEs requiring additional data collection (via specific event form)

Event type	AE via specific event form
Medication error*	X
Misuse or abuse of trial product*	X
Cardiovascular events	
Acute Coronary Syndrome	X
Cerebrovascular event	X
Heart failure	X
Coronary artery revascularisation	X
Acute pancreatitis	X
Acute gallbladder disease	X
Malignant neoplasms	X
Hepatic event	X

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

9.2.2 Method of detecting AEs and SAEs

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.

9.2.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, or if the event is otherwise explained (e.g. chronic condition) or the subject is lost to follow-up (as defined in section 8.3). Further information on follow-up procedures is given in Appendix D.

9.2.4 Regulatory reporting requirements for SAEs

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

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for SUSARs (suspected unexpected serious adverse reaction) according to local regulatory requirements and Novo Nordisk policy and forwarded to investigators as necessary.

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

9.2.5 Hypoglycaemic, Cardiovascular and death events

Hypoglycaemic, cardiovascular and death events will be handled and reported according to AE/SAEs description in section 9.2.1.

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

This section is not applicable for this trial.

9.2.7 Pregnancies and associated adverse events

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

If a pregnancy is reported in female subjects, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Figure 9-2 and Appendix E.

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.

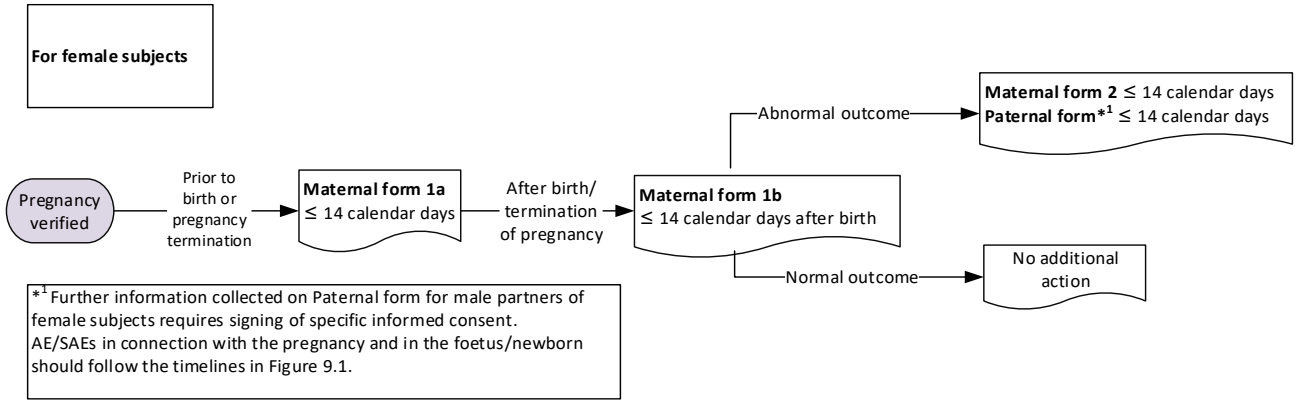


Figure 9-2 Decision tree for determining the forms to complete with associated timelines for pregnancy.

9.2.8 Medical device incidents (including malfunctions)

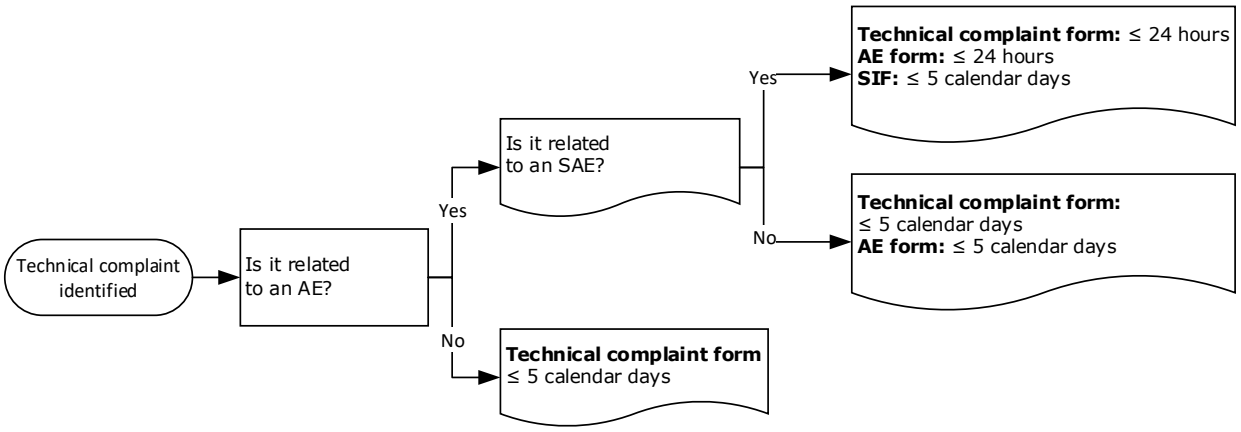
Section not applicable for this trial. Refer to technical complaints in section 9.2.9.

9.2.9 Technical complaints

The investigator must assess whether a technical complaint is related to an AE.

The definitions and reporting process for technical complaints can be found in Appendix F.

Timelines for reporting technical complaints are listed in Figure 9-3.



AE: Adverse Event, SAE: Serious Adverse Event, SIF: Safety Information Form

Figure 9-3 Decision tree for determining the forms to complete with associated timelines for technical complaints.

9.3 Treatment of overdose

Overdoses of semaglutide s.c. up to 4 mg in a single dose, and up to semaglutide s.c 4 mg in a week have been reported in clinical trials. From clinical trials and marketed use of liraglutide, overdoses have been reported up to 24 times the recommended dose (72 mg). One case of a 6-fold overdose (18 mg daily) given for 7 months has been reported.

The most commonly reported AE was nausea. All subjects recovered without complications. With liraglutide, very few post-marketing reports of severe hypoglycaemia have been observed in relation to overdose.

There is no specific antidote for overdose with semaglutide or liraglutide. In the event of an overdose, appropriate supportive treatment should be initiated according to the subject's clinical signs and symptoms.

The overdose must be reported as a medication error (Appendix D), and for reporting times see section 9.2.1 and Figure 9-1.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE and laboratory abnormalities. 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 IB[39, 40] and any updates hereof.

9.4 Safety assessments

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

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the first visit) 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 has experienced in the past. Only relevant and significant medical history as judged by the investigator should be recorded. Findings of specific medical history should de described in designated forms:

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

Follow-up questions will be asked at the end of trial related to the breast neoplasms and colon neoplasms.

In case of an abnormal and clinically significant finding, the investigator must record the finding on the Medical History/Concomitant Illness form if it is present at screening. Any new finding fulfilling the AE definition (Appendix D) during the trial and any clinically significant worsening from baseline must be reported as an AE (9.2).

9.4.1 Mental health assessment instruments

- PHQ-9[50] is a 9-item depression module of the patient health questionnaire, which is a self-administered diagnostic tool used for assessment of mental disorders. The questionnaire will be available in a linguistically validated translated version.
- C-SSRS[51] is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation. The questionnaire will be administered as an interview by the investigator or a qualified delegate. The questionnaire (C-SSRS Baseline and C-SSRS Since Last Visit) will be available in a linguistically validated translated version.
    - Prior to administering the C-SSRS questionnaire, the investigator or qualified delegate must complete sufficient training.

A PHQ-9 score ≥15 or a suicidal ideation corresponding to type 4 or 5 on the C-SSRS within the past 30 days at screening excludes the subject from participation in the trial.

The need to refer a subject to a mental health professional is at the discretion of the investigator.

9.4.2 Physical examinations

A physical examination will include assessments of the general appearance, thyroid gland, breast (females) and abdomen, as well as the cardiovascular and respiratory system.
Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.3 Vital signs

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

- Blood pressure (diastolic and systolic) and pulse 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 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.

9.4.4 Electrocardiograms

12-lead ECG will be obtained as outlined in the flowchart using an ECG machine that automatically calculates the heart rate and measures PR, QRS and QT intervals.

9.4.5 Clinical safety laboratory assessments

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

Urine pregnancy tests provided by the central laboratory must be performed for women of childbearing potential at screening and as specified in the flowchart. Urine pregnancy test must be repeated at any time during the trial if pregnancy is suspected. Further instructions can be found in the laboratory manual.

9.5 Pharmacokinetics

Not applicable for this trial.

9.6 Pharmacodynamics

Not applicable for this trial.

9.7 Genetics

Not applicable for this trial.

9.8 Biomarkers

Collection of samples for biomarker research is part of this trial to support the effect objectives. The following samples must be conducted in accordance with the laboratory manual and the flowchart:

Biomarkers linked to cardiovascular risk:

- High sensitive C-reactive protein

9.9 Severe hypersensitivity

This section is not applicable in this trial

9.10 Pen-injector use error for DV3396 pen-injector

Pen-injector use errors are assessed for all injections with the DV3396 pen-injector according to the flowchart section 2. These are defined as user action or lack of user action during use of DV3396 pen-injector leading to a different result than intended by the manufacturer or expected by the user. An example of a use error is that the user deviates from the instructions given in the DFU, e.g. if the user does not hold the pen-injector against the skin for as long as specified in the DFU.

The pen-injector use error form is filled when a subject experience a pen-injection use error. The subjects can either contact site when the injection error occur or report it at the next visit.

A pen-injector use error can be related to both a technical complaint or an adverse event.

10 Statistical considerations

General considerations

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

The placebo arms will be pooled in the statistical analyses.

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.

Results from statistical analyses will generally be accompanied by two-sided 95% confidence intervals and corresponding p-values.

10.1 Sample size determination

The tests of superiority of semaglutide 2.4 mg to liraglutide 3.0 mg for the primary and confirmatory secondary endpoints are performed using the fixed-sequence statistical strategy. 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 10-1 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.

The trial is designed with an effective power of 92% to detect differences on all endpoints in the statistical test hierarchy at one-sided alpha of 0.025 (equivalent to a two-sided alpha of 0.05). Specifically, the trial tests the null hypothesis of equal % change in body weight (or equal proportions achieving body weight loss of 10%, 15%, and 20%) against the one-sided alternative of greater % body weight loss in the semaglutide 2.4 mg arm (or greater proportions achieving body weight loss of 10%, 15%, and 20%) compared to the liraglutide 3.0 mg arm. The calculations for the primary endpoint are based on a t test on the mean difference assuming equal variances, whereas those for the confirmatory secondary endpoints are based on the Pearson chi-square test for two independent proportions. Assumptions for these calculations are based on findings from NN8022 (SCALE) and trial NN9536-4153. These assumptions are further explored across a range of sample sizes in Table 10-2. Under these assumptions and a 3:1:3:1 randomisation ratio (section 5), the desired power of more than 90% is obtained with 126 subjects randomized to each active drug arm and 42 subjects randomized to each placebo arm.

Furthermore, a sample size of 84 subjects in the pooled placebo group (42 each in the semaglutide placebo and liraglutide placebo arms) gives a power of >99% for the comparison between semaglutide 2.4 mg once-weekly and pooled placebo on the primary endpoint, as well as a power of at least 80% for the comparison between liraglutide 3.0 mg once-daily and pooled placebo on the primary endpoint.

Table 10-1 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number of 336 randomised subjects

Order	Endpoint	Expected mean (±SD) or proportion		Expected difference or proportion ratio	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Liraglutide 3.0 mg			

1	% weight change #	12.5 (±10)	7.0 (±10)	5.5%-points	99	99
2	10% responders	61%	37%	1.6	97	96
3	15% responders	39%	18%	2.2	96	93
4	20% responders	27%	6%	4.5	99	92

SD = standard deviation; # shown as a positive number

All tests in the hierarchy are based on the primary estimand. Since all tests are tests of superiority of semaglutide 2.4 mg to liraglutide 3.0 mg, power is only shown for this comparison.

Table 10-2 Assumptions and effective power for the primary and confirmatory secondary endpoints across a range of number of randomised subjects

Expected mean (±SD)		Expected proportions of 10%/15%/20% body weight loss responders		N per active arm	Total N randomised	Effective power (%)
Semaglutide 2.4 mg	**Liraglutide 3.0 mg**	**Semaglutide 2.4 mg**	**Liraglutide 3.0 mg**			
12.5 (±10)	7.0 (±10)	61%/39%/27%	37%/18%/6%	99	264	81
				126	**336**	**92**
				150	400	97

SD = standard deviation

Mean weight change shown as a positive number.

10.2 Definition of analysis sets

Two analysis sets are defined:

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

The *safety analysis set* (SAS) includes all randomised subjects exposed to at least one dose of randomised treatment.

Any observation excluded from the analysis database will be documented before database lock with the reason for exclusion provided.

Two observation periods are defined for each subject:

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

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

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

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

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

Effect endpoints will be analysed using the FAS; safety endpoints will be analysed using the SAS.

10.3 Statistical analyses

10.3.1 Primary endpoint

Definition of primary endpoint: % weight change

Change from baseline (week 0) to week 68 in body weight (%) is defined as

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

Analyses addressing the primary estimand

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

The analysis model for % weight change is a linear regression (ANCOVA) of % weight change with randomised treatment as a factor and baseline body weight (kg) as covariate. Randomised treatment will be coded in 3 levels: semaglutide 2.4 mg, liraglutide 3.0 mg, and pooled placebo. The estimated treatment difference between semaglutide 2.4 mg and liraglutide 3.0 mg will be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value. Estimated treatment differences between semaglutide 2.4 mg and pooled placebo, as well as between liraglutide 3.0 mg and pooled placebo, will also be reported together with associated two-sided 95% confidence intervals (CI).

Handling of missing week 68 values for the primary estimand

All available data at week 68 are used and missing values at week 68 will be imputed and the endpoints 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[52]. For subjects in the semgalutide 2.4 mg, liraglutide 3.0 mg and pooled placebo groups, missing body weight measurements at week 68 for non-retrieved subjects are imputed using assessments from retrieved subjects in each treatment group. This will be done according to the timing of last available observation during the on-treatment period (LAO-OT) of body weight. Missing body weight measurements at week 68 for subjects on randomised treatment are imputed by sampling from available measurements at week 68 from subjects on randomised treatment in the relevant randomised treatment arm. Details of the multiple imputation approach are provided in the SAP.

Sensitivity analyses

Tipping-point multiple imputation analysis: First, missing data are imputed according to the primary multiple imputation approach. Then, a penalty is added to the imputed values at week 68. The approach is to explore a range of penalties for both the semaglutide 2.4 mg and liraglutide 3.0 mg arms, and the impact these would have on the study conclusions. The 2-dimensional space of penalties covering the range from -30% to 30% will be explored for both arms. Penalties for the pooled placebo group will not be considered, as this sensitivity analysis evaluates the robustness of the superiority conclusions to departures from the observed change in body weight in both active treatment groups.

Analysis addressing the secondary estimand

The secondary estimand for % weight change addresses the efficacy of semaglutide 2.4 mg and will be assessed using a Mixed Model for Repeated Measurements (MMRM) approach. Week 68 assessments for retrieved subjects are not used in this analysis. The MMRM will use assessments only from subjects who are taking the randomised treatment until end of treatment or until first discontinuation of randomised treatment. For subjects who initiate rescue interventions before completion or first discontinuing of randomised treatment, the date of starting weight management drugs or undergoing bariatric surgery will be used as latest date for using assessments in this MMRM. The MMRM will be fitted using % weight change and the same factor and covariate as for the primary analysis all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

10.3.2 Secondary endpoints

10.3.2.1 Confirmatory secondary endpoints

Confirmatory secondary endpoints are listed in section 2 and are all included in the fixed-sequence statistical strategy, see above. All tests are tests of superiority of semaglutide 2.4 mg to liraglutide 3.0 mg.

Analyses addressing the primary estimand

All confirmatory secondary endpoints will be analysed using the primary imputation approach used for the primary endpoint and to address the primary estimand. The statistical model for body weight responder endpoints is a logistic regression using randomised treatment as a factor and baseline body weight (kg) as covariate. Randomised treatment will be coded in 3 levels: semaglutide 2.4 mg, liraglutide 3.0 mg, and pooled placebo. The estimated odds ratio (OR) between semaglutide 2.4 mg and liraglutide 3.0 mg will be reported together with the associated two-sided 95% confidence interval and corresponding p-value. Estimated odds ratios between semaglutide 2.4 mg and pooled placebo, as well as between liraglutide 3.0 mg and pooled placebo, will also be reported together with associated two-sided 95% confidence intervals.

Analyses addressing the secondary estimand

The confirmatory secondary endpoints will be analysed to address the secondary estimand using the same MMRM described for the primary endpoint. From the MMRM individually predicted values for % weight change at week 68 will be used to classify each subject as a responder or not. This classification will then be analysed using a logistic regression model with treatment as the only factor.

Sensitivity analyses for confirmatory secondary endpoints

For all confirmatory secondary endpoints a sensitivity analysis using non-retrieved subjects as non-responders will be carried out.

10.3.2.2 Supportive secondary endpoints

Analyses of supportive secondary endpoints will be described in the SAP.

10.4 Interim analysis

This section is not applicable in this trial

11 Appendices

Appendix A Abbreviations and Trademarks

AD	available but discontinued
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AT	available on randomised treatment
BMI	body mass index
CLAE	clinical laboratory adverse event
CRF	case report form
DFU	direction for use
DUN	dispensing unit number
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	glycated haemoglobin
HRT	hormone replacement therapy
IB	investigator's brochure
IDEA	injection device experience and acceptance questionnaire
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
KDIGO	kidney disease improving global outcome

LAO	last available observation
LDL	low-density lipoprotein
MEN2	multiple endocrine neoplasia type 2
MD	missing and discontinued
MMRM	mixed model for repeated measurements
MT	missing on randomised treatment
MTC	medullary thyroid cancer
PCD	primary completion date
RD-MI	multiple imputation using retrieved subjects
SAS	safety analysis set
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneus
SD	standard deviation
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment emergent adverse event
TEE	total energy expenditure
TMM	trial materials manual
TSH	thyroid stimulating hormone
WC	waist circumference
WOCBP	woman of child bearing potential

Appendix B Clinical laboratory tests

- The tests detailed in Table 11-1 and Table 11-2 will be performed by the central laboratory.
- Laboratory samples specified in the protocol should be sent to the central laboratory for analysis.
- Additional tests may be performed at local laboratory any time during the trial as determined necessary by the investigator or required by local regulations.
- The central lab 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 clinical trial report.
- For haematology samples (differential count) where the test result is not normal, then a part of the sample may be kept for up to two years or according to local regulations.

Table 11-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	Fasting plasma glucose[1] $HbA1_c$ Fasting serum insulin
Lipids	Total Cholesterol High density lipoprotein (HDL) cholesterol Low density lipoprotein (LDL) cholesterol Triglycerides Very-low-density lipoprotein (VLDL) cholesterol Free fatty acids
Biomarkers	high sensitive C-reactive protein
Notes: [1] A FPG result ≤ 3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as a CLAE at the discretion of the investigator, see Appendix D	

Table 11-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	Erythrocytes Haematocrit Haemoglobin Leucocytes Thrombocytes
Biochemistry[1]	Alanine Aminotransferase (ALT)[2] Albumine Albumine corrected calcium Alkaline phosphatase Amylase Aspartate Aminotransferase (AST)[2] Calcitonin Creatine kinase Creatinine Lipase Potassium Sodium Thyroid stimulating hormone (TSH)[3] Total bilirubin Urea
Pregnancy Testing	Urine human chorionic gonadotropin (hCG) pregnancy test for women of childbearing potential
Other tests	eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation as defined by KDIGO 2012[45]

Notes:
[1]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix D (Hy's Law) and section 8.
[2]If ALT or AST >3 upper normal limit (UNL), additional blood samples should be taken from the subject to analyse international normalised ratio (INR) by central laboratory (except at screening visit). Repeat testing of the abnormal labboratory assessments should be performed for the subject until abnormalities return to normal or baseline state.
[3]If TSH level is out of normal range, additional testing will be performed by central lab: total and free T3 and T4 except at screening visit.

Hepatic laboratory outlier: if the following hepatic laboratory parameters are above the cut-offs values in Table 11-3, it is considered to be a hepatic laboratory outlier and should be reported by completing a hepatic event form in the CRF. It is at the investigator's discretion to determine whether it should also be reported as an adverse event, see Appendix D.

Table 11-3 Criteria for hepatic laboratory outliers

	Cut-off
Alkaline phosphatase	>20 x UNL
ALT	>5 x UNL
AST	>5 x UNL
Total bilirubin	>10 x UNL

Please note that in case of a hepatic event defined as ALT or AST>3 x UNL and total bilirubin > 2 x UNL, where no alternative aetiology exists (Hy's law), this must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable.

Appendix C Trial governance considerations

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[53] and applicable ICH Good Clinical Practice (GCP) Guideline[54].
  - 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 clinical trial report 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 trial 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 clinical trial report synopsis to the IRB/IEC.

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.

For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

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 will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[54], Declaration of Helsinki[53] and the IRB/IEC or trial 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 of informing to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the trial.
- A copy of the informed consent form(s) must be provided to the subject.

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.

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.

Materials and items will be supplied if locally acceptable. The retention items will be relevant for the subjects' participation in the trial and/or their obesity and will not exceed local fair market value.

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

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; subject names or any information which would make the subject identifiable will not be transferred.
- 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 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.

6) Committee structure

Novo Nordisk safety committee
Novo Nordisk will constitute an internal semaglutide s.c. safety committee to perform ongoing safety surveillance. The semaglutide s.c. safety committee may recommend unblinding of any data for further analysis, and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

7) 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 clinical trial report for this trial.

One (or two) investigator(s) will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator(s) will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[55].

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 clinical trial report 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.

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[55].

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 trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

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.

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 subjects' data and will be provided with the randomisation code after results are available.

8) 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)[56], the Food and Drug Administration Amendment Act (FDAAA)[57], European Commission Requirements[58, 59] 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[57].

The Primary Completion Date (PCD) is the last assessment of the primary endpoint and is for this trial Last Subject First Treatment LSFT + 68 weeks corresponding to visit 22 (´end of treatment´ visit). If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 22 (´end of treatment´ visit). The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

9) Data quality assurance

Case Report Forms (CRFs)

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- For some data both electronic and paper CRFs are used.

- 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 electronic CRF is revoked or temporarily unavailable:
    - AE forms
    - Safety information forms
    - Technical complaint forms (also to be used to report complaints that are not subject related, e.g. discovered at trial site before allocation)

- 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.

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 trial 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 trial sites.

- Monitors will review the subject's medical records and other source data e.g. Mental health assessment instruments, to ensure consistency and/or identify omissions compared to the CRF.

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) Source documents

- All data entered in the CRF must be verifiable in source documentation other than the CRF.
- The original of the completed Mental Health assessments must not be removed from the trial site.
- If food/activity tracker is used it can be either paper based or electronic based on the decision of the subject.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the trial site.
- Data reported in the CRF 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 trial site. There will only be one source document defined at any time for any data element.

11) Retention of clinical trial documentation

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

electronic readable format to the investigator before access is revoked to the systems 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 trial 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

12) Trial and site closure

Novo Nordisk reserves the right to close the trial 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.

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

The investigator may initiate trial 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 trial 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.

13) 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 trial 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).

14) 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 site or investigator are responsible.

Novo Nordisk may pay additional costs incurred in relation to assessments relevant for following the safety of the subject. Investigator must contact Novo Nordisk on a case by case basis for whether the costs will be covered.

Appendix D Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting

AE definition
• An AE is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • An AE can be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> the AE definition
• Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • A CLAE: a clinical abnormal laboratory finding which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms or the clinical sequelae of a suspected overdose of trial product regardless of intent. • 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 <u>NOT</u> meeting the AE definition
• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product. Note: pre-existing conditions should be recorded as medical history/concomitant illness. • Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.

Definition of an SAE
An SAE is an AE that fulfils at least one of the following criteria:
• **Results in death**
• **Is life-threatening** The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
• **Requires inpatient hospitalisation or prolongation of existing hospitalisation** o 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 serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. o Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Note: ▪ Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. ▪ Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.
• **Results in persistent disability/incapacity** o The term disability means a substantial disruption of a person's ability to conduct normal life functions. o 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.
• **Is a congenital anomaly/birth defect**
• **Important medical event:** o 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. o The following adverse events must always be reported as SAEs using the important medical event criterion, if no other seriousness criteria are applicable: ▪ suspicion of transmission of infectious agents via the trial product. ▪ risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x UNL and total bilirubin >2x UNL, where no alternative aetiology exists (Hy's law).

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

AEs requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the safety of the trial products (Table 9-1). The selection of these events is based on the non-clinical and clinical data with semaglutide and liraglutide, knowledge from the GLP-1 RA drug class as well as regulatory requirements.

Event type	Description
Acute gallbladder disease	Events of symptomatic acute gallbladder disease (including gallstones and, cholecystitis)
Acute pancreatitis	The diagnosis of acute pancreatitis requires two of the following three features: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) (2) serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal (3) characteristic findings of acute pancreatitis on imaging.
Malignant neoplasm	Malignant neoplasm by histopathology or other substantial clinical evidence
Hepatic event	Hepatic event defined as: – Disorders of the liver including cholestatic conditions and liver related signs and symptoms – ALT or AST > 3x UNL and total bilirubin > 2x UNL or INR > 1.5x* – ALT or AST > 3x UNL with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). *Please note that in case of a hepatic event defined as ALT or AST > 3x UNL and total bilirubin > 2 x UNL, where no alternative aetiology exists (Hy's law), this must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable.
Acute coronary syndrome	Acute coronary syndrome conditions include all types of acute myocardial infarction and hospitalisation for unstable angina pectoris
Cerebrovascular event	Episode of focal or global neurological dysfunction that could be caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction
Coronary artery revascularisation	Coronary revascularisation procedure is a catheter-based (PCI) or a surgical procedure (CABG) designed to improve myocardial blood flow.
Heart failure	Presentation of the patient for an urgent, unscheduled clinic/office/emergency department visit or hospital admission, with a primary diagnosis of heart failure (new episode or worsening of existing heart failure)
Medication error	A medication error concerning trial products is defined as: - Administration of wrong drug.

		- Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in a confirmed administration of wrong drug. - Wrong route of administration, such as intramuscular instead of subcutaneous. - Accidental administration of more than 2.4 mg/week (semaglutide) or 3.0 mg/day (liraglutide) or a higher dose than intended during dose escalation, however, 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.
	Misuse or abuse of trial product*	Misuse is when the trial product is intentionally and inappropriately used. Abuse of trial product is persistent or sporadic, intentional excessive use, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm).

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

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the CRF.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- 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.
- 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 "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 intensity for each event reported during the trial and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.

Note: Severe is a category used for rating the intensity of an event; and both an AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the outcomes described in the definition of an SAE and not when it is rated as severe.

Assessment of causality

The investigator is obligated to assess the relationship between trial product and the occurrence of each AE/SAE.

Relationship between an AE/SAE and the relevant trial product*(s)* should be assessed as:

- Probable - Good reason and sufficient documentation to assume a causal relationship.
- Possible - A causal relationship is conceivable and cannot be dismissed.
- Unlikely - The event is most likely related to aetiology other than the trial product.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to trial product administration will be considered and investigated.

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.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data**.

The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
- **Recovering/resolving:** The condition is improving, and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
- **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 sequelae meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the subject has not improved, and the symptoms are unchanged or the outcome is not known.
- **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.

SAE reporting via electronic CRF
• Relevant forms (AE and safety information form) must be completed in the CRF. • For reporting and sign-off timelines, see box below. • If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form and if the CRF is unavailable for more than 5 calendar days then the site will use the safety information form (see box below). • The site will enter the SAE data into the CRF as soon as it becomes available, see section 9.2.1. • After the trial is completed at a given site, the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after CRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

SAE reporting via paper CRF

• Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by fax, e-mail or courier.
• 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 time frames (as illustrated in Figure 9-1
  ○ AE form within 24 hours.
  ○ Safety information form within 5 calendar days.
  ○ Both forms must be signed within 7 calendar days.
 	
Contact details for SAE reporting can be found in the investigator trial master file.

Appendix E Contraceptive guidance and collection of pregnancy information

It must be recorded in the CRF whether female subjects are of childbearing potential.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP

7. Premenarcheal
8. Premenopausal female with one of the following:
   Documented hysterectomy
   Documented bilateral salpingectomy
   Documented bilateral oophorectomy
9. 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:
   - Amenorrhoea
   - 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 treated with HRT and whose menopausal status is uncertain are considered of childbearing potential and will be required to use one of the highly effective contraception methods.

Note: Documentation can come from the site personnel'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 11-4 Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent [a and b] Failure rate of <1% per year when used consistently and correctly.
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [b] • oral • intravaginal • transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • oral • injectable
Highly effective methods that are user independent [b]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine Device • Intrauterine hormone-releasing System • Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence[b] 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 product. 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]Typical use failure rates may differ from < 1% per year if not used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials. [b]Contraception should be utilised during the treatment period and for at least 49 days after the last dose of trial product.

In certain cases, it is accepted to use double barrier methods (a condom combined with an occlusive cap (e.g. diaphragm) with/without the use of spermicide). This should only be allowed in females with:

1) known intolerance to the highly effective methods mentioned in Table 11-4 - or where the use of any of the listed highly effective contraceptive measures are contraindicated in the individual subject, and/or

2) if the risk of initiating treatment with a specific highly effective method outweighs the benefit for the female.

Justification for accepting double barrier method should be at the discretion of the investigator taking into consideration his/her knowledge about the female's obesity history, concomitant illness, concomitant medication and observed AEs. The justification must be stated in the medical records.

Pregnancy testing

- WOCBP should only be included after a negative highly sensitive urine pregnancy test.
- Additional urine pregnancy testing should be performed according to flowchart in WOCBP.
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

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.
- 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. 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 pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to Novo Nordisk as described in Appendix D. 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.

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

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

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 medical 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 trial site until the time of the last usage of the product, must be collected for products predefined on the technical complaint form.

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

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within the timelines specified in Figure 9-3. If the CRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

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

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

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

Reporting of technical complaints for Novo Nordisk products not included in technical complaint form
Technical complaints on Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk affiliate with a reference to trial ID.

Appendix G Monitoring of calcitonin

Background

Treatment with GLP-1 RAs has been shown to be associated with thyroid C-cell changes in rodents but not in non-human primates. The human relevance of this finding is unknown. However, based on the findings in rodents, monitoring of serum calcitonin (a sensitive biomarker for C-cell activation) is currently being performed in clinical trials with semaglutide.

While there is general agreement on the clinical interpretation of substantially elevated calcitonin levels (> 100 ng/L) as likely indicative of C-cell neoplasia, the interpretation of values between upper normal range (5.0 and 8.4 ng/L for women and men, respectively) and 100 ng/L is less clear with regards to indication of disease.

There are several known confounding factors affecting calcitonin levels, e.g.:

- renal dysfunction
- tobacco use
- autoimmune thyroiditis
- several drug classes (e.g. proton pump inhibitors, beta-blockers, H^2-blockers and glucocorticoids)

Physiology of C-cell activation in various clinical conditions and in different patient populations (i.e. with various comorbidities) is poorly understood. There may be various clinical conditions not identified so far which mildly or moderately affect calcitonin secretion by C-cells.

Calcitonin monitoring

A blood sample will be drawn at pre-specified trial visits for measurement of calcitonin.

In case a subject has a calcitonin value ≥ 10 ng/L, the algorithm outlined in Figure 11-1 and described below should be followed. The algorithm applies for all calcitonin values in the trial.

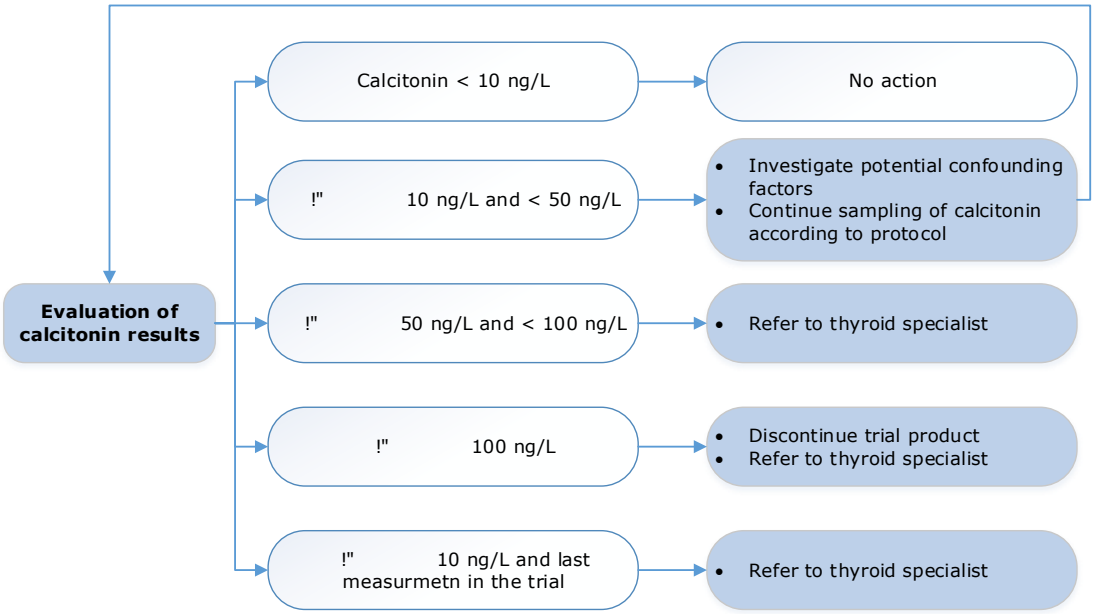


Figure 11-1 Flow of calcitonin monitoring

Calcitonin ≥ 100 ng/L

Action: The subject (even if a screen failure) must immediately be referred to a thyroid specialist for further evaluation and the trial product must be discontinued (section 8). The subject should remain in the trial; however, all medications suspected to relate to this condition must be discontinued until diagnosis has been established.

Background: These values were found in 9 (0.15%) of a population of 5817 patients with thyroid nodular disease[60]. All these patients were diagnosed with MTC, resulting in a positive predictive value of 100%.

Diagnostic evaluation should include:

- thyroid ultrasound examination
- fine needle aspiration of any nodules > 1 cm
- potentially, surgery with neck dissection

In case a subject is diagnosed with MTC, it is common clinical practice to explore the family history of MTC or MEN2 and perform a genetic test for RET proto-oncogene mutation.

Calcitonin ≥ 50 and < 100 ng/L

Action: The subject (even if a screen failure) should be referred to a thyroid specialist for further evaluation. The subject should remain in the trial and can continue trial product.

Background: These values were found in 8 (0.14%) of the population of 5817 patients with thyroid nodular disease[60]. Two of these subjects were diagnosed with MTC and two were diagnosed with C cell hyperplasia, resulting in a positive predictive value of a C-cell anomaly of 50%.

Diagnostic evaluation should include:

- thyroid ultrasound examination
- if available, and if there are no contraindications, a pentagastrin stimulation test should be done. For subjects with positive pentagastrin stimulation test, surgery should be considered.
- if pentagastrin stimulation test is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information about the need for surgery.

Calcitonin ≥ 10 and < 50 ng/L

Action: The subject can continue in the trial on trial product. Continue sampling of calcitonin according to the protocol.

If the subject is a screen failure, or if the value is from the last sample taken in the trial, the subject should be referred to a thyroid specialist for further evaluation.

Background: Calcitonin values from 20–50 ng/L were found in up to 1% of subjects of the population of 5817 patients with thyroid nodular disease[60]. The predictive value of a C-cell anomaly for this calcitonin level was 8.3%. However, the likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.

For calcitonin values between 10-20 ng/L Costante et al.[60] identified 216 (3.7%) patients. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin value of 33 ng/L and had C-cell hyperplasia at surgery. Two other studies used a cut-off of calcitonin > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT > 10 and < 20 ng/L to allow conclusions[61, 62].

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Log of Protocol Amendments

Protocol amendment no	Date	Final, Version	Country(ies) and/or trial site(s) affected	Brief content
Protocol amendment 1	17 March 2020	Protocol version 2.0	US	In order to generate clinical trial data with DV3396 pen-injector, all semaglutide/semaglutide placebo subjects will switch device from PDS290 to DV3396 at week 44 (visit 18) Further a new questionnaire (Injection Device Experience and Acceptance (IDEA) Questionnaire) will be introduced for subjects switching device. In protocol version 2.0 there was a mistake in summary of changes table, which is updated and therefore version 3.0
Protocol amendment 2	15 April 2020	Protocol version 3.0	US	In order to generate clinical trial data with DV3396 pen-injector, all semaglutide/semaglutide placebo subjects will switch device from PDS290 to DV3396 at week 44 (visit 18) Further a new questionnaire (Injection Device Experience and Acceptance (IDEA) Questionnaire) will be introduced for subjects switching device.
Protocol amendment 3	25 November 2020	Protocol version 4.0	US	Amending the discontinuation criterion 6, so that subjects are allowed to continue in the trial, while also participating in a COVID-19 trial.

[redacted]

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16.1.01 Statement Attachment I and II

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff.