Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04998136
Sponsor trial ID:	NN9536-4707
Official title of study:	Efficacy and safety of semaglutide 2.4 mg once-weekly in Asians with obesity diagnosed as BMI ≥ 25 kg/m2 according to local guidelines.
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*Document date refers to the date on which the document was most recently updated.

Protocol

Protocol Title:

Efficacy and safety of semaglutide 2.4 mg once-weekly in Asians with obesity diagnosed as BMI ≥ 25 kg/m^2 according to local guidelines.

Substance name: Semaglutide

Universal Trial Number: U1111-1265-5285

Study phase: 3b

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	**Date**	**Applicable in country(-ies) and/or site(s)**
Protocol Version 6.0	16 December 2022	Global
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Protocol version 6.0 (16 December 2022)

This amendment is non-substantial based on a criterion set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall rationale for preparing protocol, version 6.0:

It is identified that statements instructing drug accountability in protocol section 6.2 differs than that of the trial materials manual (TMM). To mitigate this discrepancy in the protocol, the statements instructing investigator or designee responsible for drug accountability have been removed and the reference to the TMM has been added for more details.

Section # and name	**Description of change**	**Brief rationale**
6.2 Preparation, handling, storage and accountability	Text revised to define the drug accountability level.	To align with project-based decisions.
6.2 Preparation, handling, storage and accountability	Removed the text "~~product should be disposed of in a safe manner and will not be retained for drug accountability purposes. Empty packaging will be used to perform accountability of used trial product.~~" Added the text "*Additional details regarding handling of drug accountability can be found in the TMM*."	To align with TMM

Table of Contents

Page

1 Protocol summary

1.1 Synopsis

This is an interventional, multi-national, multi-centre, randomised, double-blind, placebo-controlled, two-armed, parallel group clinical study.

Rationale:

The prevalence of obesity has reached epidemic proportions in most countries around the world and continues to increase.[1-7] The risk of obesity-related complications and comorbidities increases with increasing BMI, and a weight loss of 5−10% has significant health benefits by improving obesity-related comorbidities including slowing progression to T2D, and improving physical symptoms and quality of life.[8-14] 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.[15-25] Currently, only few pharmacological options are approved for weight management. The GLP-1 RA drug class is associated with multiple benefits; they have a well-documented safety profile, reduce body weight, improve blood pressure, lipid profile and other cardiovascular risk factors as well as glucose metabolism.

Most studies that examine the risk of adverse health associated with obesity have been based on data from Europe or the United States. However, the increased health risks associated with obesity occur in people with lower BMIs in the Asia Pacific region. This has supported calls by obesity researchers for lower BMI cut-offs for overweight and obesity in Asian populations than those in the international WHO classification.[26, 27]

The present 44-week study is designed to show the reduction in body weight and compare the efficacy and safety of semaglutide subcutaneous (s.c.) once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in people from Republic of Korea and Thailand with obesity, defined as BMI ≥ 25.0 kg/m^2, reflecting local diagnostic practices. Thus, the study will provide more information about the efficacy and safety of semaglutide s.c. 2.4 mg once weekly in people of Asian descent with obesity as defined by regional guidelines.

Objectives, endpoints and estimand(s):

Primary objective: To demonstrate the superiority of semaglutide s.c. 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity, classified as BMI ≥ 25 kg/m^2 according to local guidelines in Republic of Korea and Thailand on:

- Body weight
- ≥5% weight reduction

Secondary objectives:

- To compare the efficacy of semaglutide s.c. 2.4 mg once-weekly versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity, classified as BMI ≥ 25 kg/m^2 according to local guidelines in Republic of Korea and Thailand, on cardiovascular risk factors

- To compare the efficacy of semaglutide s.c. 2.4 mg once-weekly versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity, classified as BMI ≥ 25 kg/m^2 according to local guidelines in Republic of Korea and Thailand, on glucose metabolism

Co-primary endpoints:
- Change in body weight (%) from baseline (week 0) to end of treatment (week 44)
- ≥5% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44)

Confirmatory secondary endpoints:
- ≥10% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44)
- ≥15% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44)
- Change in waist circumference from baseline (week 0) to end of treatment (week 44)

Estimands:
- **Co-primary estimands:** The estimands will quantify the average treatment effect of semaglutide s.c. 2.4 mg once weekly as an adjunct to a reduced-calorie diet and increased physical activity in patients with obesity defined according to local guidelines in Republic of Korea and Thailand, measured by relative change from baseline (week 0) to week 44 in body weight, and ≥ 5% body weight reduction at week 44, regardless of discontinuation or dose reduction of randomised trial product, and regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery).
- **Secondary estimand:** The secondary estimands for both the confirmatory secondary and supportive secondary endpoints are similar to the co-primary estimands except for the endpoint attribute. For continuous endpoints, the secondary estimands for primary and secondary objectives are similar to the co-primary estimand for % weight change. For binary endpoints, the secondary estimands for primary and secondary objectives are similar to the co-primary estimand for ≥5% body weight reduction.
- **Additional estimand:** The estimand will quantify the average treatment effect of semaglutide s.c. 2.4 mg once weekly as an adjunct to a reduced-calorie diet and increased physical activity in patients with obesity defined according to local guidelines in Republic of Korea and Thailand, measured by relative change from baseline (week 0) to week 44 in body weight, and ≥ 5% body weight reduction at week 44, had they remained on their randomised treatment for the entire planned duration of the study and not initiated any other anti-obesity therapies (weight management drugs or bariatric surgery).

Overall design:

The study consists of:
- a 1-week screening period
- a 16-week dose escalation period
- a 28-week maintenance period
- a 5-week follow-up period

Study intervention groups and duration:

Following a screening period of up to 1 week, the participants will be randomised 2:1 at the randomisation visit to semaglutide s.c. 2.4 mg once weekly or placebo once weekly as an adjunct to a reduced-calorie diet and increased physical activity.

The maximum duration of the study intervention for each participant is 44 weeks and the duration of the study for each participant is 49 weeks.

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

- Semaglutide B 0.68 mg/mL and semaglutide placebo, solution for injection, 1.5 mL PDS290 pen-injector
- Semaglutide B 1.34 mg/mL and semaglutide placebo, solution for injection, 1.5 mL PDS290 pen-injector
- Semaglutide B 1.34 mg/mL and semaglutide placebo, solution for injection, 3 mL PDS290 pen-injector
- Semaglutide B 2.27 mg/mL and semaglutide placebo, solution for injection, 3 mL PDS290 pen-injector
- Semaglutide B 3.2 mg/mL and semaglutide placebo, solution for injection, 3 mL PDS290 pen-injector

Number of participants:

Approximately 176 participants will be screened to achieve 150 participants randomly assigned to study intervention.

Participant characteristics:

The participants will be adult males and females who meet the following key inclusion criteria and none of the following key exclusion criteria:

Key inclusion criteria:

- Age above or equal to 18 years at the time of signing informed consent.
- BMI $\geq$ 25.0 kg/m^2 at screening.
- Both parents of Asian descent.
- History of at least one self-reported unsuccessful dietary effort to lose body weight.

Key exclusion criteria:

- $HbA_{1c} \geq$ 48 mmol/mol (6.5%) as measured by the central laboratory at screening.
- History of type 1 or type 2 diabetes mellitus.
- A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records.
- Any participant where a substantial weight loss, in the investigator's opinion, might jeopardise the participant's safety.
- Renal impairment with estimated Glomerular Filtration Rate (eGFR) < 15 mL/min/1.73 m^2 at screening.

Efficacy and safety data will be collected at regular intervals throughout the study.

Data monitoring committee: No

1.2 Flowchart

	Screening	Randomisation	Intervention period														End of study intervention[a]	End of study
Visit	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	V11	P12	V13	P14	V15	P16	V17	P18
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	20	24	28	32	36	40	44	49
Visit Window (Days)	-7	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	+7
Informed Consent and Demography[b] (10.1.3)	X																	
Medical History/Concomitant Illness (8.2)	X																X	
Eligibility Criteria (5.1 and 5.2)	X	X																
Randomisation (6.3)		X																
Concomitant Medication (6.8)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Childbearing Potential[c] (10.4)	X																	
Tobacco Use[d] (5.3.2)	X																	
Pregnancy Test (8.2.4)	X	X		X		X		X		X	X		X		X		X	X
Evaluation of Antihypertensive Treatment (8)											X						X	
Evaluation of Glycaemic Status (8)		X									X						X	
Evaluation of Lipid-lowering Treatment (8)											X						X	
Discontinuation Criteria (7)			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Surgical Procedures Form (8.2.5)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height (8.1.1)	X																	
Body Weight (8.1.1)	X	X		X		X		X		X	X		X		X		X	
Waist Circumference (8.1.1)	X	X		X		X		X		X	X		X		X		X	
Physical Examination (8.2.1)	X																X	

	Screening	Randomisation	Intervention period														End of study intervention[a]	End of study
Visit	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	V11	P12	V13	P14	V15	P16	V17	P18
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	20	24	28	32	36	40	44	49
Visit Window (Days)	-7	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	+7
Vital Signs (8.2.2)	X	X		X				X			X		X		X		X	
Laboratory Assessments (10.2)	X	X									X						X	
Adverse Event (8.3 and 10.3)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Sampling (8.4.1)				X				X			X						X	
Breast Neoplasms Follow-up[c] (8.2)																	X	X
Colon Neoplasms Follow-up (8.2)																	X	X
Drug Dispensing (6.2)		X		X		X		X		X			X		X			
Drug Accountability (6.2)		X		X		X		X		X			X		X		X	
Training in Trial Product, Pen-handling (6.1)		X		X		X		X		X			X		X			
Hand Out Direction for Use (6.1)		X																
Hand Out Dose Reminder Card		X		X		X		X		X			X		X			
Hand Out and Instruct in PK Diary (8)		X				X				X					X			
Diet and Physical Activity Counselling (6.1)		X		X		X		X		X	X	X	X	X	X	X	X	
Barriers and Motivation Interview (8)	X																	

a. End of study intervention includes both end of IMP treatment ('end of treatment') and end of lifestyle intervention b. Demography consists of date of birth, sex, ethnicity, and race (according to local regulation); c. For all female participants; d. Smoking is defined as smoking at least one cigarette or equivalent daily

2 Introduction

2.1 Study rationale

The prevalence of obesity has reached epidemic proportions in most countries around the world and continues to increase.[1-7] Obesity is currently considered one of the most significant public health challenges worldwide due to its substantial medical, societal and economic impact.[1, 6, 7, 28-30] Obesity increases the risk of developing cardiovascular disease and certain types of cancers, which are some of the leading causes of early death in these patients.[31, 32] In addition, obesity is a well-established risk factor for other serious conditions including, but not limited to, T2D, hypertension, dyslipidaemia, obstructive sleep apnoea, osteoarthritis, urinary incontinence, asthma and non-alcoholic steatohepatitis.[33-48] Obesity also significantly impacts health-related quality of life.[49, 50]

The risk of obesity-related complications and comorbidities increases with increasing BMI, and a weight loss of 5−10% has significant health benefits by improving obesity-related comorbidities including slowing progression to T2D, and improving physical symptoms and quality of life.[8-14] Studies suggest a beneficial impact of weight loss on cardiovascular risk and mortality in people with obesity, with or without T2D.[48, 51, 52]

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.[15-25] Bariatric surgery offers an effective alternative for some people with severe obesity, but carries a risk in connection with the procedure and for complications afterwards, and requires close follow-up which can be cumbersome and costly.[15-20, 53, 54]

Pharmacotherapy may serve as a valuable alternative to bariatric surgery as a supplement to lifestyle intervention to achieve and sustain a clinically relevant weight loss. Currently, only few pharmacological options are approved for weight management. Furthermore, some are only indicated for short term use whereas others are associated with significant adverse effects.

Collectively, there is a clear unmet medical need for a convenient, efficacious, and safe weight-lowering drug with beneficial effects on obesity-related comorbidities. The GLP-1 RA drug class is associated with multiple benefits; they have a well-documented safety profile, reduce body weight, improve blood pressure, lipid profile and other cardiovascular risk factors as well as glucose metabolism.

Most studies that examine the risk of adverse health associated with obesity have been based on data from Europe or the United States. However, the increased health risks associated with obesity occur in people with lower BMIs in the Asia Pacific region. The Nurses' Health Study found that after 20 years, at a given BMI, the risk of developing T2D in Asian women was more than double that of Caucasian women.[55] Similarly, compared with Caucasians, people of Asian descent with a BMI 25.0−29.9 kg/m^2 have been shown to have a significantly elevated all-cause mortality risk.[56] This has supported calls by obesity researchers for lower BMI cut-offs for overweight and obesity in Asian populations than those in the international WHO classification.[26, 27] The WHO has proposed a BMI classification for the Asia-Pacific region with lower cut-offs for overweight (≥ 23 kg/m^2) and obesity (≥ 25 kg/m^2) compared to those in the original WHO criteria, as these were mainly based on data from Europe and the United States.[57-59] Furthermore, according to the WHO

recommendations for the Asia-Pacific region, pharmacotherapy is to be considered at BMI ≥ 25 kg/m^2.[58]

The present 44-week study is designed to show the reduction in body weight and compare the efficacy and safety of semaglutide subcutaneous (s.c.) once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in people from Republic of Korea and Thailand with obesity, defined as BMI ≥ 25.0 kg/m^2. Thus, the study will provide more information about the efficacy and safety of semaglutide s.c. 2.4 mg once weekly in people of Asian descent with obesity as defined by regional guidelines.

2.2 Background

2.2.1 Semaglutide

Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA), approved for the treatment of T2D in adults (Ozempic®), which is currently under development by Novo Nordisk for the treatment of weight management at higher doses. Semaglutide has a half-life of approximately 160 hours, making it suitable for once-weekly dosing.[60]

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.[61] In line with this, clinical and non-clinical data indicate that the body weight-reducing effect of semaglutide is mainly mediated by a reduced energy intake.[62-68]

A global phase 3a clinical development programme with semaglutide s.c. 2.4 mg once weekly has been completed (STEP programme), having enrolled approximately 4,500 adults with overweight or obesity. The programme consists of four studies (NN9536-4373, NN9536-4374, NN9536-4375 and NN9536-4376). The 68-week phase 3a weight management studies STEP 1 (NN9536-4373) and STEP 2 (NN9536-4374) have demonstrated clinically significant weight loss with semaglutide s.c. 2.4 mg once weekly. In STEP 1, 1,961 participants with overweight or obesity were included. At week 68, participants in the semaglutide s.c. 2.4 mg once-weekly group achieved an average weight loss of 14.85% compared to 2.41% in the placebo group. In STEP 2, 1,210 participants with overweight or obesity and T2D were included. At week 68, participants in the semaglutide s.c. 2.4 mg once-weekly group achieved an average weight loss of 9.64% compared to 3.42% in the placebo group. In both studies, semaglutide s.c. 2.4 mg once weekly appeared to have a safe and well-tolerated profile, consistent with previous findings.

A comprehensive review of results from the non-clinical and clinical studies of semaglutide can be found in the current edition of the investigator's brochure (IB) and any updates hereof.[69]

The study population will consist of participants from Republic of Korea and Thailand with obesity diagnosed according to local guidelines, with BMI ≥ 25 kg/m^2. Studies have shown that people of Asian descent experience co-morbidities at a lower BMI than what is observed in people of other ethnic origins.[55, 56, 70-73] These participants 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.

First line treatment in weight management should always be lifestyle modification through a reduced calorie diet and increased physical activity. Thus, only participants who have tried but failed a dietary weight loss intervention will be included in accordance with regulatory and clinical guidelines.

2.3 Benefit-risk assessment

The main benefits and risks related to participation in the study are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of semaglutide may be found in the investigator's brochure.[69]

2.3.1 Risk assessment

Table 2-1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention (semaglutide 2.4 mg)		
Gastrointestinal adverse events	Consistent with findings with other GLP-1 RAs, the most frequently reported AEs in clinical studies with semaglutide were gastrointestinal AEs (such as nausea, vomiting and diarrhoea). In general, these reactions are mild or moderate in severity, of short duration, and dose-dependent. In participants treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating participants with impaired renal function as it may cause a deterioration of renal function.	Clinical studies have shown that a low starting dose and gradual dose escalation mitigates the risk of developing gastrointestinal symptoms. Participants with GI symptoms are recommended to drink plenty of fluids to avoid volume depletion.
Cholelithiasis	Events of cholelithiasis were the most frequently reported gallbladder events in the clinical development programme for semaglutide 2.4 mg for weight management. In the phase 3a studies cholelithiasis was reported in 1.6% and led to cholecystitis in 0.6% of participants treated with semaglutide 2.4 mg.	If cholelithiasis is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.
Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 RA drug class. The frequency of adjudication-confirmed acute pancreatitis reported in phase 3a clinical studies was 0.2% for semaglutide 2.4 mg and <0.1% for placebo, respectively.	Participants should be informed of the characteristic symptoms of acute pancreatitis and if pancreatitis is suspected, semaglutide should be discontinued. If confirmed, semaglutide should not be restarted.
Medullary thyroid cancer (MTC) (based on non-clinical data)	Thyroid C-cell tumours were seen in the mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. No hyperplasia was observed in monkeys after 52 weeks exposure up to 13-fold above the clinical plasma exposure at 2.4 mg/week. The GLP-1 receptor is not expressed in the normal human thyroid, and therefore the clinical relevance of the findings is considered to be low.	To mitigate this risk, participants with a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2) are excluded from clinical studies with semaglutide.

Pancreatic cancer	There is currently no support from non-clinical studies, clinical studies, or post-marketing data that GLP-1 RA-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies.	Participants with a history of malignant neoplasms within the past 5 years prior to screening will be excluded from the study.
Neoplasms (malignant and non-malignant)	People with overweight or obesity as well as people with T2D, have an increased risk of certain types of cancer. There is no evidence from clinical trials that GLP-1-based therapies increase the risk of neoplasms. No imbalance was observed in the semaglutide 2.4 mg for weight management phase 3a trials with regards to the proportions of participants with neoplasms (malignant and non-malignant). However, in the semaglutide s.c. as well as oral semaglutide phase 3a trials for T2D, the proportion of participants with neoplasms (malignant and non-malignant) were slightly higher with semaglutide than with comparator. The number of participants exposed to semaglutide s.c. or oral semaglutide for a longer period is considered insufficient for a thorough assessment of the risk of neoplasms.	Participants with a history of malignant neoplasms within the past 5 years prior to screening will not be enrolled in this study. Basal and squamous cell skin cancer and any carcinoma *in situ* is allowed.
Allergic reactions	As is the case with all protein-based pharmaceuticals, treatment with semaglutide may evoke allergic reactions, including serious allergic reactions such as angioedema and anaphylactic reactions.	As a precaution, participants with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this study. In addition, participants will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the study product occurs.
Risk of COVID-19 infection in relation to study intervention	Available data does not suggest an increased risk of infection or a more severe progression of infection when treated with s.c. semaglutide.	Detailed information about the known risks for s.c. semaglutide can be found in the investigator's brochure and summary of product characteristics.
Study procedures		
Venous laboratory samples drawn at screening and selected visits may be associated with slight discomfort and complicated by bruising in the region.		
Risk of COVID-19 infection in relation to study participation	Participants may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country.	To minimize the risk as much as possible, local guidelines must be followed.
Other		
Pregnancy and fertility (based on non-clinical data)	Studies in animals have shown reproductive toxicity. There is limited data from the use of semaglutide in pregnant women.	Semaglutide should not be used during pregnancy.

		Women of childbearing potential are required to use highly effective contraceptive methods when participating in this study (Appendix 4, Table 10-2). If a participant wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued (please refer to protocol Section 7 for further guidance). The effect of semaglutide on fertility in humans is unknown.

Risk assessment has been conducted for PDS290 for semaglutide 2.4 mg in compliance with ISO 14971: 2019. A study-specific device risk assessment has been performed to ensure safe and accurate handling and dosing of semaglutide 2.4 mg when using PDS290 in participants with overweight and obesity.

All identified risks (see Table 2-1) associated with using PDS290 for semaglutide 2.4 mg according to the clinical procedures specified in this protocol have been reduced as far as possible and are acceptable, taking into account the current state of the art. The use of PDS290 for semaglutide 2.4 mg in this study it therefore considered to be of non-significant risk.

2.3.2 Benefit assessment

Participants 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 study. The 68-week phase 3a weight management studies, STEP 1 (NN9536-4373) and STEP 2 (NN9536-4374), have demonstrated clinically significant weight loss with semaglutide s.c. 2.4 mg once weekly. In both studies, semaglutide s.c. 2.4 mg once weekly appeared to have a safe and well-tolerated profile, consistent with previous findings.

In addition, it is expected that all participants will benefit from participation through close contact with the study site and counselling by a dietician or a similar qualified healthcare professional, all of which will most likely result in intensified weight management. It is anticipated that all participants will benefit from participation, but the effect will be greater in participants randomised to semaglutide compared to placebo.

2.3.3 Overall benefit-risk conclusion

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

Taking into account the measures taken to minimise risk to participants participating in this study, the potential risks identified in association with semaglutide s.c. 2.4 mg once-weekly are justified by the anticipated benefits that may be afforded to participants with obesity

More detailed information about the known and expected benefits and risks and expected AEs of semaglutide s.c. may be found in the IB[69] and any updates hereof.

3 Objectives, endpoints and estimands

The study endpoints are listed in Table 3-1 by their association to the objectives.

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
• To demonstrate the superiority of semaglutide s.c. 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity, classified as BMI ≥ 25 kg/m^2 according to local guidelines in Republic of Korea and Thailand on: • Body weight • ≥5% weight reduction	**Co-primary:**		
	Change in body weight	From baseline (week 0) to end of treatment (week 44)	%
	≥5% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 44)	Count of participant
	Confirmatory secondary:		
	≥10% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 44)	Count of participant
	≥15% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 44)	Count of participant
	Change in waist circumference	From baseline (week 0) to end of treatment (week 44)	cm
	Supportive secondary:		
	≥20% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 44)	Count of participant
	Change in body weight	From baseline (week 0) to end of treatment (week 44)	kg
	Change in body mass index	From baseline (week 0) to end of treatment (week 44)	kg/m^2
Secondary	**Title**	**Time frame**	**Unit**
• To compare the efficacy of semaglutide s.c. 2.4 mg once weekly versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity, classified as BMI ≥ 25 kg/m^2 according to local guidelines in Republic of Korea and Thailand, on cardiovascular risk factors	**Supportive secondary:**		
	Change in systolic blood pressure	From baseline (week 0) to end of treatment (week 44)	mmHg
	Change in diastolic blood pressure	From baseline (week 0) to end of treatment (week 44)	mmHg
	Change in total cholesterol	From baseline (week 0) to end of treatment (week 44)	mg/dL and mmol/L
	Change in high-density lipoprotein (HDL) cholesterol	From baseline (week 0) to end of treatment (week 44)	mg/dL and mmol/L
	Change in low-density lipoprotein (LDL) cholesterol	From baseline (week 0) to end of treatment (week 44)	mg/dL and mmol/L
	Change in triglycerides	From baseline (week 0) to end of treatment (week 44)	mg/dL and mmol/L
	Change in high-sensitivity c-reactive protein (hsCRP)	From baseline (week 0) to end of treatment (week 44)	mg/L

Objectives	Endpoints		
	Exploratory:		
	Change in use of antihypertensive medication (decrease/no change/increase)	From baseline (week 0) to end of treatment (week 44)	Count of participant
	Change in use of lipid-lowering medication (decrease/no change/increase)	From baseline (week 0) to end of treatment (week 44)	Count of participant
• To compare the efficacy of semaglutide s.c. 2.4 mg once weekly versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity, classified as BMI ≥ 25 kg/m^2 according to local guidelines in Republic of Korea and Thailand, on glucose metabolism	**Supportive:**		
	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 44)	% and mmol/mol
	Exploratory:		
	Shift in glycaemic status (normo-glycaemic/pre-diabetes/T2D)	From baseline (week 0) to end of treatment (week 44)	Count of participant

End of treatment (week 44) corresponds to end of study intervention.

Co-primary estimands

The primary clinical question of interest is: What is the treatment effect of semaglutide s.c. 2.4 mg once weekly as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity defined according to local guidelines in Republic of Korea and Thailand, measured by relative change from baseline (week 0) to week 44 in body weight and ≥ 5% body weight reduction at week 44, regardless of discontinuation or dose reduction of randomised trial product, and regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery).

The co-primary estimands differ only by endpoint and population level summary. The co-primary estimands are described by the following attributes:

Population: People of Asian descent with obesity defined as BMI ≥ 25.0 kg/m^2.

Endpoint: 1) relative change from baseline to week 44 in body weight and 2) ≥ 5% body weight reduction at week 44.

Treatment condition: the randomised treatment regardless of discontinuation or dose reduction of randomised trial product, and regardless of initiating other anti-obesity therapies (as defined above)

Remaining intercurrent events: none, all intercurrent events (discontinuation or dose reduction of randomised trial product and initiation of other anti-obesity therapies) are captured by the treatment condition attribute and handled by the treatment policy strategy.

Population-level summary: 1) difference in mean changes and 2) odds ratio between treatment conditions

Rationale for estimand: the co-primary estimands take into account both safety and efficacy and reflect clinical practice to the extent possible in a clinical study. The co-primary estimands are thus relevant to support regulatory decision-making.

Secondary estimand

The secondary estimands for both the confirmatory secondary and supportive secondary endpoints are similar to the co-primary estimands except for the endpoint attribute. For continuous endpoints, the secondary estimands for primary and secondary objectives are similar to the co-primary estimand for % weight change. For binary endpoints, the secondary estimands for primary and secondary objectives are similar to the co-primary estimand for ≥ 5% body weight reduction.

Additional estimand

An additional clinical question of interest for the primary objective is: what is the treatment effect of semaglutide s.c. 2.4 mg once weekly as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity defined according to local guidelines in Republic of Korea and Thailand, measured by relative change from baseline (week 0) to week 44 in body weight and ≥ 5% body weight reduction at week 44, had they remained on their randomised treatment for the entire planned duration of the study and not initiated any other anti-obesity therapies (weight management drugs or bariatric surgery).

The additional estimands differ only by endpoint and population level summary. The additional estimands are described by the following attributes:

Population: People of Asian descent with obesity defined as BMI ≥ 25.0 kg/m^2

Endpoint: 1) relative change from baseline to week 44 in body weight and 2) ≥ 5% body weight reduction at week 44.

Treatment condition: the randomised treatment if participants had adhered to the randomised trial product (regardless of dose reduction) for the entire duration of the study and not initiated any other anti-obesity therapies (as defined above). Further details on study interventions and concomitant medication can be found in Section 6.

Remaining intercurrent events: none, all intercurrent events (discontinuation or initiation of other anti-obesity therapies and dose reduction) are captured by the treatment condition attribute. Discontinuation or initiation of other anti-obesity therapies are handled by the hypothetical strategy. Dose reduction of randomised trial product is handled by the treatment policy strategy.

Population-level summary: 1) difference in mean changes and 2) odds ratio between treatment conditions

Rationale for estimand: The additional estimand aims at reflecting the treatment effect without the confounding effects of other anti-obesity therapies or trial product discontinuation.

A similar additional estimand also applies to all confirmatory and supportive secondary endpoints addressing the primary objective in the population.

4 Study design

4.1 Overall design

This is an interventional, multi-national, multi-centre, randomised, double-blind, placebo-controlled, two-armed, parallel group clinical study.

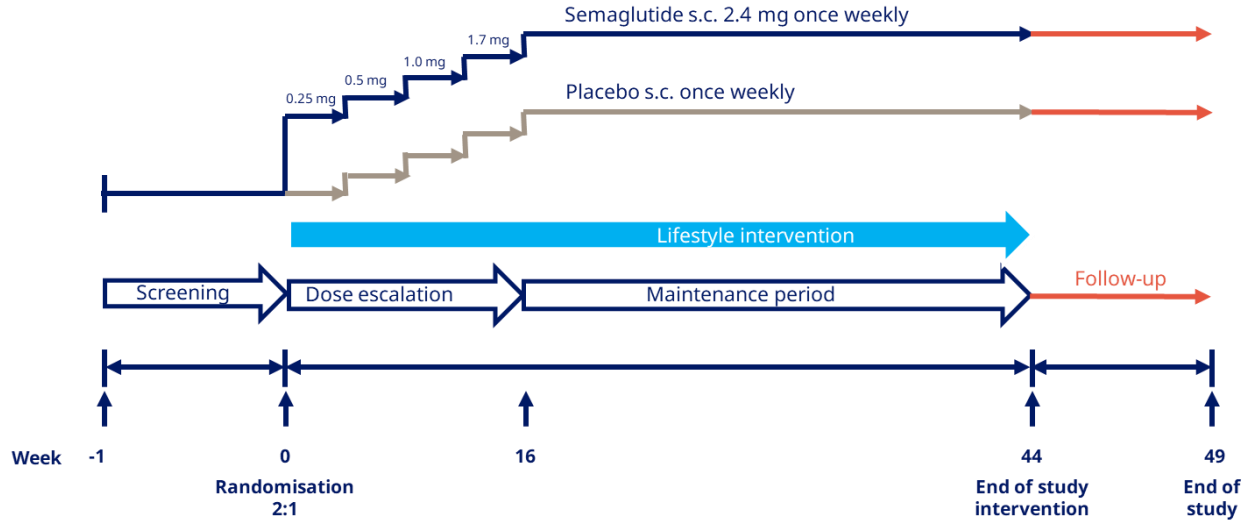
Approximately 150 eligible participants will be randomised in a 2:1 manner to receive either semaglutide s.c. 2.4 mg once weekly or placebo once weekly as an adjunct to a reduced-calorie diet and increased physical activity. The study population is participants of Asian descent with obesity, diagnosed according to local guidelines in Republic of Korea and Thailand.

The study consists of:

- a 1-week screening period
- a 16-week dose escalation period
- a 28-week maintenance period
- a 5-week follow-up period

The duration of the study intervention is 44 weeks with an additional 5 weeks follow-up (without trial product) (Figure 4-1).

Figure 4-1 Study design



Note: 'end of study intervention' (week 44) corresponds to both end of IMP treatment and end of lifestyle intervention.

4.2 Scientific rationale for study design

A 44-week study intervention duration (including 28 weeks on target dose) is considered sufficient to assess weight loss, safety, and tolerability. Results from STEP 1 has shown clinically significant weight loss with semaglutide s.c. 2.4 mg once weekly, already at 44 weeks.[74] The 5-week follow-up period is included to account for the exposure and long half-life of semaglutide.

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

The BMI inclusion criterion of ≥ 25.0 kg/m^2 is selected because it aligns with the recommended guidelines for the diagnosis and management of obesity in Republic of Korea[59] and the local practices in Thailand[75]. These Asian-specific BMI cut-offs for the diagnosis of obesity reflect recommendations from the WHO Western Pacific Region and evidence indicating that Asian individuals experience co-morbidities relating to obesity at a lower BMI compared to people of other ethnic origins.[55, 56, 70-73]

4.3 Justification for dose

Results from the phase 2 dose-finding study (NN9536-4153) showed that the semaglutide 0.4 mg once-daily dose was most effective in terms of weight loss while displaying an acceptable tolerability profile. Using population PK modelling, it was estimated that a once-weekly maintenance dose of 2.4 mg semaglutide will result in similar C_{max} at steady state as that obtained by the once-daily 0.4 mg semaglutide dose in study 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 68-week phase 3a weight management studies, STEP 1 (NN9536-4373) and STEP 2 (NN9536-4374), have demonstrated clinically significant weight loss with semaglutide s.c. 2.4 mg once weekly. In STEP 1, 1,961 participants with overweight or obesity were included. At week 68, participants in the semaglutide s.c. 2.4 mg once-weekly group achieved an average weight loss of 14.85% compared to 2.41% in the placebo group. In STEP 2, 1,210 participants with overweight or obesity and T2D were included. At week 68, participants in the semaglutide s.c. 2.4 mg once-weekly group achieved an average weight loss of 9.6% compared to 3.4% in the placebo group. In both studies, semaglutide s.c. 2.4 mg once weekly appeared to have a safe and well-tolerated profile, consistent with previous findings. A maintenance dose of semaglutide s.c. 2.4 mg once weekly in the Asian population is supported by the results from STEP 6 (NN9536-4382) with East Asian participants. With a mean baseline body weight of 87.5 kg, 86.9% of participants who were assigned semaglutide s.c. 2.4 mg, tolerated 2.4 mg at 52 weeks.

It is well known that to mitigate gastrointestinal side effects with GLP-1 RA treatment, dose escalation to the target dose is required. Based on experience from the semaglutide T2D development programme, a fixed-dose escalation regimen is selected, with dose escalation every 4 weeks until the target dose is reached. Participants will be initiated at a once-weekly dose of 0.25 mg and follow a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), until the target dose is reached after 16 weeks.

Please refer to Section 6.1 for more details on trial product doses. See Section 6.5 for dose modification.

4.4 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit (‘end of study’ according to the flowchart).

The primary endpoint is evaluated at visit 17 (week 44). The primary completion date (PCD) is defined as the date of visit 17 (week 44) on which the last participant in the clinical study has an assessment for the primary endpoint. If the last participant is withdrawn early, the PCD is considered the date when the last participant would have completed visit 17.

5 Study population

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

Pre-screening is defined as review of the participant medical records, including handing out participant information, as well as database review. Any pre-screening activities must be documented on site by the investigator.

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Male or female.
3. Age above or equal to 18 years at the time of signing informed consent.
4. BMI[1] $\geq$ 25.0 kg/m^2 at screening.
5. Both parents of Asian descent.[a]
6. History of at least one self-reported unsuccessful dietary effort to lose body weight.[a]

[1]BMI as calculated in the eCRF

For country-specific requirements, see Section 10.7.

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

1. HbA_{1c} $\geq$ 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.
4. Vaccination with approved COVID-19 vaccine within 30 days before screening.
5. A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records.
6. Treatment with any medication for the indication of obesity within the past 90 days before screening.
7. Any participant where a substantial weight loss, in the investigator's opinion, might jeopardise the participant's safety.
8. Uncontrolled thyroid disease as per investigator's discretion.
9. History of major depressive disorder within 2 years prior to screening.[a]
10. Diagnosis of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder).[a]
11. Previous or planned (during the study period) obesity treatment with surgery or a weight loss device. However, the following are allowed:
    a. Liposuction and/or abdominoplasty, if performed > 1 year before screening
    b. Adjustable gastric banding if the band has been removed > 1 year before screening
    c. Intragastric balloon if the balloon has been removed > 1 year before screening
    d. Duodenal-jejunal bypass liner (e.g. Endobarrier), if the liner has been removed > 1 year before screening.

12. History or presence of chronic pancreatitis.[a]
13. Presence of acute pancreatitis within 180 days prior to screening.[a]
14. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.[a]
15. Renal impairment with estimated Glomerular Filtration Rate (eGFR) < 15 mL/min/1.73 m^2 at screening.
16. Presence or history of malignant neoplasms (other than basal and squamous cell skin cancer, *in situ* carcinomas of the cervix, or *in situ* prostate cancer) within 5 years before screening.[a]
17. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 60 days prior to the day of screening.
18. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.
19. Surgery scheduled for the duration of the study, except for minor surgical procedures, in the opinion of the investigator.
20. Known or suspected abuse of alcohol or recreational drugs.
21. Use of any medication with unknown or unspecified content within 90 days before screening.
22. Known or suspected hypersensitivity to study intervention(s) or related products.
23. Previous participation in this study. Participation is defined as signed informed consent.
24. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using highly effective contraceptive method, as defined in Appendix 4 (Section 10.4).
25. Participation (i.e., signed informed consent) in any interventional, clinical study within 90 days before screening.
26. Other individual(s) from the same household participating in any semaglutide study.
27. Any disorder which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.

[a] As declared by the participant or reported in the medical records.

5.3 Lifestyle considerations

To ensure alignment of performance of assessments across participants and study sites, the below restrictions apply.

5.3.1 Meals and dietary restrictions

Not Applicable

5.3.2 Caffeine, alcohol, and tobacco

Participants should avoid caffeine and tobacco use at least 30 minutes prior to measuring the blood pressure.

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

5.4 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently eligible for participation according to the inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants

to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

A screen failure session must be made in the randomisation and trial supplies management system (RTSM).

Individuals who do not meet the criteria for participation in this study may not be rescreened. If the participant has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters, re-sampling is not allowed. However, in case of technical issues (e.g., haemolysed or lost samples), re-sampling is allowed for the affected parameter(s).

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

Not applicable for this study.

6 Study intervention(s) and concomitant therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. Diet and physical activity counselling is also regarded as study intervention.

Trial product comprise investigational medicinal products (IMPs), including placebo and comparators, non-investigational medicinal products (NIMPs) and/or investigational medical devices.

6.1 Study intervention(s) administered

Table 6-1 provides an overview of the study interventions.

Table 6-1 Study interventions

Intervention/Arm name	Semaglutide	Placebo	Any other interventions
Intervention name	Semaglutide B	Placebo	Diet and physical activity counselling
Intervention type	IMP	IMP, reference therapy	Background intervention
Pharmaceutical form	Solution for injection	Solution for injection	
Route of administration	Subcutaneous	Subcutaneous	
Trial product strength	See Table 6-2 for details.	See Table 6-2 for details.	
Dose and dose frequency	Dose: see Table 6-2 Dose frequency: once weekly	Dose: see Table 6-2 Dose frequency: once weekly	
Dosing instructions and administration	Once-weekly injection, at the same day of the week (to the extent possible) throughout the study. Injections may be administered in the thigh, abdomen, or upper arm, at any time of day irrespective of meals.	Once-weekly injection, at the same day of the week (to the extent possible) throughout the study. Injections may be administered in the thigh, abdomen, or upper arm, at any time of day irrespective of meals.	
Sourcing	Manufactured and supplied by Novo Nordisk A/S.	Manufactured and supplied by Novo Nordisk A/S.	
Packaging and labelling	• Labelled and packaged by Novo Nordisk A/S • Labelled in accordance with Annex 13,[76] local regulations and study requirements • IMP is provided in a PDS290 pen-injector (device constituent of non-approved drug-device combination product[76]) (see Table 6-2).	• Labelled and packaged by Novo Nordisk A/S • Labelled in accordance with Annex 13,[76] local regulations and study requirements • IMP is provided in a PDS290 pen-injector (see Table 6-2).	

The investigator must document that directions for use was given to the participant verbally and in writing as a direction for use (DFU) document at the first dispensing visit (as specified in the flowchart).

Investigational medicinal products (IMP)

All trial products listed in Table 6-2 are considered IMPs.

Table 6-2 Investigational medicinal products

Trial product name	Dose	Volume	Value shown in dose counter*	Duration
Dose escalation period				
Semaglutide 0.68 mg/mL or placebo, PDS290	0.25 mg	0.37 mL	37*	4 weeks
Semaglutide 1.34 mg/mL or placebo, PDS290	0.5 mg	0.37 mL	37*	4 weeks
Semaglutide 1.34 mg/mL or placebo, PDS290	1.0 mg	0.75 mL	75*	4 weeks
Semaglutide 2.27 mg/mL or placebo, PDS290	1.7 mg	0.75 mL	75*	4 weeks
Maintenance period				
Semaglutide 3.2 mg/mL or placebo, PDS290	2.4 mg	0.75 mL	75*	28 weeks

* Conversion to dose is calculated based on 0.01 mL/value for all strengths of semaglutide.

Dose escalation

- Participants will be initiated at a once-weekly dose of 0.25 mg and follow a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), until the target dose is reached after 16 weeks (Table 6-2). All participants should aim at reaching the recommended target dose of semaglutide 2.4 mg once weekly, or placebo.
- If a participant does not tolerate the recommended target dose of 2.4 mg once weekly, the participant may stay at a lower dose level. This should only be allowed if the participant would otherwise discontinue trial product completely and if considered safe to continue trial product, as per the investigator's discretion. It is recommended that the participant makes at least one attempt to re-escalate to the recommended target dose of 2.4 mg once weekly, as per the investigator's discretion.
- It is recommended that the investigator consults Novo Nordisk in case of persistent deviations from the planned escalation regimen.
- A dose reminder card will be handed out to the participants at each site visit during the escalation period. Once the target dose has been reached, the dose reminder card is only handed out as needed.

Missed dose(s)

- 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 participant 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 participant should be encouraged to re-commence the trial product if considered safe as per the investigator's discretion and if the participant does not meet any of the discontinuation criteria (Section 7.1). The starting dose for re-initiation of trial product is at the investigator's discretion. In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk medical experts.

Other study intervention(s)

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

Calculation of estimated total energy expenditure

The TEE is calculated by multiplying the estimated Basal Metabolic Rate (BMR) (see Table 6-3) with a Physical Activity Level value of 1.3.[77]

$$TEE = BMR \times 1.3$$

Table 6-3 Equation for estimated BMR

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

Dose adjustment

If a participant with a BMI[1] within the lower normal range continues to lose weight, and there is a health concern, the investigator must consider reducing the dose of IMP. The investigator can contact Novo Nordisk for guidance. If the participant reaches a BMI[1]<18.5 kg/m2, the dose of IMP must be reduced and Novo Nordisk should be contacted for guidance.

[1]BMI as calculated in the eCRF

Auxiliary supplies including medical device(s) not under investigation

Auxiliary supplies will be provided in accordance with the trial materials manual (TMM) and Table 6-4.

Table 6-4 Auxiliary supplies provided by Novo Nordisk A/S

Auxiliary supply	Details
Direction for use (DFU)	DFU for PDS290 pre-filled pen-injector. Not included in the dispensing unit and to be handed out separately.
Needles	Needles for pre-filled pen system. Details provided in the TMM. Only needles approved and provided by Novo Nordisk and with a maximum length of 6 mm must be used for administration of trial product.

Information about the PDS290 pen-injector may be found in the IB[69] and any updates hereof. Information about the use of the drug-device combination products can be found in the DFU.

Training in the PDS290 pen-injector

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

The following should be emphasised during training of participants:

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

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

The first dose of trial product must be taken on the day of randomisation (visit 2) at the clinical site by self-administration under supervision by trained site staff.

6.2 Preparation, handling, storage and accountability

Only participants enrolled in the study may use study intervention and only delegated site staff may supply or administer study intervention.

Each site will be supplied with sufficient trial product for the study on an ongoing basis according to recruitment and randomisation.

For selected countries and if permitted by local regulations, the investigator may offer to send trial product from the study site or pharmacy to the participant's home by courier service. The process for sending trial product from the study site or pharmacy to a participant's home is described in the "Study site/pharmacy instruction for shipment of trial product to participants' 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 study site or pharmacy staff to the courier, required

temperature monitoring of trial product, delivery to and receipt of trial product by the participant. The process for returning trial product to the study site or pharmacy by courier is also described in this document. Investigators, study site/pharmacy staff and participants who will be involved in shipment of trial product to the participant's home will be adequately trained in this process.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.

All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.

The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any participant before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the Trial Materials Manual (TMM).

The investigator or designee is responsible for trial product accountability and record maintenance (i.e., receipt, accountability and final disposition records). Drug accountability is performed on item level by using the RTSM.

The investigator or designee must instruct the participant in what to return at next visit (see flowchart Section 1.2). The participant must return all used and unused trial product including empty packaging materials during the study as instructed by the investigator. Additional details regarding handling of drug accountability can be found in the Trial Materials Manual (TMM). The investigator or designee must instruct the participant on how to manage the in-use time of the dispensed products.

Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.

All returned, expired or damaged trial products (for technical complaint samples, see Appendix 5 [Section 10.5]) must be stored separately from non-allocated trial products. No temperature monitoring is required.

Non-allocated trial products, including expired or damaged products, must be accounted as unused, at the latest at closure of the site.

6.3 Measures to minimise bias: Randomisation and blinding

All participants will be screened and centrally randomised using the RTSM and assigned to the next available trial product according to the randomisation schedule. Trial product will be allocated by the RTSM and dispensed by the investigator at the study visits summarised in the flowchart.

This is a double-blind study in which participants, care providers, investigators and outcome assessors are blinded to trial product allocation.

The RTSM is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention is warranted. Participant safety must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Novo Nordisk prior to unblinding a participant's study intervention unless this could delay emergency treatment of the participant.

If a participant's trial product is unblinded, Novo Nordisk (Global Safety department) must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation. The person breaking the blind must print the blind break confirmation notification generated by the RTSM, sign and date the document. If RTSM is not accessible at the time of blind break, the RTSM helpdesk should be contacted. Contact details are listed in Attachment I.

Participant will continue on trial product if there are no safety concerns at the discretion of the investigator.

6.4 Study intervention compliance

Trial product treatment compliance

Throughout the study, the investigator will remind the participants to follow the study procedures and requirements to encourage participant compliance. Treatment compliance will be assessed by monitoring of drug accountability and by discussing treatment compliance and dosing conditions with the participant. If a participant is found to be non-compliant the investigator will remind the participant of the importance of following the instructions given, including taking the trial products as prescribed.

When participants self-administer trial product at home, compliance with trial product administration will be assessed, and the assessment documented in source documents at each visit where information is available. The participant will be asked about date of first dose information about missed doses, if any, and current treatment dose at every visit. Information on treatment dose and periods > 14 days without treatment will be recorded in the CRF. If any suspicion of non-compliance arises, the site must enter into a dialogue with the participant, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented.

Trial product start and stop dates will be recorded in the CRF.

6.5 Dose modification

Not applicable for this study. Please refer to Section 6.1 for description of missed dose(s) and for recommended action if participants' BMI falls into the normal range.

6.6 Continued access to study intervention after end of study

There is no intervention following the end of the study. When discontinuing study intervention, the participant should be transferred to a suitable marketed product at the discretion of the investigator.

6.7 Treatment of overdose

Overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical studies. The most commonly reported AE was nausea. All participants recovered without complications.

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

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

In the event of an overdose, the investigator should closely monitor the participant for overdose-related AEs/SAEs. 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 participant.

For more information on overdose, also consult the current version of the semaglutide investigator's brochure (IB).[69]

6.8 Concomitant therapy

Any medication or vaccine (including over-the-counter or prescription medicines) that the participant is receiving at the time of the first visit or receives until end of study must be recorded along with:

- Trade name or generic name
- Dose (unit) and dosing frequency
- Primary indication
- Dates of administration including start and stop dates

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

7 Discontinuation of study intervention and participant discontinuation/withdrawal

Discontinuation of specific sites or of the study as a whole is detailed in Appendix 1 (Section 10.1.11).

7.1 Discontinuation of study intervention

Study intervention may be discontinued at any time during the study at the discretion of the participant or at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

The end-of-study visit (visit 18) is scheduled approximately 5 weeks after end of study intervention to ensure the safety of the participant. If the participant has discontinued trial product > 5 weeks prior to the 'end of treatment' visit, and the requirements for the follow-up period prior to the end-of-study visit are fulfilled, then the end-of-study visit can be omitted.

Efforts must be made to have participants attend and complete all scheduled visit procedures. Only participants who withdraw consent will be considered as withdrawn from the study. Participants must be informed about the continued scientific importance of their data, even if they discontinue study intervention.

If the participant 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 participant 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 study' visit.

The trial product must be discontinued, if any of the following applies for the participant:
1. Safety concern as judged by the investigator
2. Suspicion of pancreatitis
3. Pregnancy
4. Intention of becoming pregnant
5. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study

If acute pancreatitis is suspected, appropriate actions should be initiated, including local measurements of amylase and lipase (see Appendix 3 [Section 10.3.3] for reporting).

Participants meeting trial product discontinuation criterion no. 2 are allowed to resume trial product at the investigator's discretion if the Atlanta criteria[78] are not fulfilled and thus, the suspicion of acute pancreatitis is not confirmed. Trial product may be resumed for participants with a gallstone-induced pancreatitis in case of cholecystectomy.

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

See the flowchart for data to be collected at the time of trial product discontinuation (early discontinuation visit) and follow-up and for any further evaluations that need to be completed.

The primary reason for discontinuation of trial product must be specified in the CRF, and final trial product accountability must be performed. A treatment discontinuation must be made in the RTSM.

7.1.1 Temporary discontinuation of study intervention

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

In such cases a treatment discontinuation should not be made in the RTSM.

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

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

7.2 Participant discontinuation/withdrawal from the study

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

If a participant withdraws consent or is withdrawn by the investigator prior to randomisation, he/she will not be asked to have any follow-up assessments performed. The following data must be collected: Demography, eligibility criteria, date of informed consent, date of screening and the date when participant’s participation ended. The end of study form must be completed.

If a participant withdraws consent or is withdrawn by the investigator after randomisation, the investigator must ask the participant if he/she is willing, as soon as possible, to have assessments performed according to visit 17 (end of treatment). See the flowchart (Section 1.2) for data to be collected.

Final trial product accountability must be performed even if the participant is not able to come to the site. A treatment discontinuation must be made in the RTSM.

If the participant withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent for the purpose of the study or scientific research.

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

Although a participant 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 participant’s rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the CRF.

7.2.1 Replacement of participants

If a participant discontinues study intervention, withdraws consent or is withdrawn by the investigator, he/she will not be replaced.

7.3 Lost to follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, at least three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's source document.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.

8 Study assessments and procedures

The following sections describe the assessments and procedures, while their timing is summarised in the flowchart.

Informed consent must be obtained before any study-related activity, see Appendix 1 (Section 10.1.3).

All screening evaluations must be completed and reviewed to confirm that potential participants meet all inclusion criteria and none of the exclusion criteria.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reason for screen failure, as applicable.

At screening, participants will be provided with a card stating that they are participating in a study and giving contact details of relevant site staff that can be contacted in case of emergency.

Adherence to the study design requirements, including those specified in the flowchart, is essential and required for study conduct.

Review of laboratory reports must be documented in the source documents or the participant's medical record. If clarification of entries or discrepancies in the PK diary is needed, the participant must be questioned, and a conclusion made in the participant's source documents. Care must be taken not to bias the participant.

Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 (Section 10.2) for further details on laboratory samples.

Assessments should be carried out according to the clinic's standard of practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments. The suggested order of the assessments:

1. Vital signs (see Section 8.2.2) and body measurements (see Section 8.1.1)
2. Blood samples
3. Other assessments

Results of pregnancy testing must be documented in the participant's medical records.

For participants receiving antihypertensive or lipid-lowering treatment, the investigator should evaluate changes in the participants' treatment intensity within each therapeutic area. The evaluation should be based on whether an overall change in treatment intensity 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.

Participants must receive training in how to collect dosing information prior to PK sampling in a designated paper diary (PK diary) to be handed out as outlined in the flowchart. See Section 8.4.1 for a description of the data to be entered in the PK diary.

The barriers and motivation interview identifies barriers to and motivation for lifestyle change and compliance with the protocol. The interview will be conducted at screening to assist in identifying subjects who are unable or unwilling to comply with protocol procedures as per the exclusion criteria. In addition, the interview will ensure that any minor barriers are addressed during lifestyle counselling. The results of the interview will not be entered into the CRF. It will be at the investigator's discretion to evaluate the motivation of the participant and related eligibility.

8.1 Efficacy assessments

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

8.1.1 Body measurements

Body weight must be measured at all site visits without shoes, with an empty bladder and only wearing light clothing. Body weight must be measured on a digital scale and recorded in kilograms or pounds (one decimal) using the same scale throughout the study. The scale must be calibrated according to manufacturer's recommendation or local requirements – the strictest requirement must be followed.

Height is measured without shoes in centimetres or inches (one decimal). BMI will be calculated in the eCRF at each clinic visit based on height at screening and body weight at the clinic visit. BMI calculated in the eCRF at screening must be in agreement with inclusion criterion no. 4 and thus verified after entry of screening results in the eCRF.

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 participant should be asked to breathe normally. The same measuring tape should be used throughout the study. The measuring tape will be provided by Novo Nordisk to ensure standardisation.

8.1.2 Clinical efficacy laboratory assessments

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

8.2 Safety assessments

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

Medical history is a medical event that the participant experienced prior to the time point from which AEs are collected. Only relevant and significant medical history as judged by the investigator should be recorded. Findings of specific medical history should de described in designated forms.

As part of the medical history, information related to history of gallbladder disease, breast neoplasm, colon neoplasm, skin cancer, and psychiatric disorder will be recorded. Information on weight related co-morbidities will be collected as part of medical history at screening (visit 1) and an evaluation will be done at the end of study intervention (visit 17). Follow-up questions related to the breast neoplasm and colon neoplasm will be asked at the end of study visit.

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

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

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

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

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 (see Appendix 3, Section 10.3) during the study and any clinically significant worsening from baseline must be reported as an AE (see Section 8.3).

8.2.1 Physical examinations

A physical examination will include assessments of the cardiovascular, respiratory, gastrointestinal, neurological system and skin.

A physical examination will include assessments of:

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

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

8.2.2 Vital signs

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

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

However, as a minimum:

- Blood pressure (diastolic and systolic) and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., no use of television, cell phones).
- Blood pressure and pulse rate measurements will be assessed sitting with a completely automated device. Manual techniques must be used only if an automated device is not available.

Blood pressure and pulse rate are collected at visit 1 (screening), visit 2 (week 0), visit week 4 (week 4), visit 8 (week 12), visit 11 (week 20), visit 13 (week 28), visit 15 (week 36) and visit 17 (week 44, end of treatment).

8.2.3 Clinical safety laboratory assessments

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

8.2.4 Pregnancy testing

Urine pregnancy tests provided by central laboratory must be performed for women of childbearing potential at screening and as specified in the flowchart.

Woman of childbearing potential (WOCBP) should only be included after a negative, highly sensitive urine pregnancy test (refer to Appendix 2, Section 10.2).

Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.

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

8.2.5 Surgical procedures assessment

While enrolled in this study, participants are not encouraged to commence other anti-obesity medication or bariatric surgery. However, if due to clinical reasons a participant does undergo bariatric surgery or knee surgery while enrolled in this study, the investigator should record this in the Procedures Form described below.

During site and/or phone visits marked in the Flowchart, the investigator should ask the participant if they have undergone the surgical procedures listed below, since their previous assessment. If the participant has undergone the procedure(s), the investigator should fill out the Procedures Form. A separate form should be filled out for separate procedures.

Bariatric surgery – including bariatric gastric balloon insertion/removal, duodenal-jejunal bypass sleeve therapy, endoscopic sleeve gastroplasty, gastric binding (includes laparoscopic adjustable gastric band), gastric band repositioning, gastric band reversal, gastric bypass, gastric bypass reversal or duodenal switch.

Knee surgery – including baker's cyst excision, joint debridement, revision arthroplasty, partial knee replacement or total knee replacement.

8.3 Adverse events and other safety reporting

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

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

Some AEs require additional data collection on a specific event form. The relevant event(s) are listed below in Table 8-1.

Table 8-1 AEs requiring additional data collection

Event type	AE requiring additional data collection
Medication error	X
Misuse and abuse	X
Acute pancreatitis	X
Acute gallbladder disease	X
Hepatic event	X
Malignant neoplasm	X

Definitions and reporting timelines for the events mentioned in the above table can be found in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE information

All AEs and SAEs must be collected from the first study-related activity after obtaining informed consent and until the end of study visit in accordance with the flowchart (Section 1.2) or whenever, within the above time period, the site becomes aware of an AE or SAE.

Conditions present prior to the timepoint from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or during other study-related procedures performed before exposure to study intervention under clinical investigation, will be recorded as medical history/concomitant illness.

AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3). All SAEs must be recorded and reported to Novo Nordisk within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has

been discontinued from/completed the study, and the investigator considers the event to be related to the IMP or related to study participation, the investigator must promptly notify Novo Nordisk.

8.3.2 Method of detecting AEs

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

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

8.3.3 Follow-up of AEs

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

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 study intervention under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR).

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

8.3.5 Pregnancy

Details of pregnancies in female participants will be collected after obtaining informed consent and until the end-of-study visit. For details regarding collection and reporting of pregnancy information, please refer to Appendix 4 (Section 10.4).

8.3.6 Cardiovascular and death events

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

8.3.7 Technical complaints

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

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

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

8.4 Pharmacokinetics and pharmacodynamics

8.4.1 Pharmacokinetics

Single blood samples for measuring plasma concentration of semaglutide will be drawn for both semaglutide and placebo participants on visits specified in the flowchart (Section 1.2).

The purpose of measuring plasma semaglutide levels is to perform population pharmacokinetic (Pop-PK) analyses. Having Pop-PK in this study will further support bridging of Pop-PK from studies conducted in other populations.

Samples will be used to evaluate the pharmacokinetics of semaglutide. Each plasma sample will be divided into 2 aliquots (e.g. one for PK and a backup) and may also be used to evaluate safety or efficacy aspects that address concerns arising during the study. Participant confidentiality will be maintained.

The PK dosing information from the PK diary (i.e. the actual dose of trial product (mg), the date and time of administration) should be transcribed into the CRF for the last 2 doses of trial product prior to the PK assessment as outlined in the flowchart.

The exact timing of obtaining the PK sample must be recorded on the laboratory form.

8.4.2 Pharmacodynamics

Not applicable for this study.

8.5 Genetics

Not applicable for this study.

8.6 Biomarkers

Not applicable for this study.

8.7 Immunogenicity assessments

Not applicable for this study.

8.8 Health economics

Not applicable for this study.

9 Statistical considerations

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

9.1 Statistical hypotheses

The tests of superiority of semaglutide s.c. 2.4 mg once weekly to placebo for the two primary and all confirmatory secondary endpoints are performed using a fixed-sequence statistical strategy and will be based only on analyses addressing the primary estimand. This strategy tests the endpoints using a predefined hierarchical order, all at the significance level of 5%, moving to test the next endpoint only after a statistically significant superiority result (p-value < 5%) on the previous endpoint.

For the co-primary estimands with the primary endpoints, 1) change in body weight (%) from baseline to end of treatment (week 44) and 2) ≥ 5% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44), the following confirmatory 1-sided hypotheses are planned to be tested for semaglutide s.c. 2.4 mg once weekly versus placebo. Let the mean difference in 1) be defined as:

μ_1 = ([semaglutide s.c. 2.4 mg] minus [placebo])

and let the odds ratio of 2) be defined as:

OR = (odds[semaglutide s.c. 2.4 mg] divided by odds[placebo])

Superiority

1) $H0_1 : \mu_1 \geq 0.0$ percentage points against $Ha_1 : \mu_1 < 0.0$ percentage points.

and

2) $H0_2 : OR \leq 1$ against $Ha_2 : OR > 1$

Operationally, the hypotheses will be evaluated by 2-sided tests.

9.1.1 Multiplicity adjustment

The type I error will be controlled in the strong sense using a hierarchical (fixed sequence) testing procedure. This is based on priority ordering of the null hypotheses and testing them in this order using the 2-sided 95% confidence interval approach until an insignificant result appears. For example, the second null hypothesis will only be tested if the first null hypothesis has been rejected in favour of semaglutide s.c. 2.4 mg.

The steps in the hierarchical testing procedure are as follows:

- Step 1: change in body weight (%) from baseline (week 0) to end of treatment (week 44) superiority of semaglutide s.c. 2.4 mg versus placebo
  and
  ≥ 5% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44) superiority of semaglutide s.c. 2.4 mg versus placebo
- Step 2: ≥ 10% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44) superiority of semaglutide s.c. 2.4 mg versus placebo
- Step 3: ≥ 15% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44) superiority of semaglutide s.c. 2.4 mg versus placebo
- Step 4: Change in waist circumference from baseline (week 0) to end of treatment (week 44) superiority of semaglutide s.c. 2.4 mg versus placebo

9.2 Analysis sets

For the purposes of analysis, the following analysis sets (Table 9-1) and observation periods (Table 9-2) are defined:

Table 9-1 Analysis sets

Participant Analysis Set	Description
Full analysis set (FAS)	All randomised participants. Participants will be included in the analyses according to the randomised intervention.
Safety analysis set (SAS)	All participants who are exposed to at least one dose of randomised IMP. Participants will be included in the analyses according to the intervention they actually received.

Table 9-2 Defined data point sets

Defined data point sets (DPS)	Description
In-trial (DPS1)	The time period where the participant is assessed in the study. The in-trial observation period for a participant begins on the date of randomisation and ends at the first of the following dates (both inclusive): • 'End of study' visit • withdrawal of consent • last contact with participant (for participants lost to follow-up) • death
On-treatment (DPS2)	The time period where participants are treated with trial product. A time-point is considered as "on-treatment" if any dose of trial product has been administered within the prior 2 weeks (14 days). The participant is considered "on-treatment" regardless of dose reduction. 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 and potential pregnancies, the lag time for each on-treatment time interval is 5 weeks (35 days).
On-treatment until first discontinuation of trial product or initiation of other anti-obesity therapies (DPS3)	The time period where participants are treated with trial product. A time-point is considered as "on-treatment" if any dose of trial product has been administered within the prior 2 weeks (14 days). The participant is considered "on-treatment" regardless of dose reduction. Observations after the first discontinuation of trial product or initiation of other anti-obesity therapies will not be included.

FAS and DPS1 are used to estimate the co-primary estimands and the secondary estimands for the primary and secondary objectives.

FAS and DPS3 are used to estimate the additional estimand for the primary objective and secondary objectives.

SAS and either DPS1 or DPS2 are used to present safety data.

The in-trial (DPS1) and on-treatment (DPS2) periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

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

9.3 Statistical analyses

9.3.1 General considerations

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

All tests are tests of superiority of semaglutide s.c. 2.4 mg once weekly to placebo. All estimated treatment contrasts between semaglutide s.c. 2.4 mg and placebo will be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

9.3.2 Primary estimands analysis

The co-primary endpoints are:

- Change in body weight (%) from baseline (week 0) to end of treatment (week 44)
- ≥ 5% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44)

The two primary analyses are aligned with the two co-primary estimands defined in Section 3.

The analysis model for change in body weight (%) will be a linear regression (ANCOVA) with randomised study intervention as factor and baseline body weight (kg) as covariate.

The analysis model for the 5% responder endpoint is a logistic regression using randomised study intervention as factor and baseline body weight (kg) as covariate.

All available data at week 44 are used and missing values at week 44 will be imputed and the endpoint will be derived from the imputed values. The imputation approach for the primary analysis is a multiple imputation similar to the one described by McEvoy et al.[79]. For participants in the semaglutide s.c. 2.4 mg once weekly and the placebo groups, missing measurements at week 44 for non-retrieved participants are imputed using assessments from retrieved participants in each intervention group. The timing of last available observation during the on-treatment period (LAO-OT) will be included in the imputation model as a continuous covariate. Missing measurements at week 44 for participants on randomised study intervention (at week 44) are imputed by sampling from available measurements at week 44 from participants on randomised study intervention in the relevant randomised intervention group. Details of the multiple imputation approach are provided in the SAP.

Sensitivity analyses

Jump to reference multiple imputation approach (J2R-MI): Missing values of body weight at week 44 for both the semaglutide 2.4 mg and placebo group are imputed by sampling among all available assessments at week 44 in the placebo group. This approach makes the assumption that participants instantly after discontinuation lose any effect of randomised treatment beyond what can be expected from placebo treatment as adjunct to reduced-calorie diet and increased physical activity. Details of the multiple imputation approach are provided in the SAP.

Tipping-point multiple imputation analysis (TP-MI): First, missing data are imputed according to the primary multiple imputation approach. Second, for the semaglutide 2.4 mg treatment arm a

penalty will be added to the imputed values at week 44. The approach is to gradually increase this penalty until all confirmed conclusions from the primary analysis are reversed. For each hypothesis tested the specific value of the penalty that reverses the conclusion will be used to evaluate the robustness of the primary analysis results. This sensitivity analysis evaluates the robustness of the superiority conclusions.

Non-retrieved participants as non-responders: For the 5% responder analysis an analysis using non-retrieved participants as non-responders in the logistic regressions will be done.

ANCOVA for unequal variances: An alternative analysis model for the change in body weight (%) similar to the primary analysis model (ANCOVA), but assuming unequal variances instead of equal variances. The analysis model includes randomised treatment as factor and baseline body weight (kg) as covariate.

Supplementary analyses

The following statistical analyses are designed to address the additional estimand for the primary endpoints.

The analysis model for change in body weight (%) will be a mixed model for repeated measurements (MMRM). The MMRM will be fitted using randomised study intervention as factor and baseline body weight (kg) as covariate all nested within visit. An unstructured covariance matrix for measurements within the same participant will be employed, assuming that measurements for different participants are independent.

The analysis model for the 5% responder endpoint is a logistic regression where any missing values at week 44 will be predicted from the MMRM. The predicted values will be used to classify each participant as 5% responder or not. This classification will then be analysed using a logistic regression model with randomised study intervention as factor and baseline body weight (kg) as covariate.

Week 44 assessments for retrieved drop-outs are not used in these analyses. The MMRM will use assessments only from participants who are taking the randomised study intervention until end of treatment or until first discontinuing of randomised study intervention or initiation of other anti-obesity therapies (weight management drugs or bariatric surgery).

9.3.3 Secondary estimands analysis

9.3.3.1 Confirmatory secondary estimands

The confirmatory secondary endpoints are:

- ≥10% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44)
- ≥15% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44)
- change in waist circumference from baseline (week 0) to end of treatment (week 44)

All confirmatory secondary endpoints will be analysed using the same analysis model and imputation approach as used to address the primary estimand for the primary endpoints.

The analysis model for change in waist circumference will be a linear regression (ANCOVA) with randomised study intervention as factor and baseline waist circumference as covariate.

The analysis model for the responder endpoints is a logistic regression using randomised study intervention as factor and baseline body weight (kg) as covariate.

Sensitivity analysis

For the change in waist circumference, a sensitivity analysis using jump to reference as imputation approach will be carried out. For both binary confirmatory secondary endpoints, a sensitivity analysis using non-retrieved participants as non-responders will be carried out.

Supplementary analysis

The confirmatory secondary endpoints will be analysed using the same analysis model as used to address the additional estimand for the primary endpoints.

The analysis model for change in waist circumference will be a mixed model for repeated measurements (MMRM). The MMRM will be fitted using randomised study intervention as factor and baseline waist circumference as covariate all nested within visit. An unstructured covariance matrix for measurements within the same participants will be employed, assuming that measurements for different participants are independent.

The analysis model for the responder endpoints is a logistic regression where any missing values at week 44 will be predicted from the MMRM. The predicted values will be used to classify each participant as a responder or not. This classification will then be analysed using a logistic regression model with randomised study intervention as factor and baseline body weight (kg) as covariate.

9.3.3.2 Supportive secondary estimands

Supportive secondary endpoints are listed in Section 3. For details on analyses of supportive secondary endpoints, please refer to the SAP.

9.3.4 Exploratory endpoints analysis

Exploratory endpoints are listed in Section 3. Exploratory endpoints will be summarised by descriptive statistics. For further details, please refer to the SAP.

9.3.5 Safety analyses

Adverse events will be summarised by descriptive statistics using the SAS. For further details, please refer to the SAP.

9.3.6 Other analyses

Please refer to the SAP for details.

Pharmacokinetic and/or pharmacodynamic modelling

Pop-PK and exposure-response analyses will be used as supportive evidence for the evaluation of efficacy and safety and further to support the recommended dose of semaglutide in people with obesity. First, plasma semaglutide concentrations will be analysed using a population

pharmacokinetic model, quantifying covariate (such as baseline body weight, age, gender, race, ethnicity and injection site) effects on semaglutide exposure. Second, model-based estimates of steady-state average concentrations will be derived for each participant to facilitate subsequent exposure-response analyses. Relevant efficacy and safety endpoints will be related to steady-state average concentrations and subjected to model-based analysis.

A modelling analysis plan will be prepared before first database lock. Individual drug concentration data will be tabulated in the CSR, and the results of the modelling will be included in a separate report.

9.4 Interim analysis

Not applicable.

9.5 Sample size determination

The study is designed with an effective power of > 95% to detect differences on the primary endpoints. The effective power was calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively which is a conservative approach. The power calculations for continuous endpoints are based on a t-test on the mean difference assuming equal variances, whereas those for the categorical endpoints are based on the Pearson chi-square test for two independent proportions.

Assumptions for these power calculations are presented in Table 9-3 and are based on findings from NN9536-4382 (STEP 6 East Asian study).

Based on the multinational study STEP 1, where 18.9% permanently discontinued trial product and on East Asian study STEP 6, where 6.0% permanently discontinued trial product, it is assumed that 13% of participants will discontinue trial product permanently before week 44. It is assumed that approximately 75% will be retrieved at week 44 which is similar to that observed in STEP 6 which however was of longer duration (68 weeks). All participants in the placebo arm are assumed to have same effect as participants who complete the study on placebo. Retrieved participants in the semaglutide s.c. 2.4 mg once-weekly arm are assumed to have an effect corresponding to half the treatment difference (compared to placebo) of participants who complete the study on semaglutide s.c. 2.4 mg once weekly. Non-retrieved participants in the semaglutide s.c. 2.4 mg once weekly arm are assumed to have an effect corresponding to placebo.

Based on data from the NN9536 global phase 3a studies, it is expected that <1% of participants will initiate other anti-obesity therapies, so the impact of this intercurrent event is expected to be negligible.

The impact of dose reduction is expected to be comparable to the effect in STEP 6 which is included in the assumed mean and proportions in Table 9-3.

Under these assumptions and a 2:1 randomisation ratio, a sample size of 150 participants randomised to either receive semaglutide s.c. 2.4 mg once weekly (100 participants) or placebo (50 participants) yields an effective power of > 95% for both primary endpoints and 81% power for all confirmatory endpoints.

Table 9-3 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number of 150 randomised participants

Order	Endpoint	Assumed mean (±SD) or proportion for completers		Expected mean (±SD) or proportion	Expected difference or proportion ratio	Marginal power (%)	Effective power (%)
		Semaglutide s.c. 2.4 mg once weekly	Placebo	Semaglutide s.c. 2.4 mg once weekly			
1	% body weight change	12.0 (±10)	3.0 (±10)	11.3 (±10)	8.3%-points	> 99	> 99
2	5% responders	75.8%	42.1%	73.2%	1.7	96	96
3	10% responders	57.9%	24.2%	55.1%	2.3	96	92
4	15% responders	38.2%	11.5%	35.9%	3.1	92	85
5	Change in waist circumference	10.0 (±10)	3.0 (±10)	9.4 (±10)	6.4	96	81

How the design assumptions in terms of the assumed mean and standard deviation of the % body weight change affect the power of the first four endpoints is shown in Table 9-4.

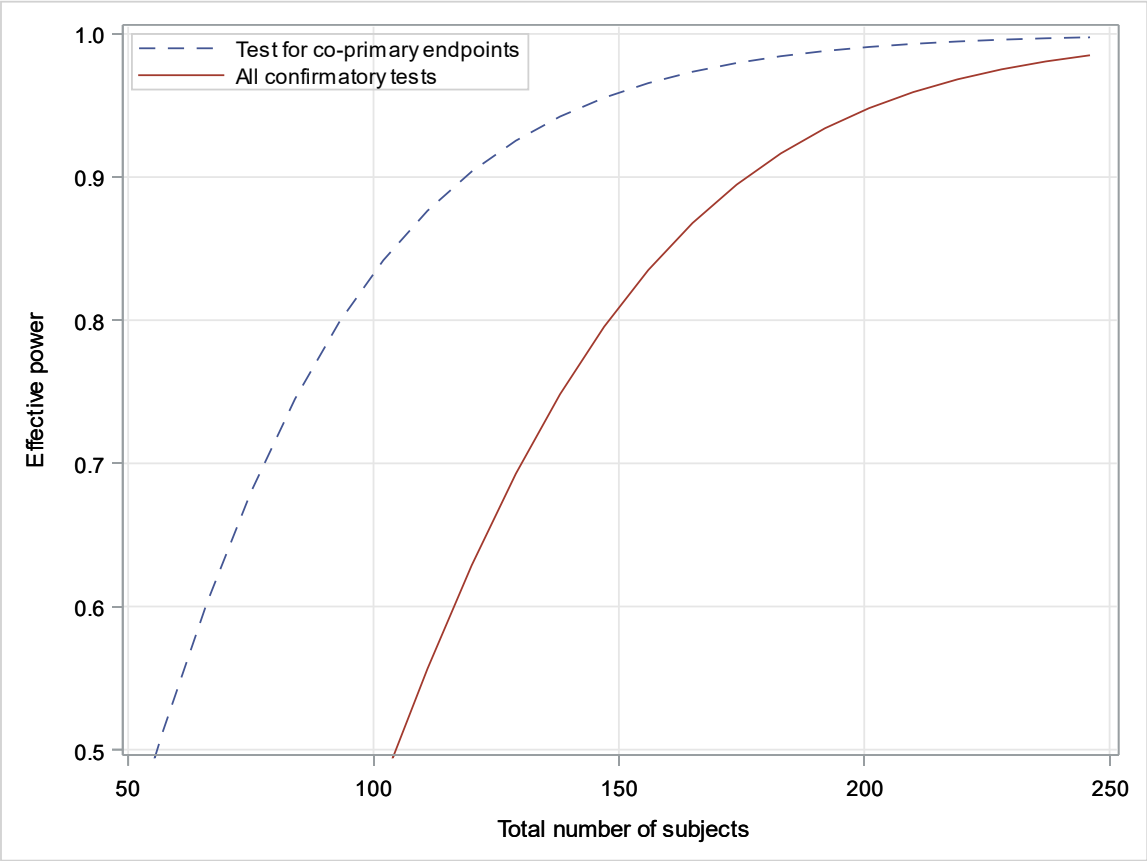
Table 9-4 Marginal and effective power by assumed mean and standard deviation in % body weight change with a sample size of 150 participants

Endpoint	**Semaglutide s.c. 2.4 mg: 10.0 (±10)**	**Semaglutide s.c. 2.4 mg: 12.0 (±10)***	**Semaglutide s.c. 2.4 mg: 14.0 (±10)**	**Semaglutide s.c. 2.4 mg: 12.0 (±8)**	**Semaglutide s.c. 2.4 mg: 12.0 (±12)**
	Marginal power (%) / Effective power (%)	Marginal power (%) / Effective power (%)	Marginal power (%) / Effective power (%)	Marginal power (%) / Effective power (%)	Marginal power (%) / Effective power (%)
% body weight change	96 / 96	>99 / >99	>99 / >99	>99 / >99	97 / 97
5% responders	85 / 81	96 / 96	>99 / >99	>99 / >99	88 / 86
10% responders	83 / 67	96 / 92	>99 / 99	>99 / >99	88 / 75
15% responders	71 / 48	92 / 85	99 / 98	98 / 97	82 / 62

* Assumption used in the sample size calculation

The effective power of the co-primary and all confirmatory tests versus total number of participants randomised in shown in Figure 9-1.

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



All above-outlined sample size and power considerations are based on the treatment policy strategy used in the co-primary and secondary estimands. It is assumed that up to 13% of participants discontinue permanently and 75% of these are retrieved at week 44, which amounts to around 3% expected missing data at week 44. This is similar to that observed in STEP 6, in which 2% missing in-trial body weight data were observed after both 44 and 68 weeks for the primary estimand. Any superiority conclusions will be based on the primary estimand.

For the additional estimand however, data from retrieved participants are not used. Hence, it is expected that up to 13% of data will be missing at week 44. Based on STEP 6, approximately 6% on-treatment data were missing after 68 weeks for the additional estimand. This included missing data not only due to treatment discontinuation, but also due to initiation of other anti-obesity therapies.

Finally, based on STEP 6 it is expected that approximately 95% of participants will attend the end of study visit at week 49. Therefore, a sample size of 150 randomised participants is expected to give 142 participants attending the end of study visit at week 49.

10 Supporting documentation and operational considerations

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

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[80] and applicable ICH Good Clinical Practice (GCP) Guideline[81]
- 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 study is initiated.

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CSR according to national requirements.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate safety hazard to study participants.

Before a site is allowed to start screening participants, written notification from Novo Nordisk must be received.

The investigator will be responsible for:

- providing written summaries of the status of the study 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 study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- ensuring submission of the CSR synopsis to the IRB/IEC
- reporting any potential serious breaches to the sponsor immediately after discovery

10.1.2 Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and one year after completion of the study.

10.1.3 Informed consent process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. This includes the use of an impartial witness where required according to local requirements.

The investigator must ensure the participant ample time to come to a decision whether or not to participate in the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH GCP[81] guidelines, Declaration of Helsinki,[80] privacy and data protection requirements, where applicable, and the IRB/IEC or site.

The medical record must include a statement that written informed consent was obtained before any study-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 study-related activity.

The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.

Participants must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

A copy of the informed consent form(s) must be provided to the participant.

10.1.4 Information to participants during the study

The site will be offered a communication package for the participant during the conduct of the study. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the participants. The written information will be translated and adjusted to local requirements and distributed to the participant at the discretion of the investigator. The participant may receive a “thank you for your participation letter” after completion of the study. Further, the participant may receive other written information during the study like “dose reminder card” and “what is Semaglutide”.

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

10.1.5 Data protection

Participants will be assigned a 6-digit unique identifier, a participant ID. Any participant records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the participant are transferred to Novo Nordisk.

The participant and any biological material obtained from the participant will be identified by participant ID, visit number and study ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of participants as required by local, regional and national requirements.

The participant must be informed about his/her privacy rights, including that his/her personal study-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 participant.

The participant 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.

Personal data may be collected from participants due to process requirements from Novo Nordisk's suppliers. This data is needed to ensure that the relevant data analysis for the study can be performed, but will not be part of the data transferred to Novo Nordisk, the assessment of the study endpoints or the clinical study report. A list of any such data values must be kept as part of the study documentation along with an explanation of why it was required.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee.

10.1.7 Dissemination of clinical study data

Study information will be disclosed at clinicaltrials.gov and novonordisk-trials.com and, if applicable, also on other national or regional study registries. It will be disclosed according to applicable requirements, relevant recommendations or regulations, such as the Declaration of Helsinki,[80] the International Committee of Medical Journal Editors (ICMJE),[82] the Food and Drug Administration Amendment Act (FDAAA),[83] European Commission Requirements[84-86] and in accordance with Novo Nordisk commitment to clinical transparency. If a participant requests to be included in the study via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the participant. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

Novo Nordisk or designee is responsible for the data management of this study including quality checking of the data.

To demonstrate his/her oversight of the collected data, the investigator should sign the CRF on a regular basis during the conduct of the study as well as at the end of the study, as described in the CRF completion guideline.

All participant data relating to the study will be recorded on CRFs unless transmitted electronically to Novo Nordisk or designee (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The following will be provided as paper CRFs:

- Pregnancy forms

The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints on study intervention not yet allocated to a participant)

Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

10.1.8.2 Monitoring

The investigator must permit study-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 study. If the electronic source data does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone).

Study monitors will perform ongoing source data verification of critical data points to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents. Study monitors will perform ongoing source data review to ensure that the study is being conducted in accordance with the current approved protocol and any other study agreements, ICH GCP[81], and all applicable regulatory requirements, evaluating the adequacy of critical processes at site for the execution of the protocol, collection of study data, to ensure that the safety and rights of participants are being protected.

Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.

Quality tolerance limits (QTLs) will be predefined in the relevant monitoring plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.

10.1.8.3 Protocol compliance

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

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

10.1.9 Source documents

All data entered in the CRF must be verifiable in source documentation other than the CRF.

If source data is entered directly in a paper CRF, each data entry or clear series of data entries must be signed and dated separately by the study staff making the entry.

The original of the completed diaries must not be removed from the site, unless they form part of the CRF and a copy is kept at the site.

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the site. Any source data generated by investigator's subcontractors must be archived and accessible by the site.

Data that is transcribed into the CRF 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 participant's medical history in source documents, such as participant's medical record.

The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.

Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical study documentation

Records and documents, including signed informed consent forms, pertaining to the conduct of this study must be retained by the investigator for 15 years after end of study 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 study documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other participant 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 participant data (in an electronic readable format or as

paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.

Participant's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

10.1.11 Study and site closure

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

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

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

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

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines
- inadequate recruitment of participants by the investigator
- discontinuation of further study intervention development.

10.1.12 Responsibilities

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

A qualified physician, who is an investigator or a sub investigator for the study, must be responsible for all study-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 study and the quality of the data produced) in the investigator trial master file. The documents, including the participant identification code list must be kept in a secure locked facility so that no unauthorised 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. This also includes ensuring that no indirect sharing of user credentials for IT systems used in this study takes

place (e.g., by not sharing IT equipment with others in a way where user credentials have the possibility of being shared). 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 participants to a specific qualified physician who will be readily available to participants during that time.

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

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

10.1.13 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical studies 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 study or by persons for whom the said site or investigator are responsible.

Novo Nordisk accepts liability in accordance with country-specific laws, acts and guidelines.

10.1.14 Publication policy

The information obtained during the conduct of this study 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 study intervention. All information supplied by Novo Nordisk in connection with this study 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 study.

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

Novo Nordisk may publish on its clinical studies website a redacted CSR for this study.

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

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of studies 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 study will be participant 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 CSR 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 study.

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

10.1.14.2 Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the study 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.[87]

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

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

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

For a multicentre clinical study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or participants, 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 study.

10.1.14.4 Investigator access to data and review of results

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

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

10.2 Appendix 2: Clinical laboratory tests

The tests detailed in Table 10-1 will be performed by the central laboratory.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g., to follow up on AEs, this must be done at a local laboratory.

The central 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 laboratory SOPs. These data will not be transferred to the study 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.

The investigator must keep an overview, e.g. a log, of laboratory samples not handled according to the laboratory manual. In addition, the investigator must keep an overview, e.g. a log, of laboratory samples stored at site.

Laboratory samples will be destroyed no later than at end of study or no later than at finalisation of the CSR.

Table 10-1 Protocol-required efficacy and safety laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism Visit 1, 2, 11, 17	• HbA_{1c}
Lipids Visit 2, 11, 17	• Total cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides
Biomarkers Visit 2, 11, 17	• High-sensitive C-Reactive Protein (hsCRP)
Haematology Visit 2, 11, 17	• Haemoglobin • Thrombocytes • Leukocytes • Neutrophils • Lymphocytes • Basophils • Eosinophils • Monocytes
Biochemistry[a] Visit 2, 11, 17	• Alanine Aminotransferase (ALT) • Alkaline phosphatase • Aspartate Aminotransferase (AST) • Amylase • Lipase • Bilirubin • Creatinine • Potassium • Sodium
Pregnancy Testing[b] Visit 1, 2, 4, 6, 8, 10, 11, 13, 15, 17, 18	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test
Other tests Visit 1, 11, 17	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation
Notes: [a]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 3 (Section 10.3) (Hy's Law) and Section 7.1. [b]For women of childbearing potential, as needed, local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC, see Appendix 4 (Section 10.4).	

Laboratory results that could unblind the study will not be reported to the sites until the study has been unblinded.

10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1 Definition of AE

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

Events to be reported as AEs:

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

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

Events NOT to be reported as AEs:

- Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions. This includes those conditions identified during screening or identified during other study procedures performed before exposure to IMP.
  Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.
- Medical or surgical procedures (e.g., endoscopy, appendectomy). The condition that leads to the procedure is the AE.
- Medical or surgical procedures not preceded by an AE or worsening of a known condition.

10.3.2 Definition of an SAE

An SAE is any untoward medical occurrence that fulfils at least one of the following criteria:

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' refers to an event in which the participant 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**
  - Hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the

physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

- Hospitalisation for elective treatment (e.g., elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE.
  Note: Hospitalisations for administrative, study-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for medical or surgical procedures, planned before study inclusion, are not considered AEs or SAEs

- **Results in persistent or significant disability/incapacity**
  - The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Important medical event:**
  - Medical or scientific judgment should be exercised by the investigator 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
  - The following must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:
    - Suspicion of transmission of infectious agents via IMP
    - 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)

10.3.3 Description of AEs requiring additional data collection

Adverse events requiring additional data collection
An AE requiring additional data collection is an AE where Novo Nordisk has evaluated that additional data is needed in the evaluation of safety.

Medication error:

- A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the participant, such as:
  - administration of wrong drug
    Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
  - wrong route of administration, such as intramuscular instead of subcutaneous
  - accidental administration of a higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the study participant were likely to happen as judged by the investigator, although they did not necessarily occur.

Misuse and abuse:

- Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g., overdose to maximise effect)
- Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g., overdose with the intention to cause harm)

Note: Medication error, misuse and abuse must always be reported on an AE form and a specific event form must be completed. The AE diagnosis on the AE form must reflect what occurred (e.g., accidental overdose, intentional overdose or other). If the medication error and/or misuse and abuse resulted in a clinical consequence, this must be reported on an additional AE form.

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:

- Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
- Serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal
- Characteristic findings of acute pancreatitis on imaging

Malignant neoplasm: Malignant neoplasm by histopathology or other substantial clinical evidence

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 > 1.5[a]
- ALT or AST > 3x UNL with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

[a] Please note that in case of a hepatic event defined as ALT or AST > 3x UNL and total bilirubin > 2x 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.

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

10.3.4.1 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.

There may be instances when copies of source documents (e.g., medical records) for certain cases are requested by Novo Nordisk. In such cases, all participant identifiers, with the exception of the participant ID, must be redacted on the copies of the source documents before submission to Novo Nordisk.

For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the study at the latest. For sign-off of SAE-related forms, refer to "AE and SAE reporting via 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 study, 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.

10.3.4.2 Assessment of severity

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

- **Mild**: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: An AE that is assessed as severe should not be confused with an SAE. Both AEs and SAEs can be assessed as severe.

10.3.4.3 Assessment of causality

The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

Relationship between an AE/SAE and the relevant IMP should be assessed as:

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

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, should 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 update the causality assessment in the CRF.

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

10.3.4.4 Final outcome

The investigator will select the most appropriate outcome:

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

10.3.4.5 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, Hy's law). This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information should be recorded in the CRF.

10.3.5 Reporting of SAEs

AE and SAE reporting via CRF

Relevant forms must be completed in the CRF.

For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information forms within the designated reporting timelines (see Table 10-1):

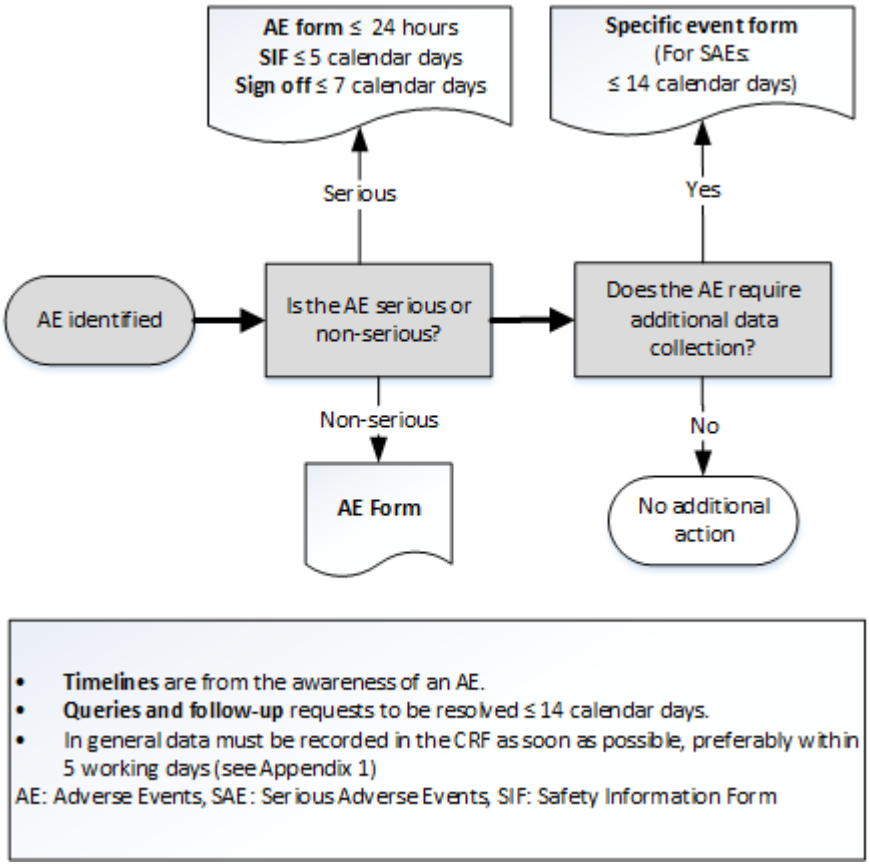
- AE form within 24 hours
- Safety information form within 5 calendar days
- Both forms must be signed within 7 calendar days after first knowledge by the investigator.
- Specific event form within 14 calendar days.

If the eCRF is unavailable for more than 24 hours, then the sites will use the paper AE form, and if the eCRF is unavailable for more than 5 calendar days, then the site will use the paper safety information form. The site should enter the SAE data in the eCRF as soon as it becomes available.

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

After the study is completed, the study database will be locked, and the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a participant or receives updated information on a previously reported SAE after CRF decommission, the site can report this information on a paper AE and safety information form (see below) or to Novo Nordisk by telephone.

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



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

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

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

Females in the following categories are not considered WOCBP

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

   For females with permanent infertility due to an alternate medical cause other than the above (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining study enrolment.
3. Postmenopausal female:
   - A postmenopausal state is defined as amenorrhoea for at least 12 months without an alternative medical cause in a female > 45 years of age. Alternative medical causes for amenorrhoea include, but are not limited to, hormonal contraception or hormonal replacement therapy.
   - Females ≥ 60 years of age can be considered postmenopausal.

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

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

10.4.2 Contraceptive guidance

Male participants

No contraception measures are needed for male participants.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly. Table 10-2 lists the highly effective methods of contraception allowed. Local regulations may apply, see Appendix 7 (Section 10.7).

Highly effective contraception should be utilised until the end of study.

Table 10-2 Highly effective contraceptive methods allowed[88]

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

NOTES a. Contraceptive use by men or women should comply with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

The following methods are not acceptable methods of contraception: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM).

10.4.3 Collection of pregnancy information

Female participants who become pregnant

Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.

Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a participant's pregnancy (see Figure 10-2).

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate which will be forwarded to Novo Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.

Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

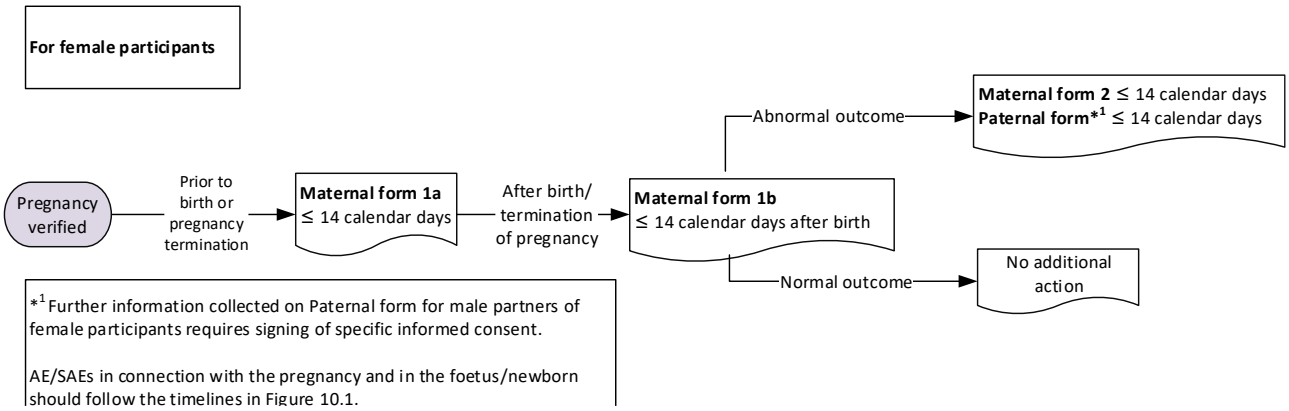
While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or

SAE. If relevant, consider adding 'gestational', 'pregnancy-related' or a similar term when reporting the AE/SAE.

Pregnancy outcome should be documented in the participant's medical record. Abnormal pregnancy outcome (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE. In case of abnormal pregnancy outcome, paternal information should be recorded in the appropriate form after obtaining the necessary signed paternal informed consent.

If the investigator learns of an SAE occurring as a result of a post-study pregnancy which is considered related to the IMP by the investigator, the SAE should be reported to Novo Nordisk as described in Appendix 3 (Section 10.3).

Figure 10-2 Decision tree for determining the forms to complete for collection of pregnancy information and timelines for reporting – For female participants



Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

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

10.5.1 Definition of technical complaint

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

Time period for detecting technical complaints

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

10.5.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk

For contact details for Customer Complaint Center, please refer to Attachment I.

Technical complaints on products allocated to a participant must be reported on a separate technical complaint form:

1. For products with DUN: One technical complaint form must be completed for each affected DUN.
2. For products without DUN: One technical complaint form must be completed for each batch, code or lot number.

Timelines for reporting technical complaints to Novo Nordisk

The investigator must complete the technical complaint form in the CRF within:

- 24 hours if related to an SAE
- 5 days calendar for all other technical complaints

If the CRF is unavailable, or when reporting a technical complaint on a product that is not yet allocated to a participant, the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

Follow-up of technical complaints

The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples

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

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

10.5.3 Reporting of technical complaints from products not included in the technical complaint form

Technical complaints on products not included in the technical complaint form should be reported to manufacturing holder.

10.6 Appendix 6: Mitigations to ensure participant safety and data integrity during an emergency situation

10.6.1 Definition and scope of appendix

A major emergency is defined as a situation that causes substantial restrictions to study site access for participants and/or sponsor representatives.

In case local restrictions due to a major emergency lead to lock-down of a site, the site must contact Novo Nordisk to allow for implementation of mitigations mentioned in this appendix based on mutual agreement.

According to local regulation, health authorities and independent ethics committees should be notified in case elements of the emergency appendix are activated.

Table 10-3 indicates the minimum requirements for assessments that should be performed during a lock-down, but sites should always try to follow the assessments outlined in the original flowchart (Section 1.2) to the extent possible. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.

Sites should comply with local regulations, requirements and/or guidelines if they are issued.

10.6.2 Visits

Screening (Visit 1) and randomisation/baseline (Visit 2) should always be performed as on-site visits. If a site is unable to perform these visits on-site, screening and randomisation of new participants at that site should be on hold until on-site visits are possible.

Visits 11 and 17 should be performed as on-site visits, if in any way possible. If not, assessments can be conducted remotely (video, phone or similar) or as home or off-site visits.

On-site visits (Visits 4, 6, 8, 10, 13, and 15) can be converted to remote visits (video, phone or similar) or home or off-site visits.

At each visit, the investigator must indicate in the CRF how the visit was performed and specify the reason for the preferred assessment method.

10.6.3 Assessments

Assessments used for safety or the confirmatory endpoints (i.e., body weight and waist circumference) should be prioritised. The preferred order for the method of assessment is: on-site, video, phone, home visit. Specifications regarding how to perform these assessments using remote visits or as home visits will be provided by Novo Nordisk. Specifications will include training for raters performing remote assessments and adoption of modifications for equivalent administration of assessments using remote visits (video, phone or similar).

Local laboratories or diagnostic facilities can be used for glucose metabolism, lipids, biomarkers, haematology, biochemistry at the investigator's discretion if on-site visits are not possible or in case of temporary lockdown of the central laboratory. Only findings meeting the definition for an AE (refer to Appendix 3 [Section 10.3]) should be reported in the CRF.

Home measurements of body weight can be performed if on-site visits are not possible and if deemed feasible for the participant. This is applicable only for emergency situations, and in this instance, Novo Nordisk will be in contact with the sites to provide further instructions.

If the assessments indicated in Table 10-3 cannot be performed as on-site visits, remote visits or be analysed at a local laboratory or diagnostic facility, they should be performed at the first possible timepoint following the originally scheduled visit in agreement with Novo Nordisk.

10.6.4 Study intervention

Alternative dispensing methods of study intervention may be implemented, and details will be communicated and documented. The dispensing options will be provided by Novo Nordisk A/S and will be based on options and requirements at country level and if permitted by local regulations.

Table 10-3 Minimum assessments following randomisation

	Screening	Randomisation	Intervention period														End of study intervention[a]	End of study
Visit	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	V11	P12	V13	P14	V15	P16	V17	P18
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	20	24	28	32	36	40	44	49
Visit Window (Days)	-7	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	+7
Informed Consent and Demography[b] (10.1.3)	X																	
Medical History/Concomitant Illness (8.2)	X																X	
Eligibility Criteria (5.1 and 5.2)	X	X																
Randomisation (6.3)		X																
Concomitant Medication (6.8)	X	X									X						X	X
Childbearing Potential[c] (10.4)	X																	
Tobacco Use[d] (5.3.2)	X																	
Pregnancy Test (8.2.4)	X	X									X						X	X
Evaluation of Antihypertensive Treatment (8)											X						X	
Evaluation of Glycaemic Status (8)		X									X						X	
Evaluation of Lipid-lowering Treatment (8)											X						X	
Discontinuation Criteria (7)											X							
Surgical Procedures Form (8.2.5)											X						X	X
Height (8.1.1)	X																	
Body Weight (8.1.1)	X	X									X						X	
Waist Circumference (8.1.1)	X	X									X						X	
Physical Examination (8.2.1)	X																X	

	Screening	Randomisation	Intervention period														End of study intervention[a]	End of study
Visit	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	V11	P12	V13	P14	V15	P16	V17	P18
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	20	24	28	32	36	40	44	49
Visit Window (Days)	-7	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	+7
Vital Signs (8.2.2)	X	X									X						X	
Laboratory Assessments (10.2)	X	X									X						X	
Adverse Event (8.3 and 10.3)		X									X						X	X
PK Sampling (8.4.1)											X						X	
Breast Neoplasms Follow-up[c] (8.2)																	X	X
Colon Neoplasms Follow-up (8.2)																	X	X
Drug Dispensing (6.2)		X															X	
Drug Accountability (6.2)		X															X	
Training in Trial Product, Pen-handling (6.1)		X																
End of Treatment (4.1)																	X	
Hand Out Direction for Use (6.1)		X																
Hand Out Dose Reminder Card		X																
Hand Out and Instruct in PK Diary (8)		X																
Diet and Physical Activity Counselling (6.1)		X									X						X	
Barriers and Motivation Interview (8)	X																	

a. End of study intervention includes both end of IMP treatment ('end of treatment') and end of lifestyle intervention b. Demography consists of date of birth, sex, ethnicity, and race (according to local regulation); c. For all female participants; d. Smoking is defined as smoking at least one cigarette or equivalent daily

10.7 Appendix 7: Country-specific requirements

Republic of Korea:

Section 5.1, Inclusion criteria

3. Age above or equal to 19 years at the time of signing informed consent.

10.8 Appendix 8: Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
BMR	basic metabolic rate
hCG	human chorionic gonadotropin
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	coronavirus disease
CRF	case report form
CSR	clinical study report
DFU	directions for use
DPS	defined data point sets
DUN	dispensing unit number
FAS	full analysis set
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
GLP-1	glucagon-like protein-1
GLP-1 RA	glucagon-like protein-1 receptor agonist
HDL	high-density lipoprotein
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
LAO-OT	last available observation during the on-treatment period
LDL	low-density lipoprotein
MEN2	multiple endocrine neoplasia type 2
MMRM	mixed model for repeated measurements
MTC	medullary thyroid cancer
NIMP	non-investigational medicinal product
NN	Novo Nordisk
NYHA	New York Heart Association
OR	odds ratio
PCD	primary completion date
PK	pharmacokinetics
PYE	patient-years of exposure

PYO	patient-years of observation
QTL	quality tolerance limit
RTSM	randomisation and trial supplies management system
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SOP	standard operating procedure
STEP	Semaglutide Treatment Effect in People with obesity
SUSAR	suspected unexpected serious adverse reaction
TEE	total daily energy expenditure
TMM	trial materials manual
TP-MI	tipping-point multiple imputation analysis
UNL	upper normal limit
WHO	World Health Organization
WOCBP	woman of childbearing potential

10.9 Appendix 9: Protocol amendment history

The Protocol amendment summary of changes table for the current protocol version is located directly before the table of contents.

Protocol version 2.0, including version 1.0: 25 June 2021, global

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall rationale for preparing protocol version 2.0

Section # and name	Description of change	Brief rationale
Section 8.2 Safety assessment	Under Medical History, the sentence ”*Information on weight related co-morbidities will be collected as part of medical history at screening (visit 1) and an evaluation will be done at the end of study intervention (visit 17).”* has been added.	Added to clarify the procedure related to evaluation of weight-related comorbidities.

Protocol version 3.0: 15 September 2021, global

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall rationale for preparing protocol, version 3.0:

The randomisation system to be used in this study has been changed from the IWRS (interactive web response system) to the RTSM (randomisation and trial supplies management system).

Section # and name	Description of change	Brief rationale
Section 5.4 Screen failures Section 6 Study intervention(s) and concomitant therapy Section 7 Discontinuation of study intervention and participant discontinuation/withdrawal Appendix 8 Abbreviations	Throughout the protocol, the IWRS (interactive web response system) has been updated to the RTSM (randomisation and trial supplies management system).	The randomisation system for the trial has been updated to the RTSM instead of the IWRS.
Section 6.2 Preparation, handling, storage and accountability	Sentence with reference to Appendix 7 has been deleted.	Wrong reference to Appendix 7.

Section # and name	Description of change	Brief rationale
Section 9.3 Statistical analyses	Minor change of wording: subjects updated to participants.	Align wording

Protocol version 4.0 (09 February 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, because the change of device impacts the conduct of the study.

Overall rationale for preparing protocol, version 4.0:

The device used for administration of semaglutide 2.4 mg or placebo was changed from DV3396 single-dose pen-injector to a PDS290 pen-injector. In addition, the editorial changes were made to the statistic sections and it was specified that PK samples will not be stored after end of study. Additional minor editorial changes have been made throughout the document.

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis Section 6.1 Study intervention(s) administered	Throughout the protocol the device for administration of semaglutide 2.4 mg and placebo has been changed from DV3396 single-dose pen-injector to PDS290 pen-injector.	The device used for administration of semaglutide 2.4 mg and placebo in this study has been changed from DV3396 single-dose pen-injector to PDS290 pen-injector. The reason for change was to reflect the devices expected to be marketed in the involved countries.
Section 1.1 Synopsis	Editorial changes to objectives, endpoints and estimands.	Editorial changes were made to reflect the intention of the statistical analyses more accurately. The planned statistical analyses and the conduct of the study has not been changed.
Section 3 Objectives, endpoints and estimands	Editorial changes to objectives, endpoints and estimands and additional information added to the secondary estimand, treatment condition, remaining intercurrent events and rationale for estimand.	
Section 9 Statistical considerations	'Breaking the blind to trials product assignment' was changed to 'database lock.'	
Section 9.2 Analysis sets	Definition of Safety analysis set (SAS) specified. Use of FAS and DPS1 amended to include primary objectives.	
Section 1.1 Synopsis Section 2.1 Study rationale Section 2.2.1 Semaglutide Section 3 Objectives, endpoints and estimands Section 4.1 Overall design	The term Asians was changed to people, participants or deleted.	Alignment of wording.

Section # and name	Description of change	Brief rationale
Section 1.2 Flowchart	Actions related to drug dispensing and accountability were updated.	The flowchart was updated to reflect the change in device.
Section 2.3.1 Risk assessment	Risk assessment statement added.	To comply with template and change in device.
Section 5.2 Exclusion criteria	'adequate' changed to 'highly effective'	To align with Section 10.4 Appendix 4
Section 8.4.1 Pharmacokinetics	Text specified: additional analyses will only be conducted during the study. Sentence about residual samples has been deleted. Sentence on genetic analyses has been deleted.	Change was made to clarify the use of PK samples and that genetic analyses will not be performed.
Section 9.3.2 Primary estimands analysis	Week 68 corrected to week 44.	Wrong week number stated.
Section 10.2	Additional haematology parameters added.	To align with previous studies.
Section 10.5.1 Definition of technical complaint	List of examples amended.	Examples updated to reflect the PDS290 device.
Section 10.5.3 Reporting of technical complaints from products not included in the technical complaint form	New section added.	New section added to align with requirements for the PDS290 device.
Throughout the protocol	Minor editorial changes. Updated IB reference to ed. 7	General update of the document with no impact on the conduct of the study.

Protocol version 5.0 (20 June 2022)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall rationale for preparing protocol, version 5.0:

Fasting requirements are not required in this study and have been removed throughout the protocol. Body Mass Index (BMI) is calculated via the electronic Case Report Form (eCRF), this has been specified in the protocol. Dose adjustment guidance has been revised for clarity.

Section # and name	Description of change	Brief rationale
1.2 Flowchart 5.3.1 Meals and dietary restrictions	Removal of description of fasting requirements.	Fasting is not required at any visit during the study.
5.1 Inclusion Criteria, 6.1 Study intervention(s) administered 8.1.1 Body measurements	Description of BMI calculation via the eCRF has been added throughout the protocol.	To avoid incorrect calculation of BMI, protocol has been updated to clarify how BMI is calculated via the eCRF.
6.1 Study intervention(s) administered	Revised dose adjustment procedure for participants with BMI within lower normal range.	To ensure participant safety, dose adjustment guidance has been revised for clarity.

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