Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05564117
Sponsor trial ID:	NN9932-4954
Official title of study:	Efficacy and safety of oral semaglutide 25 mg once daily in adults with overweight or obesity (OASIS 4)
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Protocol

Protocol Title:

Efficacy and safety of oral semaglutide 25 mg once daily in adults with overweight or obesity (OASIS 4)

Substance: Semaglutide

Universal Trial Number: U1111-1271-9056

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Study phase: 3b

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
Protocol version 2.0	16 August 2022	Germany only
Protocol version 1.0	28 February 2022	US, Canada and Poland

Protocol version 2.0 (16 August 2022)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union[1], because it neither significantly impact the safety nor 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 8.3.1 Time period and frequency for collecting AE information	Additional text with reference to country specific requirements	Request from the German Health Authorities BfArm
Section 10.8 Appendix 8 Country-specific requirements	Additional text for reporting of SAEs in Germany	Request from the German Health Authorities BfArm to include the wording “immediate” in the reporting of SAEs.
Section 10.8 Appendix 8 Country-specific requirements	Deletion of text inserted in error	Radiation is not included in the study.

Table of Contents

Page

1 Protocol summary

1.1 Synopsis

This is an interventional 64 week, randomised, placebo-controlled, double-blind two-armed, multi-centre, multinational clinical study comparing the efficacy of body weight reduction of once daily 25 mg oral semaglutide versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in adults with obesity or with overweight and weight-related comorbidities.

Rationale:

Oral semaglutide in a tablet formulation has the potential of becoming an option for the treatment of obesity with benefits on body weight and its convenient administration.

Dose-dependent reductions in body weight and HbA_{1c} have been demonstrated with oral semaglutide, at dose levels up to 40 mg (study NN9924-3790). Similarly, dose-dependent effects on body weight reduction were seen for once daily s.c. semaglutide (NN9536-4153). Oral semaglutide 50 mg is predicted to correspond to semaglutide 2.4 mg s.c., which has shown clinically meaningful reductions in body weight with acceptable safety and tolerability (NN9536, STEP programme).

Oral semaglutide 50 mg for weight management is being tested in NN9932-4737 (OASIS 1). However, due to the complex multifactorial aetiology of obesity, people with obesity have variable responses to treatment, meaning that some people with obesity may require a lower treatment dose to achieve their weight loss goal. To this end, 25 mg oral semaglutide is anticipated to provide an additional, lower dose option to the 50 mg treatment dose, and has therefore been selected as the maintenance dose for the current study.

The study population will consist of adults with overweight (BMI $\geq$ 27.0 kg/m^2) and at least one weight-related comorbidity, or with obesity (BMI $\geq$ 30.0 kg/m^2). 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.

The present randomised placebo-controlled study has been designed to compare the efficacy and safety of 25 mg oral semaglutide versus placebo in participants with overweight and at least one weight-related comorbidity or obesity.

Objectives and endpoints

Objectives	Endpoints		
Primary	**Title**	**Time frame**	**Unit**
• To confirm superior efficacy on body weight reduction from baseline (week 0) to end-of-treatment (week 64) of oral semaglutide 25 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.	**Co-primary**		
	Relative change in body weight	From baseline (week 0) to end-of-treatment (week 64)	%
	Achievement of body weight reduction ≥ 5% (Yes/No)	At end-of-treatment (week 64)	Count of participant
	Confirmatory secondary		
	Achievement of body weight reduction ≥ 10% (Yes/No)	At end-of-treatment (week 64)	Count of participant
	Achievement of body weight reduction ≥ 15% (Yes/No)	At end-of-treatment (week 64)	Count of participant
	Achievement of body weight reduction ≥ 20% (Yes/No)	At end-of-treatment (week 64)	Count of participant
Secondary	**Title**	**Time frame**	**Unit**
• To confirm superior efficacy on physical function from baseline (week 0) to end-of-treatment (week 64) of oral semaglutide 25 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.	**Confirmatory secondary**		
	Change in Physical function domain (5-items) score (Impact of Weight on Quality of Life-Lite-Clinical Trials version [IWQOL-Lite-CT)]	From baseline (week 0) to end-of-treatment (week 64)	Score points[a]
• To estimate the efficacy on cardio-metabolic parameters from baseline (week 0) to end-of-treatment (week 64) of oral semaglutide 25 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.	**Supportive secondary**		
	Change in body mass index (BMI)	From baseline (week 0) to end-of-treatment (week 64)	kg/m^2
	Change in waist circumference	From baseline (week 0) to end-of-treatment (week 64)	cm
	Change in systolic blood pressure	From baseline (week 0) to end-of-treatment (week 64)	mmHg
	Change in diastolic blood pressure	From randomisation (week 0) to end-of-treatment (week 64)	mmHg
	Change in HbA_{1c}	From baseline (week 0) to	%-point

Objectives	Endpoints		
		end-of-treatment (week 64)	
	Change in lipids: • Total cholesterol • HDL cholesterol • LDL cholesterol • VLDL cholesterol • Triglycerides • Free fatty acids	From baseline (week 0) to end-of-treatment (week 64)	Ratio to baseline
	Change in high sensitivity C-Reactive Protein	From baseline (week 0) to end-of-treatment (week 64)	Ratio to baseline
	Change in fasting plasma glucose (FPG)	From baseline (week 0) to end-of-treatment (week 64)	Ratio to baseline
	Change in fasting serum insulin	From baseline (week 0) to end-of-treatment (week 64)	Ratio to baseline
• To compare the safety and tolerability from baseline (week 0) to end-of-study (week 71) of oral semaglutide 25 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.	Number of treatment emergent adverse events	From baseline (week 0) to end-of-study (week 71)	Count of events
	Number of treatment emergent serious adverse events	From baseline (week 0) to end-of-study (week 71)	Count of events
Exploratory	**Title**	**Time frame**	**Unit**
• To estimate the efficacy on clinical outcome assessments baseline (week 0) to end-of-treatment (week 64) of oral semaglutide 25 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.	Change in IWQOL-Lite-CT: • Physical domain score • Psychosocial domain score • Total score	From baseline (week 0) to end-of-treatment (week 64)	Score points
	Change in Impact of Weight on Daily Activities Questionnaire (IWDAQ) total score	From randomisation (week 0) to end-of-treatment (week 64)	Score points
	Change in Control of Eating Questionnaire (COEQ): • Craving Control domain score • Positive Mood domain score • Craving for Sweet domain score • Craving for Savoury domain score	From randomisation (week 0) to end-of-treatment (week 64)	Score points

Objectives	Endpoints		
	• Hunger item score • Fullness item score		

[a] The range of possible scores for the IWQOL-Lite-CT Physical Function is 0-100. Higher scores indicate better physical function.

Estimands:

For the primary objective, an estimand of primary interest (primary estimand) and an additional estimand are defined. The estimands are used to address the primary objective in two different ways by quantifying the efficacy of oral semaglutide 25 mg (vs placebo) on body weight.

The primary estimand addresses the main clinical question of interest: What is the efficacy of oral semaglutide 25 mg on body weight in participants with overweight or obesity regardless of premature randomised treatment discontinuation and initiation of rescue intervention?

For continuous endpoints, the secondary estimands for secondary objectives are similar to the primary estimand for % weight change. For binary endpoints, the secondary estimands for secondary objectives are similar to the primary estimand for ≥ 5% body weight reduction.

The additional estimand addresses an additional question of interest: What is the efficacy of oral semaglutide 25 mg on body weight in participants with overweight or obesity if all participants remained on randomised treatment and did not initiate rescue intervention?

Overall design:

The study consists of a screening period of up to 2 weeks to assess the participant's eligibility followed by a randomisation visit and a 64-week treatment period. The treatment period is divided into a dose escalation period of 12 weeks and a maintenance period of 52 weeks. After the end-of-treatment visit (V19), all participants will enter a follow-up period of 7 weeks, ended by a follow-up visit (V20, end-of-study).

Study intervention groups and duration:

The planned total study duration for the individual participant is approximately 73 weeks (including screening).

Eligible participants will be randomised 2:1 at the Randomisation visit to receive either:

- oral semaglutide 25 mg once daily
- oral semaglutide placebo once daily

as an adjunct to reduced calorie diet and increased physical activity.

Tablets of oral semaglutide (3 mg, 7 mg, 14 mg and 25 mg) and semaglutide placebo in dose packs and/or HDPE (high density polyethylene) bottles will be provided by Novo Nordisk.

The study intervention will not be available to the participants after the end of the study.

Number of participants:

In total, approximately 300 participants will be assigned to randomised study intervention in a 2:1 ratio.

Participant characteristics:

The participants will be male or female with overweight (BMI ≥ 27.0 kg/m^2) and at least one weight related comorbidity, or with obesity (BMI ≥ 30.0 kg/m^2).

The following key inclusion and exclusion criteria apply:

Key inclusion criteria:

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

Key exclusion criteria:

1. A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records
2. HbA_{1c} ≥ 6.5% (48 mmol/mol) as measured by the central laboratory at screening

Data monitoring committee:

No data monitoring committee.

1.2 Flowchart

	Protocol Sections	Screening	Randomisation	Dose escalation period				Treatment period												End of treatment	End of study
Visit		V1	V2	P3	V4	V5	V6	V7	P8	V9	P10	V11	P12	V13	P14	V15	P16	V17	P18	V19	V20
Timing of Visit (Weeks)		-1	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	71
Visit Window (Days)		-7 to 0	±0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	0 to +5
Informed Consent and Demography[a]	10.1.3	X																			
Eligibility Criteria	5.1, 5.2	X	X																		
Discontinuation Criteria	7.1			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication	6.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History/Concomitant Illness	8.2	X																			
Risk Factors	8.2	X																			
Tobacco Use	5.3.2	X																			
Body Weight	8.1.2	X	X		X	X	X	X		X		X		X		X		X		X	X
Height	8.2.1	X																			
Waist Circumference	8.1.3		X		X	X	X	X		X		X		X		X		X		X	X
Body Mass Index (BMI)	8.1.2	X																			
Adverse Event	8.3, 10.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments	10.2	X	X		X		X	X				X				X				X	X
Childbearing Potential[b]	10.4	X																			

	Protocol Sections	Screening	Randomisation	Dose escalation period				Treatment period												End of treatment	End of study
Visit		V1	V2	P3	V4	V5	V6	V7	P8	V9	P10	V11	P12	V13	P14	V15	P16	V17	P18	V19	V20
Timing of Visit (Weeks)		-1	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	71
Visit Window (Days)		-7 to 0	±0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	0 to +5
Pregnancy Test	8.2.6, 10.4	X	X		X	X	X	X		X		X		X		X		X		X	X
Biosamples for Future Analysis	8.8, 10.2, 10.7	X						X												X	
Biosamples for Genetic Analysis	8.5, 10.2, 10.7	X																			
Attend Visit Fasting	5.3.1		X					X								X				X	
ECG	8.2.3		X					X												X	
Physical Examination	8.2.1	X																		X	
Vital Signs	8.2.2	X	X		X	X	X	X		X		X		X		X		X		X	X
Clinical Outcome Assessments	8.1.4, 8.2.4	X	X				X	X				X				X				X	X
Drug Dispensing	6.1		X		X	X	X	X		X		X		X		X		X			
Drug Handling	6.1		X		X	X	X	X		X		X		X		X		X		X	
Hand Out ID Card	8	X																			
Hand Out and Instruct in Diary	8		X		X	X	X	X		X		X		X		X		X			
Collect, Review and Transcribe Diaries	8				X	X	X	X		X		X		X		X		X		X	
Diet and Physical Activity Counselling	5.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Breast and Colon Neoplasms Follow-up	8.2																			X	X

	Protocol Sections	Screening	Randomisation	Dose escalation period				Treatment period												End of treatment	End of study
Visit		V1	V2	P3	V4	V5	V6	V7	P8	V9	P10	V11	P12	V13	P14	V15	P16	V17	P18	V19	V20
Timing of Visit (Weeks)		-1	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	71
Visit Window (Days)		-7 to 0	±0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	0 to +5
Evaluation of Antihypertensive and Lipid-lowering Treatment	6.8																			X	

a: Demography consists of date of birth, sex, race and ethnicity (according to local regulation). Germany: For country-specific requirements, please refer to Appendix 8, Section 10.8.

b: For women of childbearing potential only. In addition to the planned assessments, urine dipstick pregnancy test should be performed at any time during the study if a menstrual period is missed, or if pregnancy is suspected.

2 Introduction

The prevalence of obesity is increasing and has reached epidemic proportions in most countries around the world with considerable medical and societal impacts as well as significant public health challenges.[1-7] Obesity is associated with increased mortality and risk of a variety of complications including type 2 diabetes (T2D), hypertension, dyslipidaemia, obstructive sleep apnoea, non-alcoholic steatohepatitis and cardiovascular (CV) diseases.[8-22] Moreover, obesity adversely affects physical and mental health and reduces health-related quality-of-life (HRQOL).[23, 24]

The risk of obesity-related complications increases with increasing body mass index (BMI). Even a 5–10% weight loss has significant health benefits; it prevents or slows the progression to T2D,[25-28] and improves physical symptoms, HRQOL and other obesity-related complications. Finally, studies suggest a beneficial impact of weight loss on CV risk and mortality in both people with diabetes and people with obesity.[29-31]

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 without pharmacotherapy.[32-41] Pharmacotherapy serves as a valuable adjunct to lifestyle intervention for individuals with obesity in order to achieve and sustain a clinically relevant weight loss, to improve complications and quality of life, and to facilitate a healthier lifestyle. Few anti-obesity medications are currently available and there is a need for more safe and effective weight management therapies, especially treatments that also target weight maintenance, as well as prevention and treatment of complications. In chronic diseases, poor adherence to therapies is a general concern and may be due to needle aversion.[32-37, 42, 43] Oral semaglutide may alleviate this issue by offering a more convenient option compared with injectable therapies.

Semaglutide

Semaglutide is a potent glucagon-like peptide-1 (GLP-1) analogue with a high degree of homology to human GLP-1. GLP-1 is a physiological regulator of appetite and GLP-1 receptors are present in several areas of the brain involved in appetite regulation.[44] In addition, the blood glucose-lowering effect of GLP-1 can provide glycaemic control.

Once-weekly semaglutide 2.4 mg s.c. is developed for weight management in a global development programme (project number NN9536), which includes the phase 3a programme, STEP. Four (4) completed STEP studies (STEP 1–4) have shown that people with obesity treated with semaglutide 2.4 mg achieved a statistically significant and superior reduction in body weight compared to placebo and a safe and well-tolerated profile. Semaglutide 2.4 mg s.c. is approved by FDA, MHRA and Health Canada under the brand name Wegovy®. Semaglutide is also approved as a s.c. formulation (0.5 mg, 1 mg and 2 mg Ozempic®, NN9535) for once-weekly administration for the treatment of T2D and reduction of CV risk in adults with T2D and established CV disease.

Oral semaglutide (3 mg, 7 mg and 14 mg Rybelsus®, NN9924, based on the global clinical programme PIONEER) is the first peptide-based anti-diabetic therapy available for oral administration to improve glycaemic control as an adjunct to diet and exercise in adults with T2D. In addition to the established benefit of oral semaglutide on glycaemic control, oral semaglutide (Rybelsus®) also reduces body weight.

2.1 Study rationale

Oral semaglutide is the first approved GLP-1 receptor agonist (RA) in a tablet formulation. It has been approved for glycaemic control in adults with T2D and has the potential to become a new attractive option in the treatment of obesity due to its benefits on body weight and its convenience as compared to injectables.

Dose-dependent reductions in body weight have been demonstrated with oral semaglutide, at dose levels up to a well-tolerated and safe dose of 40 mg (study NN9924-3790, a phase 2 study for T2D). Similarly, dose-dependent effects on body weight reduction were seen for once daily semaglutide s.c. (NN9536-4153). Oral semaglutide 50 mg for weight management is being tested in NN9932-4737 (OASIS 1). The multifactorial aetiology of obesity contributes to variation in treatment responses. Because of this variation, some people with obesity will achieve their weight loss goal with a lower dose. Therefore, 25 mg oral semaglutide has been selected for the current study as maintenance dose in order to add more flexibility to the treatment by providing an additional, lower treatment dose option to the 50 mg treatment dose. See Section 4.3 for details on the justification of dose.

The present randomised placebo-controlled study has been designed to support the approval of oral semaglutide 25 mg for weight management, by comparing the efficacy, safety and tolerability of 25 mg oral semaglutide versus placebo in adults with overweight and at least one weight-related comorbidity, or with obesity.

Study population

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

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.[45-47]

2.2 Background

Semaglutide has demonstrated dose-dependent reductions in body weight independent of administration route in doses exceeding the currently maximum approved doses for improvement of glycaemic control in adults with T2D, of 1 mg once daily (semaglutide s.c., NN9535-4191) and 14 mg once daily (oral semaglutide, NN9924-3790). In participants with T2D, the 40 mg once daily oral semaglutide reduced body weight by 7.6% by week 26 (NN9924-3790), and up to 44% of participants treated with 14 mg oral semaglutide achieved a clinically meaningful weight loss of ≥5% by week 26 (phase 3 PIONEER studies). In addition, once-weekly semaglutide 2.4 mg s.c. reduced body weight up to 14.9% by week 68 in participants with overweight or obesity (NN9536-4373, STEP 1), and reduced body weight up to 10.6% in participants with overweight or

obesity and T2D (NN9536-4374, STEP 2). Please see Section 4.3 regarding correlation of oral and s.c. semaglutide doses.

A total of 5,707 participants have previously been exposed to oral semaglutide 3, 7 or 14 mg as part of the global clinical development programme PIONEER. The programme confirmed a favourable benefit-risk profile of oral semaglutide in a broad and representative population of participants with T2D. Superior, clinically relevant and sustained reductions in HbA_{1c} and body weight were demonstrated with the approved maintenance doses (7 mg and 14 mg), and the safety and tolerability profiles of oral semaglutide were consistent with those of other GLP-1 RAs.[48]

The number of adverse events (AEs) has been observed to increase with increasing oral and s.c. semaglutide dose in studies NN9924-3790 and NN9536-4153, respectively, and the AEs were mainly gastrointestinal (GI) related. The proportion of participants who discontinued randomised treatment prematurely due to an AE increased with increasing dose of both oral and s.c. semaglutide. Dose-escalation helps to mitigate unacceptable tolerability concerns for semaglutide (as for any GLP-1 RA) and is implemented in clinical studies with semaglutide. No apparent dose-dependency was seen for any serious adverse events (SAEs) across oral and s.c. semaglutide groups, and no fatal events related to treatment with semaglutide were reported for any treatment group in either of these dose-finding studies. Thus, all dose levels investigated in study NN9924-3790 (up to once daily 40 mg oral semaglutide) and NN9536-4153 (up to once daily semaglutide 0.4 mg s.c.) were found to be safe and well tolerated, and no unexpected safety concerns were identified.

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

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 oral semaglutide may be found in the IB[49] and any updates hereof.

2.3.1 Risk assessment

This section describes identified and potential risks associated with oral semaglutide treatment. For classification and further details of the risks, please refer to the current version of the IB[49] or any updates hereof. The risks are based on findings in non-clinical studies and clinical studies with semaglutide (both s.c. and oral) as well as other GLP-1 RAs. For each of these risks, mitigating actions have been implemented to minimise the risks for participants enrolled in this study.

Table 2-1 Risk assessment

Identified/Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention (oral semaglutide)		
Identified risks		
Gastrointestinal adverse events	Consistent with findings for other GLP-1 RAs, the most frequently reported AEs in clinical studies with semaglutide were gastrointestinal (GI) disorders, including nausea, diarrhoea, and vomiting. In general, these reactions are mild or moderate in severity, of short duration, and dose dependent. In adults treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating adults 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 GI symptoms. A low starting dose and dose escalation steps has been implemented in the study to mitigate the risk of GI AEs. Participants with GI symptoms are recommended to drink plenty of fluids to avoid volume depletion. Adults with renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR <15 ml/min/1.73 m^2 will not be enrolled in the study (see Section 5.2).
Acute gallbladder disease (Cholelithiasis)	Events of cholelithiasis were reported more frequently with semaglutide than with placebo in the clinical development programme for semaglutide 2.4 mg s.c. for weight management (NN9536). The increased risk of cholelithiasis with semaglutide 2.4 mg s.c. appeared to be at least partly explained by the larger weight loss. Cholelithiasis may lead to complications such as cholecystitis or acute pancreatitis.	If cholelithiasis is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.
Acute pancreatitis	Generally, acute pancreatitis is considered a risk associated with the use of the GLP-1 RA drug class. The frequency of adjudication-confirmed acute pancreatitis reported in the NN9536 phase 3a clinical studies was 0.2% for semaglutide 2.4 mg s.c. and <0.1% for placebo.	Adults with a history of chronic pancreatitis or recent acute pancreatitis will not be enrolled in the study (see section 5.2). Participants should be informed of the characteristic symptoms of acute pancreatitis. In addition, in case of suspicion of acute pancreatitis, study intervention should be promptly interrupted in accordance with Section 7.1. If confirmed, semaglutide should not be restarted.
Potential risks		
Allergic reactions	As with all protein-based pharmaceuticals, treatment with semaglutide may evoke allergic reactions, including serious allergic reactions such as angioedema and anaphylactic reactions.	Adults with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this study (see Section 5.2). In addition, participants will be instructed to contact the site staff as soon as possible for further guidance if

Identified/Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
		suspicion of a hypersensitivity reaction to the IMP occurs.
Neoplasms (*malignant and non-malignant)*	Adults with overweight or obesity have an increased risk of certain types of cancer. There is no evidence from clinical studies that GLP-1 based therapies increase the risk of neoplasms. However, in the semaglutide s.c.as well as oral semaglutide phase 3a studies 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.	Adults with presence or history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this study. Basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in-situ prostate cancer is allowed (see Section 5.2).
Pancreatic cancer (*potential GLP-1 RA class risk)*	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 based on the unknown long-term effects on β-cell stimulation and α-cell suppression.	Adults with presence or history of malignant neoplasm within 5 years prior to screening will not be enrolled in this study (see Section 5.2).
Medullary thyroid cancer (*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 C-cell tumours were observed in monkeys after 52 weeks exposure up to 11-fold above the clinical plasma exposure at 50 mg/day. The GLP-1 receptor is not expressed in the normal human thyroid,[50] and therefore the clinical relevance of the findings is considered to be low.	Adults with a family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2) are excluded from the study (see Section 5.2).
Study procedures		
Risk of Coronavirus disease-19 (COVID-19) infection in relation to participation in the study	Participants may be exposed to COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country.	The risk of COVID-19 transmission in relation to site visits is overall considered to be low, however this may vary between geographical area. To minimise the risk of COVID-19 transmission as much as possible, local guidelines must be followed.
Risk of externally induced unforeseen events with a global impact (e.g., global pandemic)	Sites and participants may be impacted to a degree where certain parts of the protocol cannot be adhered to.	In case of externally induced unforeseen events, some deviations to the planned visit schedule will be allowed. Please reach out to monitor for guidance, as with all other unforeseen events occurring at site level. For a description of visits that should be performed as on-site visits, please refer to Section 7.1.
Other		

Identified/Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Risk of COVID-19 infection in relation to study treatment	Available data does not suggest an increased risk of infection or a more severe progression of infection when treated with oral semaglutide.	More detailed information about the known risks for oral semaglutide may be found in the current version of the IB[49] or any updates hereof.
Pregnancy and lactation (exposure and outcome) (*based on non-clinical data*)	Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. The effect of semaglutide on fertility in humans is unknown. Therefore, semaglutide should not be used during pregnancy. In lactating rats, semaglutide and SNAC and/or metabolites were excreted in milk. A risk to a breast-fed child cannot be excluded. Semaglutide should not be used during breast-feeding.	Exclusion and discontinuation criteria related to pregnancy have been implemented in this study. Women of childbearing potential are required to use highly effective contraceptive methods when participating in this study (Appendix 4, Section 10.4, Table 10-3). If a participant wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Please refer to Section 8.3 for further guidance.

2.3.2 Benefit assessment

Both oral and s.c. semaglutide have demonstrated clinically relevant, dose-dependent improvements in body weight reduction. It is therefore expected that oral semaglutide 25 mg will provide clinically meaningful body weight reduction in adults with overweight or obesity.

Participants will be treated with a regimen anticipated to be better than or equal to the weight management regimen they receive at study entry. In addition, all participants will undergo thorough medical evaluations/assessments during the study, including physical exams, blood tests and electrocardiograms (ECGs).

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 optimise retention and likely result in intensified weight management.

All participants in this study will receive IMP, diet, and physical activity counselling free of charge.

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 oral semaglutide up to 25 mg once daily. In addition, the safety profile for oral semaglutide for weight management is expected to be in line with the safety profile of s.c. semaglutide for weight management and other drugs within the GLP-1 RA drug class.

Results from phase 2 and phase 3a studies (see Section 2.2) indicate that treatment with oral semaglutide 25 mg will provide clinically meaningful reduction of body weight.

In conclusion, the potential benefits of the study are expected to outweigh the potential risks associated with the administration of oral semaglutide for weight management. Therefore, the perceived benefit–risk balance is favourable.

More detailed information about the known and expected benefits and risks and reasonably expected AEs associated with oral semaglutide can be found in the IB[49] and any updates thereof.

3 Objectives, endpoints and estimands

The primary and secondary objectives of the study are listed below followed by an introduction of the estimands used to address the efficacy-related objectives.

The objectives and endpoints are summarised in Table 3-1.

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
• To confirm superior efficacy on body weight reduction from baseline (week 0) to end-of-treatment (week 64) of oral semaglutide 25 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.	**Co-primary**		
	Relative change in body weight	From baseline (week 0) to end-of-treatment (week 64)	%
	Achievement of body weight reduction ≥ 5% (Yes/No)	At end-of-treatment (week 64)	Count of participant
	Confirmatory secondary		
	Achievement of body weight reduction ≥ 10% (Yes/No)	At end-of-treatment (week 64)	Count of participant
	Achievement of body weight reduction ≥ 15% (Yes/No)	At end-of-treatment (week 64)	Count of participant
	Achievement of body weight reduction ≥ 20% (Yes/No)	At end-of-treatment (week 64)	Count of participant
Secondary	**Title**	**Time frame**	**Unit**
• To confirm superior efficacy on physical function from baseline (week 0) to end-of-treatment (week 64) of oral semaglutide 25 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.	**Confirmatory secondary**		
	Change in Physical function domain (5-items) score (Impact of Weight on Quality of Life-Lite-Clinical Trials version [IWQOL-Lite-CT])	From baseline (week 0) to end-of-treatment (week 64)	Score points[a]
• To estimate the efficacy on cardio-metabolic parameters from baseline (week 0) to end-of-treatment (week 64) of oral semaglutide 25 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.	**Supportive secondary**		
	Change in body mass index (BMI)	From baseline (week 0) to end-of-treatment (week 64)	kg/m^2
	Change in waist circumference	From baseline (week 0) to end-of-treatment (week 64)	cm
	Change in systolic blood pressure	From baseline (week 0) to	mmHg

Objectives	**Endpoints**		
		end-of-treatment (week 64)	
	Change in diastolic blood pressure	From randomisation (week 0) to end-of-treatment (week 64)	mmHg
	Change in HbA_{1c}	From baseline (week 0) to end-of-treatment (week 64)	%-point
	Change in lipids: • Total cholesterol • HDL cholesterol • LDL cholesterol • VLDL cholesterol • Triglycerides • Free fatty acids	From baseline (week 0) to end-of-treatment (week 64)	Ratio to baseline
	Change in high sensitivity C-Reactive Protein	From baseline (week 0) to end-of-treatment (week 64)	Ratio to baseline
	Change in fasting plasma glucose (FPG)	From baseline (week 0) to end-of-treatment (week 64)	Ratio to baseline
	Change in fasting serum insulin	From baseline (week 0) to end-of-treatment (week 64)	Ratio to baseline
• To compare the safety and tolerability from baseline (week 0) to end-of-study (week 71) of oral semaglutide 25 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.	Number of treatment emergent adverse events	From baseline (week 0) to end-of-study (week 71)	Count of events
	Number of treatment emergent serious adverse events	From baseline (week 0) to end-of-study (week 71)	Count of events
Exploratory	**Title**	**Time frame**	**Unit**
• To estimate the efficacy on clinical outcome assessments baseline (week 0) to end-of-treatment (week 64) of oral semaglutide 25 mg once daily versus placebo as an adjunct to reduced-calorie diet	Change in IWQOL-Lite-CT: • Physical domain score • Psychosocial domain score • Total score	From baseline (week 0) to end-of-treatment (week 64)	Score points
	Change in Impact of Weight on Daily Activities Questionnaire (IWDAQ) total score	From randomisation (week 0) to	Score points

Objectives	Endpoints		
and increased physical activity in adults with overweight or obesity.		end-of-treatment (week 64)	
	Change in Control of Eating Questionnaire (COEQ): • Craving Control domain score • Positive Mood domain score • Craving for Sweet domain score • Craving for Savoury domain score • Hunger item score • Fullness item score	From randomisation (week 0) to end-of-treatment (week 64)	Score points

a: The range of possible scores for the IWQOL-Lite-CT Physical Function is 0-100. Higher scores indicate better physical function.

Estimands

For the primary objective, an estimand of primary interest (primary estimand) and an additional estimand are defined. As described below, the estimands are used to address the primary objective in two different ways by quantifying the efficacy of oral semaglutide 25 mg (vs placebo) on body weight under different relevant assumptions regarding the pre-defined intercurrent events (i.e., events occurring after initiation of randomised treatment and affecting the use of the randomised treatment and the body weight of the participants). Two intercurrent events are considered: premature randomised treatment discontinuation and initiation of rescue interventions (other anti-obesity medication or bariatric surgery).

The estimands for the primary objective are introduced below and the attributes of the estimands are summarised in Table 3-2.

Primary estimand

The primary estimand addresses the main clinical question of interest: What is the efficacy of oral semaglutide 25 mg on body weight in adults with overweight or obesity regardless of premature randomised treatment discontinuation and initiation of rescue intervention?

For this estimand, the treatment policy strategy is applied for all intercurrent events.

Results based on the primary estimand are expected to mirror the clinical practice scenario because the estimand considers both the efficacy and tolerability of the randomised treatment. In addition, a similar primary estimand is represented in the prescribing information for oral semaglutide (Rybelsus®)[51] and is being applied as the primary estimand in the development programme for semaglutide 2.4 mg s.c. in weight management (STEP, NN9536).

Secondary estimand

For continuous endpoints, the secondary estimands for secondary objectives are similar to the primary estimand for % weight change. For binary endpoints, the secondary estimands for secondary objectives are similar to the primary estimand for ≥ 5% body weight reduction.

Additional estimand

The additional estimand addresses an additional question of interest: What is the efficacy of oral semaglutide 25 mg on body weight in adults with overweight or obesity if all participants remained on randomised treatment and did not initiate rescue intervention?

For this estimand, a hypothetical strategy is applied for two of the intercurrent events (randomised treatment discontinuation and initiation of rescue intervention).

The additional estimand is considered relevant because it quantifies the achievable treatment effect without potentially confounding effects of any rescue interventions. Further, results obtained with the additional estimand are comparable with results from the STEP programme, which applied a similar estimand.

Table 3-2 Estimands

Objective	Estimand category	Attributes				
		Treatment condition	**Variables / endpoints**	**Population of interest**	**Intercurrent events and strategy**	**Population-level summary measure**
Primary objective: To confirm superior efficacy on body weight reduction from baseline (week 0) to end-of-treatment (week 64) of oral semaglutide 25 mg once daily versus placebo as adjuncts to reduced-calorie diet and increased physical activity in adults with overweight or obesity	Primary	The effect of oral semaglutide with or without rescue intervention versus the effect of placebo with or without rescue intervention, each as adjunct to reduced-calorie diet and increased physical activity	From baseline (week 0) to week 64: • relative change in body weight • Achievement of body weight reduction ≥ 5% (yes/no)	Adults with overweight or obesity	**Treatment policy** strategy for: • Premature randomised treatment discontinuation • Initiation of rescue intervention	• Difference in means in relative weight change • Treatment odds-ratio for proportion of participants achieving body weight reduction ≥ 5%
	Additional[a]	The effect of oral semaglutide without rescue intervention versus the effect of placebo without rescue intervention, each as adjunct to reduce-calorie diet and increased physical activity			**Hypothetical strategy** for: • Premature randomised treatment discontinuation • Initiation of rescue intervention	

[a] Not related to the confirmatory hypotheses

4 Study design

4.1 Overall design

This is an interventional 64 week, randomised, placebo-controlled, double-blind two-armed, multi-centre, multinational clinical study comparing the efficacy of once daily 25 mg oral semaglutide versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in adults with overweight and weight-related comorbidities, or with obesity (Figure 4-1).

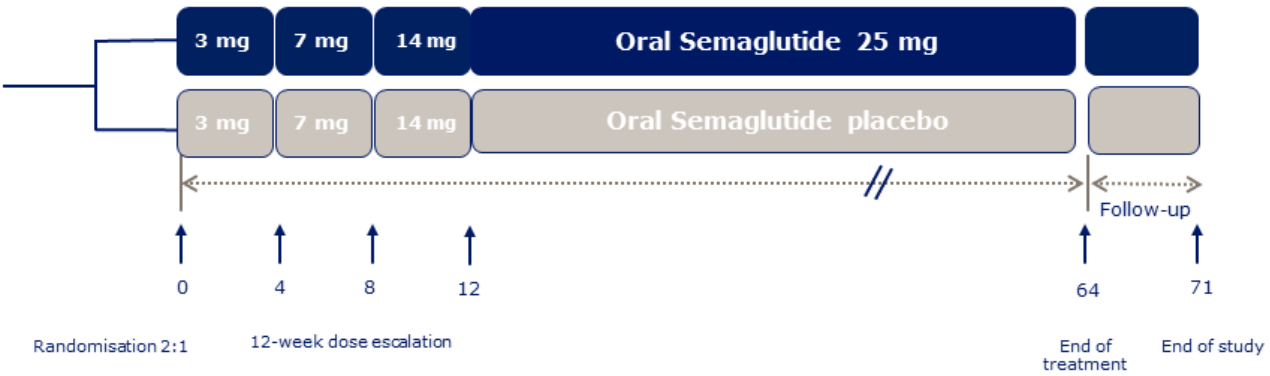
In total, approximately 300 participants will be randomised in a 2:1 ratio to receive either:

- oral semaglutide 25 mg once daily
- oral semaglutide placebo once daily

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

The study consists of a 1-week screening period to assess the participant's eligibility followed by a randomisation visit and a 64-week treatment period. The treatment period is divided into a dose escalation period of 12 weeks and a maintenance period of 52 weeks. After the end-of-treatment visit (V19), all participants will enter a follow-up period of 7 weeks, ended by a follow-up visit (V20, end-of-study). The planned total study duration for the individual participant is approximately 72 weeks (including screening).

Figure 4-1 Study design



4.2 Scientific rationale for study design

The study population will consist of adults with overweight (BMI ≥ 27.0 kg/m^2) and at least one weight-related comorbidity, or with obesity (BMI ≥ 30.0 kg/m^2). These participants represent a clinically relevant population for pharmacological weight management as they are at significant risk for weight-related complications and increased mortality and are likely to benefit from body weight reduction.

First line treatment in weight management is 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 guidelines.[45, 46]

The study has been designed as a parallel, two-armed, placebo-controlled study to compare once daily oral semaglutide 25 mg versus placebo to support the objective of the study. To mitigate

potential bias, the study is randomised, and the active treatment arm is controlled against placebo in a double-blinded design.

The planned treatment duration will be 64 weeks, including 12 weeks of dose escalation followed by 52 weeks on maintenance dose, with an additional 7 weeks follow-up period to account for the exposure and long half-life of semaglutide. A 64-week treatment duration (including 52 weeks on maintenance dose) is considered sufficient to assess weight loss, safety and tolerability in accordance with regulatory guidelines.[45, 46]

4.3 Justification for dose

Due to the complex multifactorial aetiology of obesity, people with obesity have variable responses to treatment, meaning that some people with obesity will require a lower treatment dose to achieve their weight loss goal. To add more flexibility to the treatment, 25 mg oral semaglutide has been selected as the maintenance dose for this study.

The dose of 50 mg oral semaglutide that is being tested in NN9932-4737 (OASIS 1) was originally supported by population PK modelling predicting that exposure levels of 50 mg will reasonably match the exposure levels following 2.4 mg semaglutide s.c. (STEP). The 25 mg oral dose of semaglutide is expected to provide lower exposure levels than 50 mg oral semaglutide and 2.4 mg semaglutide s.c. However, due to variability in exposure levels following oral administration, some subjects taking 25 mg oral semaglutide are expected to achieve exposure levels in the same range as 2.4 mg semaglutide s.c.

Based on prior experience with semaglutide (the PIONEER and SUSTAIN programmes and the phase 2 dose finding trials for oral and s.c. semaglutide, NN9924-3790, and NN9536-4153) and other GLP-1 RAs, a low starting dose and gradual dose escalation of oral semaglutide is expected to mitigate the risk of developing GI AEs. To increase GI tolerability, dose level reductions and extensions of dose-escalation periods will be allowed based on clinical evaluation made by the investigator (Section 6.5.1). Participants will be initiated at a once-daily dose of 3 mg and follow a fixed-dose escalation regimen, with dose increases every 4 weeks to doses of 7, 14 and 25 mg, until the target dose of 25 mg/day is reached after 12 weeks.

4.4 End of study definition

The end of the study is defined as the date of the last visit (V20) 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 (V20).

The primary endpoint is evaluated at visit 19 (week 64). The primary completion date (PCD) is defined as the date of visit 19 (week 64) 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 19 (week 64).

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 patient 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, age ≥ 18 years at the time of signing informed consent
3. Body mass index (BMI) of
   a) ≥ 27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or CV disease OR
   b) ≥ 30.0 kg/m^2

4. History of at least one self-reported unsuccessful dietary effort to lose body weight

5.2 Exclusion criteria

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

Obesity-related:
1. A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records
2. Treatment with any medication indicated for weight management within 90 days prior to screening
3. Previous or planned (during the study period) obesity treatment with surgery or a weight loss device. However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed >1 year prior to screening, (2) lap banding, if the band has been removed >1 year prior to screening, (3) intragastric balloon, if the balloon has been removed >1 year prior to screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year prior to screening
4. Uncontrolled thyroid disease per investigator's discretion

Glycaemia-related:
5. HbA_{1c} ≥ 6.5% (48 mmol/mol) as measured by the central laboratory at screening
6. History of type 1 or type 2 diabetes
7. Treatment with glucose-lowering agent(s) within 90 days prior to screening

Mental health:
8. History of major depressive disorder within 2 years prior to screening

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

General Safety:

14. Presence of acute pancreatitis within 180 days prior to screening
15. History or presence of chronic pancreatitis
16. Personal or first-degree relative history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
17. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR <15 ml/min/1.73 m^2 according to CKD-EPI creatinine equation as defined by KDIGO 2012 classification[52] by the central laboratory at screening
18. History of major surgical procedures involving the stomach potentially affecting absorption of drugs and/or nutrients, as judged by the investigator
19. Presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in situ prostate cancer) within 5 years prior to screening
20. Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina or transient ischaemic attack within 60 days prior to screening
21. Participant presently classified as being in New York Heart Association (NYHA) Class IV
22. Surgery scheduled for the duration of the study, except for minor surgical procedures, in the opinion of the investigator
23. Known or suspected abuse of alcohol or recreational drugs
24. Known or suspected hypersensitivity to study intervention or related products
25. Previous participation in this study. Participation is defined as signed informed consent
26. Participation (i.e., signed informed consent) in any clinical study of an approved or non-approved IMP within 90 days prior to screening
27. Other participant(s) from the same household participating in any oral semaglutide study
28. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method, as defined in Appendix 4 (Section 10.4)
29. Any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the participant's safety or compliance with the protocol

Germany: For country-specific requirements, please refer to Appendix 8 (Section 10.8).

5.3 Lifestyle considerations

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

5.3.1 Dosing instructions, meals and dietary restrictions

- The IMP must:
  - be taken once daily

- be taken on an empty stomach in the morning at least 30 minutes before intake of food, liquids, or other oral medicinal products
    - waiting less than 30 minutes, or taking with food, beverages (other than water) or other oral medication will lessen the effect of oral semaglutide
    - waiting more than 30 minutes might increase the absorption of oral semaglutide.
- be taken with no more than half a glass of water equivalent to 120 mL (4 ounces)
- be swallowed whole
- not be split, crushed, or chewed

- Participants must attend visits fasting according to the flowchart (Section 1.2).
    - Fasting is defined as:
        - no food or liquid, except for water, for at least 8 hours prior to the visit
        - no water 2 hours prior to the visit
    - IMP and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood samples have been obtained

If the participant is not fasting as required, the participant must be called in for a new visit within the visit window to have the fasting procedures performed. However, all non-fasting required procedures can be performed.

5.3.2 Caffeine and tobacco

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

Participants should avoid caffeine and smoking at least 30 minutes prior to measurement of blood pressure.

5.3.3 Diet and physical activity counselling

All participants in both treatment arms will receive counselling with regards to diet (500 kcal deficit per day relative to the estimated total energy expenditure (TEE) calculated once at randomisation) and physical activity (150 min of physical activity per week is encouraged, e.g., walking or use the stairs). Counselling should be done by a dietician or a similar qualified healthcare professional according to the flowchart (see Section 1.2). Participants will be encouraged to record their food intake and physical activity daily via an app or similar tool to assist and evaluate their lifestyle intervention.

Calculation of estimated Total energy expenditure

The TEE is calculated by multiplying the estimated Basal Metabolic Rate (BMR) (See Table 5-1) with a Physical Activity Level value of 1.3.[53]

$$\mathrm{TEE} = \mathrm{BMR} \times 1.3$$

Table 5-1 Equation for estimated Basal Metabolic Rate

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

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

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 SAE.

A screen failure must be made in the randomisation and trial supplies management system/interactive web response system (RTSM/IWRS).

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 sample), re-sampling is allowed for the affected parameter(s).

If a participant is inadvertently randomised in violation of the inclusion and exclusion criteria the following procedure must be performed:

1. Temporary discontinuation of study intervention
   - Treatment discontinuation should be made in the RTSM/IWRS
2. Safety risk evaluation by the principal investigator and the medical responsible from Novo Nordisk to determine whether randomised treatment should be resumed or permanently discontinued
   - In case treatment should be resumed, resumption of treatment should be made in RTSM/IWRS
3. Submission of an important protocol deviation and notification of the IEC/IRB and regulatory authorities according to local requirements

5.5 Run-in criteria and 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), or placebo intended to be administered to a study participant according to the study protocol.

IMP comprise both placebo and comparator.

6.1 Study intervention(s) administered

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

Table 6-1 Study interventions

Intervention/Arm name	Treatment arm 1	Treatment arm 2
Intervention name	Semaglutide/semaglutide C	Oral semaglutide placebo
Intervention type	IMP, test product	IMP, reference therapy
Pharmaceutical form	Tablet	Tablet
Route of administration	Oral	Oral
IMP strength	Maintenance dose: 25 mg per tablet	N/A
Dose and dose frequency	• Semaglutide 3 mg, 7 mg, 14 mg, once daily • Semaglutide C 25 mg, once daily	• Once daily
Dosing instructions and administration	1 tablet in the morning See Section 5.3.1	1 tablet in the morning See Section 5.3.1
Sourcing	Provided by Novo Nordisk	Provided by Novo Nordisk
Packaging[1] and labelling	• Labelled and packaged by Novo Nordisk A/S • Labelled in accordance with Annex 13,[54] local regulations and study requirements • IMP provided in dose pack/HDPE bottle	• Labelled and packaged by Novo Nordisk A/S • Labelled in accordance with Annex 13,[54] local regulations and study requirements • IMP provided in dose pack/HDPE bottle

[1]: A dose pack contains one blister card with 7 tablets. A HDPE (high density polyurethane) bottle contains 30 tablets.

Directions for use

The investigator must document that directions for use was given to the participant verbally and in writing at the first dispensing visit (as specified in the flowchart [Section 1.2]). The investigator should remind the participant of dosing instruction (as described in Section 5.3.1) regularly during dose escalation and afterwards continually throughout the study, as applicable.

Investigational medicinal products (IMP)

The IMP provided by Novo Nordisk are listed in Table 6-2.

Table 6-2 Investigational medicinal product provided by Novo Nordisk

Description	IMP name	Dosage form	Route of administration	Dosing instruction	Packaging [1]
Semaglutide	Semaglutide 3 mg	Tablet	Oral	1 tablet in the morning as described in Section 5.3.1	Dose pack
Semaglutide	Semaglutide 7 mg	Tablet	Oral	1 tablet in the morning as described in Section 5.3.1	Dose pack
Semaglutide	Semaglutide 14 mg	Tablet	Oral	1 tablet in the morning as described in Section 5.3.1	Dose pack
Semaglutide	Semaglutide C 25 mg	Tablet	Oral	1 tablet in the morning as described in Section 5.3.1	HDPE bottle
Placebo	Semaglutide placebo	Tablet	Oral	1 tablet in the morning as described in Section 5.3.1	Dose pack
Placebo	Semaglutide placebo	Tablet	Oral	1 tablet in the morning as described in Section 5.3.1	HDPE bottle

[1]: A dose pack contains one blister card with 7 tablets. A HDPE (high density polyurethane) bottle contains 30 tablets.

6.2 Preparation, handling, storage and accountability

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

- Each site will be supplied with sufficient IMP of all dose levels for the study on an ongoing basis. Study intervention will be distributed to the sites according to number of subjects screened and randomised.

- For selected countries and if permitted by local regulations, the investigator may offer to send IMP from the study site or pharmacy to the participant's home by courier service. The process for sending study intervention from the study site or pharmacy to a participant's home is described in the "Study site/pharmacy instruction for shipment of IMP to participants' homes" document. This document contains detailed instructions for preparing packaging and setting up the pick-up of IMP, handover of IMP from the study site or pharmacy staff to the courier, required temperature monitoring of study intervention, delivery to and receipt of study intervention by the participant. The process for returning IMP 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 study intervention 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 IMP received, and that any discrepancies are reported and resolved before use of the IMP.

- All IMP 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 IMP has been stored outside specified conditions. The IMP 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 IMP accountability and record maintenance (i.e., receipt, accountability and final disposition records).
- The investigator or designee must instruct the participant in what to return at next visit.
- The investigator or designee must ensure the participant is aware of the in-use time of the dispensed IMP (25 mg).
- Drug accountability must be performed in the RTSM/IWRS by registering tablets as either returned, unused or as lost.
- Destruction of IMP 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, opened, un-used, expired or damaged IMP (for technical complaint samples, see Appendix 6 [Section 10.6]) must be stored separately from non-allocated IMP. No temperature monitoring is required.
- Non-allocated IMP, 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/IWRS and assigned to the next available treatment according to the randomisation schedule. IMP will be dispensed/allocated at the study visits summarised in the flowchart (Section 1.2).

At screening, each participant will be assigned a unique 6-digit subject number which will remain the same throughout the study. Each site is assigned a 3-digit number and all subject numbers will start with the site number.

Placebo tablets are visually identical to oral semaglutide tablets and will be available in identical primary and secondary packaging (see Table 6-1). Consequently, investigators and site staff will remain blinded throughout the study.

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

The RTSM/IWRS is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's IMP 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 IMP unless this could delay emergency treatment of the participant.

If a participant's IMP 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/IWRS, sign and date the document. If RTSM/IWRS is not accessible at the time of blind break, the RTSM/IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

6.4 Study intervention compliance

Drug treatment compliance

Throughout the study, the investigator will remind the participants to follow the study procedures and requirements to encourage participant compliance.

When participants self-administer IMP at home, compliance with IMP administration will be assessed, and the assessment documented in source documents at each visit where information is available. If any suspicion of non-compliance arises, apart from occasionally missed doses, the site must enter into a dialogue with the participant, re-emphasising the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Accountability information; counting returned IMP
- Review of dosing diaries
- Questioning of participants about missed doses

IMP start and stop dates will be recorded in the electronic case report form (eCRF).

6.5 Dose modification

Not applicable for this study. Please refer to Section 6.1 for description of missed doses.

6.5.1 Dose escalation studies

Dose escalation should take place during the first 12 weeks after randomisation as illustrated in Table 6-3. All participants should aim at reaching the recommended maintenance dose of 25 mg semaglutide once daily or the corresponding placebo.

Table 6-3 Dose escalation and maintenance of oral semaglutide/semaglutide placebo

		Dose escalation			Maintenance	Follow-up
Study periods	**Screening**	**Randomisation/ Treatment-period 1**	**Treatment-period 2**	**Treatment-period 3**	**Treatment-period 4**	**End-of-treatment**
Duration of each period	2 weeks	4 weeks	4 weeks	4 weeks	52 weeks	7 weeks
Treatment arm						
Oral semaglutide 25 mg	Screening	Oral semaglutide 3 mg Dose pack	Oral semaglutide 7 mg Dose pack	Oral semaglutide 14 mg Dose pack	Oral semaglutide C 25 mg HDPE bottle	Follow-up
Semaglutide placebo	Screening	Placebo Dose pack	Placebo Dose pack	Placebo Dose pack	Placebo HDPE bottle	Follow-up

If a participant does not tolerate the current dose during dose escalation, the participant may prolong the dose escalation phase. If a participant does not tolerate the recommended maintenance dose of 25 mg, the participant may stay at a lower dose level as per the investigator's discretion. However, it is recommended that the participant makes at least one attempt to re-escalate or stay at the recommended maintenance dose of 25 mg. Deviations from the planned dose regimen should only be allowed if randomised treatment would otherwise be discontinued.

It is recommended that the investigator consults Novo Nordisk in case of persistent deviations from the planned escalation regimen.

Missed doses

If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day.

If several doses of IMP are missed, and the participant does not meet any of the discontinuation criteria, the participant should be encouraged to re-commence the treatment if considered safe as per the investigator’s discretion (Section 7.1). The IMP should be continued as early as the situation allows. In case of questions related to re-initiation of IMP, the investigator should consult Novo Nordisk.

6.6 Continued access to study intervention after end of study

When discontinuing study intervention, the participant should be transferred to a suitable marketed product at the discretion of the investigator.

Considering the long half-life of semaglutide, and to avoid over-exposure to GLP-1RAs and interference with safety data collection, initiating GLP-1RA should be avoided between the end-of-treatment visit (V19) and the end-of-study visit (V20).

6.7 Treatment of overdose

There is no specific antidote to semaglutide. Effects of overdose with semaglutide may be associated with GI disorders.

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 and laboratory abnormalities, and appropriate supportive treatment should be initiated according to the participants' clinical signs and symptoms. A prolonged period of observation and/or treatment for these symptoms may be necessary, taking into account the long half-life of oral 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 oral semaglutide for weight management IB[49] and any updates hereof.

6.8 Concomitant therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) and vaccines other than the IMP 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
- Primary indication
- Dates of administration including start and stop dates
- Dose (only to be recorded for antihypertensive, lipid-lowering medication and levothyroxine)
- Time of dosing (only to be recorded for levothyroxine)

Need for change in antihypertensive or lipid-lowering treatment should be continuously evaluated by the investigator at every visit, and any changes should be recorded as outlined above. The overall evaluation of change (i.e., either increase, decrease or no change) from randomisation should be recorded at the end-of-treatment (V19) in the relevant forms.

During the study, participants should not initiate any anti-obesity medication or treatment which is not part of the study procedures. If such treatment is initiated, the participants should be instructed to stop the treatment.

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 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 IMP must be discontinued if any of the following applies for the participant:
1. Safety concern as judged by the investigator
2. Suspicion of acute pancreatitis
3. Pregnancy
4. Intention of becoming pregnant
5. Simultaneous use of an approved or non-approved IMP in another clinical study

Participants meeting discontinuation of study intervention criterion no. 1, 2, 3 and 4 are allowed to resume study intervention if the criteria are no longer met (see Section 7.1.1).

Efforts must be made to have the participants who discontinue study intervention attend and complete all scheduled visit procedures until the time of the originally scheduled end-of-treatment visit (V19) and end-of-study visit (V20) to collect the required data for the analysis of the primary (and confirmatory secondary) estimands/endpoints.

If the participants do not wish to attend the scheduled clinic visits, efforts should be made to have the remaining visits converted to phone contacts, however, efforts should be made to have the subject attend at least the following visits on-site:
- V7 (week 16)
- V15 (week 48)
- V19 (end-of-treatment visit, week 64)
- V20 (end-of-study visit, week 71)

A visit window of ±2 days is allowed for visits V7, V15 and V19. For the end-of-study visit (V20), the visit window is +5 days.

For participants who have discontinued study intervention >7 weeks prior to the end-of-treatment visit (V19) and under no circumstances are willing to attend the scheduled end-of-study visit (V20), the site can suggest combining the two visits. If a participant is unwilling to attend the remaining visits, information about the attempts to follow up with the subject must be documented in the participant's medical record. Participants must be informed about the continuous scientific importance of their data, even if they discontinue study intervention.

Pregnancy testing is advised 7 weeks after premature discontinuation of study intervention (see Appendix 4, Section 10.4).

The primary reason for discontinuation of study intervention must be specified in the eCRF at the end of treatment visit, and final IMP accountability must be performed. Discontinuation of treatment must be made in the RTSM/IWRS.

7.1.1 Temporary discontinuation of study intervention

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

In case of suspicion of acute pancreatitis, the randomised treatment should promptly be interrupted. Appropriate actions should be initiated, including local measurement of amylase and lipase (see Appendix 3, Section 10.3 for AE reporting).

If acute pancreatitis is confirmed, treatment with IMP should not be resumed. If the Atlanta criteria[55] are not fulfilled, and thus, the suspicion of acute pancreatitis is not confirmed, treatment with IMP can be resumed. IMP may be resumed for participant with a gallstone-induced pancreatitis in case of cholecystectomy.

Treatment discontinuation should always be made in the RTSM/IWRS when IMP is paused/temporarily discontinued. If IMP can be resumed, treatment resumption must be made in the RTSM/IWRS to resume IMP. If IMP is not allowed to be resumed, and thus permanently discontinued, no treatment resumption should be made in the RTSM/IWRS.

Missed doses must be recorded in the diary by the participant. At each visit, the investigator must evaluate if the participant is still taking the IMP, e.g., by reviewing the diary. If doses have been missed for more than 3 consecutive days, it must be recorded in the eCRF. If a treatment discontinuation has previously been made in the RTSM/IWRS to indicate discontinuation of study intervention, a new treatment resumption must be made to resume study intervention.

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 the end-of-treatment visit (V19). See the flowchart (Section 1.2) for data to be collected.

Final IMP accountability must be performed even if the participant is not able to come to the site. A discontinuation session must be made in the RTSM/IWRS.

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 eCRF.

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 at the end-of-study visit (V20), 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 (Section 1.2) and Appendix 2 (Section 10.2).

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 (Section 1.2), is essential and required for study conduct.

The investigator must ensure to keep regular contact with each participant throughout the entire study, and always have updated contact information. Even if a visit is missed and it is not possible to reschedule, every effort must be made to have all participants followed for the primary endpoint and AEs.

It is the responsibility of the investigator to schedule the visits and contacts as per the flowchart (Section 1.2) and to ensure they take place. See Section 6.4 for treatment compliance.

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

1. Electrocardiogram (ECG) (Section 8.2.3) and vital signs (Section 8.2.2)
2. Blood samples
3. Clinical outcome assessments: patient reported outcome (PRO) instruments (Section 8.1.4) and mental health assessment instruments (see Section 8.2.4)
4. Other assessments

Paper diaries will include the following in relation to the visit they support:

- Reminder to return diary at next site visit
- Instruction on how to use the diary
- Information to be recorded:
    - dose taken for each study day
    - time of dose (for PK visits)
    - actual dose taken

Participants must receive training in how to record dosing information in the designated paper diary. Only the participant can make entries and corrections in the diaries, unless otherwise stated.

Source data of clinical assessments performed and recorded in the eCRF must be available and will usually be the participant's medical records. Additional recordings to be considered source data include, but are not limited to, laboratory reports, ECGs, diary recordings, clinical outcome assessments. Ensure to transcribe into the eCRF:

- Evaluation of ECG
- Information collected in the diary

Review of diaries, PRO and mental health assessment instruments, ECG, laboratory reports, etc., must be documented in the source documents or the participant's medical record. If clarification of entries or discrepancies in the 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 laboratory samples may be taken for technical issues, e.g., lost or haemolysed sample, and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 (Section 10.2) for further details on laboratory samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart (Section 1.2) and in Appendix 2 (Section 10.2).

8.1.1 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.

8.1.2 Body weight

Body weight will be measured and recorded as specified in the flowchart (Section 1.2).

Body weight should be measured on a digital scale, preferably using the same scale throughout the study. The scale must be calibrated yearly as a minimum, unless the manufacturer or local requirements certifies that calibration of the scale is valid for the duration of the study.

Measurement must be performed without shoes, on an empty bladder, and only wearing light clothing and recorded in the eCRF in kilogram [kg] or pounds [lb] with the precision of 1/10 unit (e.g., 75.3 kg /166.0 lb).

At the screening visit, the body weight and height must be recorded in the eCRF, which calculates the BMI based on the screening data.

8.1.3 Waist circumference

Waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest.

Waist circumference will be measured and recorded as specified in the flowchart (Section 1.2).

The measurement of waist circumference should be performed using the non-stretchable measuring tape provided by Novo Nordisk and recorded in the eCRF with one decimal.

Measurement must be performed in a standing position with arms down the side and feet together while the participant is breathing normally. The measuring tape should touch the skin but not compress soft tissue and twists in the tape should be avoided.

8.1.4 Clinical outcome assessments

Participants should be given the opportunity to complete the questionnaires by themselves without interruption. The questionnaires take approximately 20 minutes to complete. The questionnaires will be available in a linguistically validated translated version. The following PRO instruments will be used:

- Impact of Weight on Quality of Life-Lite Clinical Trials (IWQOL-Lite-CT) Version 1.1
    - IWQOL-Lite-CT is a 20-item obesity-specific PRO measure used to assess the impact of body weight changes on patient's physical and psychosocial functioning in three composite scores (Physical Function, Physical and Psychosocial) and a Total score.[56]
    - IWQOL-Lite-CT must be completed at V2, V6, V7, V11, V15 and at end-of-treatment (V19).

- Impact of Weight on Daily Activities Questionnaire (IWDAQ) version 1.0
    - IWDAQ is an 18-item obesity-specific PRO measure developed to evaluate daily activity limitations associated with excess weight. It uses an adaptive questionnaire design where the participant chooses the three IWDAQ activities they would most like to improve with weight loss and rate the degree of limitations in each of the three activities at baseline. The same three activities are assessed for degree of limitations at follow-up to allow for tracking of activities relevant to each individual.[57]
    - IWDAQ must be completed at V2, V11 and at end-of-treatment (V19).

- Patient Global Impression of Status (PGI-S) and Patient Global Impression of Change (PGI-C)

PGI-S and PGI-C are single-item global rating PRO measures that are used to evaluate the responder threshold. The following PGI-S and PGI-C measures are included:

- PGI-S Physical Functioning
- PGI-C Physical Functioning
- PGI-S Ability to do things needed
- PGI-C Ability to do things needed
- PGI-S Ability to do things would like
- PGI-C Ability to do things would like

PGI-S must be completed at V2, V11 and at end-of-treatment (V19).
PGI-C must be completed at V11 and at end-of-treatment (V19).

- Control of Eating questionnaire (COEQ)

Control of Eating Questionnaire (COEQ) is designed to assess the intensity and type of food cravings, as well as subjective sensations of appetite and mood. For this trial a 19-item

11-point numeric rating scale version will be used. The two items "How hungry have you felt?" and "How full have you felt?" are scored individually and the remaining 17 items in the questionnaire are grouped into 4 domains: Craving Control, Positive Mood, Carving for Sweet, and Craving for Savoury. The COEQ must be completed at V2, V11, end-of-treatment (V19) and at follow up (V20).

- Three Factor Eating Questionnaire-Revised 18-item (TFEQ-R18V2) Version 2
  TFEQ-R18V2 was developed to assess eating behaviour in people with obesity and people without obesity in epidemiological studies and clinical studies. It includes 18 items which are aggregated to 3 separate scales: cognitive restraint, uncontrolled eating, and emotional eating. Higher scores indicate more uncontrolled, restrained, and emotional eating. It has no specified recall period. The TFEQ-R18V2 must be completed at V2, V11, end-of-treatment (V19) and at follow up (V20).

8.2 Safety assessments

Planned time points for all safety assessments are provided in the flowchart (Section 1.2) and in Appendix 2, Section 10.2.

Medical history is a medical event that the participant experienced prior to the time point from which AEs are collected.

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.

Only relevant and clinically significant medical history including COVID-19, as judged by the investigator, must be recorded in the Medical history/Concomitant illness forms in the eCRF according to the flowchart (Section 1.2). Relevant medical history/concomitant illness includes, but is not limited to, the following pre-specified disease classes:

- Breast neoplasm
- CV disorder and procedure
- Gallbladder disease and procedure
- Gastrointestinal disorder and neoplasm
- Genitourinary tract disorder
- Glucose metabolism disorder
- Kidney disease
- Liver disease
- Musculoskeletal system disorder
- Pancreatic disease
- Psychiatric disorder
- Respiratory disorder
- Skin cancer and skin disorder

- Thyroid disorder
- Weight disorder
- Risk factors for breast (for female participants only), colon and skin cancer (including family history of breast, colon and/or skin cancer, age at time of diagnosis for relevant family members, predisposing factors for breast and skin cancer, menarche/menopause, breast cancer screening, and hormone replacement therapy)
- Weight history (including previous weight, debut time of overweight, previous weight loss attempts, previous use of anti-obesity prescription medication, and considerations regarding bariatric surgery)

A lack of any records of the above mentioned relevant medical history/concomitant illness is interpreted as if the participant did not have the condition at or prior to baseline.

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 Appendix 3, Section 10.3).

8.2.1 Physical examinations

A physical examination will include assessments of general appearance, the CV, respiratory, gastrointestinal, central and peripheral nervous systems, skin, abdomen, thyroid gland and breasts (female only).

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

Height will be measured and recorded as specified in the flowchart (Section 1.2).

- Height should be measured without shoes in centimetres or inches and recorded to nearest ½ cm or ¼ inch.

8.2.2 Vital signs

Pulse rate as well as systolic and diastolic blood pressure will be assessed as specified in the flowchart (Section 1.2). The method for measuring systolic and diastolic blood pressure needs to follow the standard clinical practice at site.

Blood pressure 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.

8.2.3 Electrocardiograms

12-lead ECG will be obtained as outlined in the flowchart (Section 1.2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS and QT intervals.

The investigator must perform review of the ECG for clinically significant abnormal findings.

ECG must be performed according to the manual from the supplier.

8.2.4 Mental health assessment instruments

- Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline and C-SSRS Since Last Visit[58]

  C-SSRS is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation. The questionnaires will be conducted as an interview by the investigator or a qualified delegate. The questionnaires will be available in a linguistically validated translated version.

  The investigator or qualified delegate must complete sufficient training prior to conducting the C-SSRS questionnaire interview.

  C-SSRS Baseline must be completed at screening (V1).
  C-SSRS Since Last Visit must be completed at V11 and at end-of-treatment (V19).

- Patient Health Questionnaire-9 (PHQ-9)[59]

  PHQ-9 is a 9-item depression module of the participant health questionnaire, which is a self-administered diagnostic tool used for assessment of mental disorders. The questionnaire will be available in a linguistically validated translated version.

  Participants should be given the opportunity to complete the questionnaire by themselves without interruption. The questionnaire takes approximately 5 minutes to complete.

If a participant has a PHQ-9 score of 10-14 (both inclusive) the participant should be referred to a mental health professional (MHP) if judged relevant by the investigator. If referral is not deemed relevant this, along with the reason why, must be documented in the participants medical records.

A participant must be referred to an MHP if:
- the participant has a PHQ-9 score ≥15 or
- the participant has any suicidal behaviour or
- the participant has any suicidal ideation of type 4 or type 5 on any C-SSRS assessment or
- in the opinion of the investigator, it is necessary for the safety of the participant

Referral to an MHP should be performed if any of the above referral criteria are met at any time during the trial, including at the screening and end-of-trial visit. If one or more of the referral criteria are met, the investigator should explain to the participant why the referral and psychiatric evaluation by an MHP is needed. If the participant refuses to be referred to an MHP, the participants decision should be documented in the participants medical record and the investigator must assess if it is safe for the participant to continue in the study or if the participant should be discontinued from randomised treatment.

If a participant's psychiatric disorder can be adequately treated with psychotherapy and/or pharmacotherapeutic treatment, then the participant, at the discretion of the investigator (and in agreement with the MHP), may continue in the study. Otherwise, the participant must be discontinued from randomised treatment due to safety concern as judged by the investigator.

PHQ-9 must be completed at screening (V1), at V11 and at end-of-treatment (V19).

8.2.5 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 (Section 1.2).

8.2.6 Pregnancy testing

Women 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 according to the flowchart (Section 1.2).

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

Pregnancy testing is advised 7 weeks after premature discontinuation of randomised study intervention (see Appendix 4, [Section 10.4]).

Additional pregnancy testing should be performed during the treatment period, if required locally (see Appendix 8, [Section 10.8]).

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. This always includes medication error, misuse and abuse of IMP. The relevant event(s) are listed below in Table 8-1.

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

Event type
Medication error
Misuse and abuse of IMP
Acute pancreatitis
Acute gallbladder disease
Neoplasms
Hepatic events

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 screening visit and until the end-of-study visit (V20) at the time points specified in 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. Germany: For country-specific requirements, please refer to Appendix 8 (Section 10.8).

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 IB 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 first exposure to IMP and until pregnancy outcome.

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

Participant must discontinue randomised IMP as described in Section 7.1.

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 6 (Section 10.6).

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

8.4 Pharmacokinetics and pharmacodynamics

8.4.1 Pharmacokinetics

- The purpose of measuring plasma semaglutide levels is to perform population PK (Pop-PK) analyses and to assess the level of drug interference in the anti-semaglutide antibody analysis. The samples will also be used to evaluate the PK of semaglutide as well as safety or efficacy aspects that address concerns arising during or after the study. Residual sample material may be used for exploratory investigation of metabolites and bioanalysis assay development and troubleshooting in relation to the pharmacokinetic assay.

- Single blood samples will be drawn for all participants on visits specified in the flowchart (Section 1.2) and in Appendix 2 (Section 10.2). The PK sample taken at V20 (end-of-study) will not be included in the Clinical Study Report (CSR) and instead provided together in a separate analytical report.

- Participants must be instructed to withhold their IMP dose in the morning of the clinic visit where fasting is required (see Section 1.2 and Section 5.3.1).

- The exact timing (date and time) of last IMP dose prior to PK sampling must be recorded in the diary by the participant and transcribed into the eCRF and recorded on the laboratory form.

- Blood samples for PK assessments must be collected, handled and shipped according to the description in the laboratory manual. The bioanalysis of semaglutide PK will be performed by a special laboratory. Semaglutide PK samples will be stored at the special laboratory responsible for PK until final CSR in case Novo Nordisk requests further analysis of the PK samples. Details of the bioanalysis will be outlined in a bioanalytical study plan issued by the special laboratory. Bioanalysis of plasma samples for semaglutide will be carried out using a validated LC-MS/MS assay.

8.4.2 Pharmacodynamics

Not applicable for this study.

8.5 Genetics

A blood sample for DNA analysis will only be collected from subjects who have consented to participate in the genetic analysis. Participation and donation of a blood sample for the genetic research is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

Sampling will be done according to Appendix 2 (Section 10.2). In the event of sample handling failure, a replacement genetic blood sample may be requested from the participant.

Refer to Appendix 5 (Section 10.5) for further details.

Genetic samples are collected for future research. Refer to Section 8.8 for further details and Appendix 7 (Section 10.7) for retention.

8.6 Biomarkers

Collection of samples for biomarker research is part of this study. The following sample is required and will be collected from all participants in this study:

- Biomarker linked to CV risk:
  - High sensitive C-reactive protein

Biosamples are collected for future biomarker analysis. Refer to Section 8.8 for further details and Appendix 7 (Section 10.7) for retention.

8.7 Immunogenicity assessments

Anti-semaglutide antibodies
Blood samples for measurements of binding antibodies against semaglutide will be collected at prespecified time points according to Appendix 2 (Section 10.2), and first sample should be collected prior to the first dose of IMP at the randomisation visit. The collected blood samples will only be analysed if deemed necessary for clarification of unexpected drug exposure or other safety issues that may be related to antibody formation, or if deemed relevant for other reasons. The analysis will be performed by Novo Nordisk or a special lab appointed by Novo Nordisk. If the analysis is performed only for clarification of unexpected drug exposure or other safety issues, data as well as assay method description will be reported outside the CSR for this study.

Procedures for sampling, handling, storage, labelling and shipment of samples must be performed in accordance with the laboratory manual. Residual antibody samples will be retained (see Appendix 7 [Section 10.7]).

Hypersensitivity

In the event of a systemic hypersensitivity reaction, as judged by the investigator, the participant should be called in as soon as possible to have additional blood samples taken in order to analyse the following parameters:

- Tryptase (optimal 0.5–2 hours post the hypersensitivity reaction)
- Anti-semaglutide IgE antibodies
- Anti-semaglutide binding antibodies

The blood sampling should be repeated 1–2 and 4+ weeks following the systemic hypersensitivity reaction. In addition, the test should also be performed on samples drawn prior to first administration of study product. Analysis of anti-semaglutide IgE, anti-semaglutide binding antibodies and tryptase will be performed at Novo Nordisk.

8.8 Human biosamples for future research

Collection of biosamples for future analysis is a component of this study. The samples will be stored in a biobank to allow for future analyses of biomarkers, both genetic and circulating. The analysis may include biomarkers currently known or discovered in the future. Participation in the future research is optional, and participants must sign a separate informed consent to indicate their participation in the biobank component of the study. Participants who do not wish to participate in the biobank component(s) may still participate in the study. Blood samples will be collected according to Appendix 7 (Section 10.7) and stored for future use.

Genetic analyses may include analysis of candidate genes or agnostically investigating the whole genome with the purpose of understanding and predicting response to semaglutide as well as to understand obesity or other related conditions.

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

The samples may be analysed as part of a multi-study assessment. Results will not be reported to the investigator for assessments of AEs nor will they be part of the CSR. The primary objective of the analysis is to investigate biomarkers on a population level and results are very unlikely to have clinical utility on an individual level. Furthermore, the analyses will be done on pseudonymised data. Therefore, any outcome of the analyses will not be reported directly to participants or sites. The result may be reported in publications, at scientific conferences or to authorities.

The analyses are purely exploratory and are likely to be performed after the study has come to an end. Accordingly, results will therefore not be part of the CSR.

The human biosamples for future research will be stored for up to 15 years after end-of-study at a central laboratory or appropriate storage facility (see Appendix 7 [Section 10.7]).

South Korea: For country-specific requirements, please refer to Appendix 8, Section 10.8.

8.9 Health economics

Not applicable for this study.

9 Statistical considerations

The statistical analysis plan (SAP) will be finalised prior to partial database lock (DBL) (see Section 9.6) 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 key secondary endpoints.

9.1 Statistical hypotheses

The confirmatory hypotheses to be tested are superiority of oral semaglutide 25 mg once daily vs placebo for the co-primary endpoints, as well as superiority of oral semaglutide 25 mg once daily vs placebo for the confirmatory secondary endpoints. Superiority needs to be confirmed for both primary endpoints to confirm the primary objective. More details on the statistical models are given in Section 9.3.

For the primary estimands with the co-primary endpoints, 1) change in body weight (%) from baseline to end of treatment (week 64) and 2) ≥ 5% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 64), the following confirmatory 1-sided hypotheses are planned to be tested for semaglutide 25 mg versus placebo. Operationally, the hypotheses will be evaluated by 2-sided tests.

The superiority tests of oral semaglutide 25 mg once daily vs. placebo will be carried out as follows:

Let $\mu_{semaglutide}$ and $\mu_{placebo}$ denote the true mean of % weight change for oral semaglutide 25 mg once daily and placebo group, respectively. The hypothesis and alternative hypothesis tested are

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

The null hypothesis will be rejected, and superiority claimed, if the upper limit of the estimated two-sided 95% CI for the true treatment difference ($\mu_{semaglutide}$ minus $\mu_{placebo}$) is below 0.

Let $OR_{semaglutide/placebo}$ denote the true odds ratio between oral semaglutide 25 mg once daily and placebo. The hypothesis and alternative hypothesis tested are:

$$H: OR_{semaglutide/placebo} \leq 1 \; vs$$
$$H_A: OR_{semaglutide/placebo} > 1.$$

The null hypothesis will be rejected, and superiority claimed, if the lower limit of the estimated two-sided 95% CI is above 1.

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. Consequently, all previous hypotheses must be rejected in order to proceed to the next hypothesis

test thereby preserving the type I error rate. The order of hypothesis tests is shown in Table 9-1. All hypothesis tests are for the superiority of semaglutide 25 mg versus placebo.

Table 9-1 Hierarchical order for hypothesis testing

Test order	Endpoint	Target	Comparator
1	Relative change in body weight	Semaglutide	Placebo
2	Achievement of body weight reduction ≥ 5% (Yes/No)	Semaglutide	Placebo
3	Achievement of body weight reduction ≥ 10% (Yes/No)	Semaglutide	Placebo
4	Achievement of body weight reduction ≥ 15% (Yes/No)	Semaglutide	Placebo
5	Achievement of body weight reduction ≥ 20% (Yes/No)	Semaglutide	Placebo
6	Change in IWQOL-Lite for CT Physical Function Score	Semaglutide	Placebo

9.2 Analysis sets

The following populations are defined:

Table 9-2 Defined populations

Participant Analysis Set	Description
Full analysis set (FAS)	All participants randomised. Participants will be analysed according to the randomised treatment.
Safety analysis set (SAS)	All participants randomly assigned to study treatment and who take at least 1 dose of IMP. Participants are analysed according to the treatment they actually received.

The full analysis set is used to analyse endpoints related to the efficacy objectives and the safety analysis set is used to analyse the endpoints and assessments related to safety.

Two observation periods are defined for each participant:
1. In-study: The in-study period is defined as the uninterrupted time interval from date of randomisation to date of last contact with study site.
2. On-treatment (with IMP): In general, the on-treatment period will be from the date of first IMP administration to date of last IMP administration plus three days, except when randomised treatment is temporarily discontinued. If randomised treatment is temporarily discontinued, the on-treatment period ends 3 days after the treatment discontinuation and resumes on the day randomised treatment is resumed. Hence, the on-treatment period can consist of several disjoint periods.

In general, the on-treatment period will therefore be from the date of first IMP administration to date of last IMP administration excluding potential off-treatment time intervals of at least 3 consecutive days.

For the evaluation of adverse events, the lag time for each on-treatment time interval is 7 weeks.

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

The primary estimand uses all data from the in-study observation period and the additional estimand uses data from the on-treatment observation period.

9.3 Statistical analyses

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

Results from statistical analyses will generally be accompanied by two-sided 95% confidence intervals and corresponding two-sided p-values. Superiority will be claimed if p-values are less than 5% and the estimated treatment contrasts favours oral semaglutide 25 mg once daily.

9.3.1 General considerations

Taxonomy of week 64 assessments

For each participant, a given week 64 assessment may be available or missing as specified in Table 9-3. The assessment availability is defined by participant and by assessment; thus, for body weight at week 64, a participant may be characterised as 'available on randomised treatment (AT)', whereas for waist circumference, the participant may be characterised as 'missing on randomised treatment (MT)'.

Table 9-3 Taxonomy for participants based on week 64 assessments

Availability	Participants on randomised treatment at week 64	Description	Abbreviation
Available	Yes	**Available on randomised treatment**: Participants who complete the study on randomised treatment with an assessment at week 64: Includes those that stop and restart IMP.	AT
	No	**Available but discontinued** Participants who discontinued randomised treatment prematurely but returned to have an assessment at week 64. These are also called retrieved participants	AD
Missing	Yes	**Missing on randomised treatment**: Participants who complete the study on randomised treatment without an assessment at week 64: Includes those that stop and restart IMP.	MT
	No	**Missing and discontinued**: Participants who discontinued randomised treatment prematurely and did not return to have an assessment at week 64. These are also called non-retrieved participants	MD

Handling of missing baseline data

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.

9.3.2 Primary endpoint(s)/estimand(s) analysis

Relative change from baseline (week 0) to week 64 in body weight (%)

Relative change from baseline (week 0) to week 64 in body weight (%) is defined as:

$$\% \text{ weight change} = \frac{(\text{body weight at week 64} - \text{body weight at baseline})}{\text{body weight at baseline}} \times 100.$$

Analyses addressing the primary estimand

The analysis model for % weight change is a linear regression (ANCOVA) of % weight change with randomised treatment as a factor and baseline body weight (kg) as a covariate. Further, the model will allow for heterogeneous residual variances across treatment groups. The estimated treatment differences between oral semaglutide 25 mg once daily and placebo will be reported together with the associated two-sided 95% confidence intervals (CI) and corresponding two-sided p-values.

Handling of missing week 64 values for the primary estimand

All available data at week 64 (AT and AD) are used and missing values (MT and MD) at week 64 will be imputed and the endpoints will be derived from the imputed values. Several approaches for imputation will be applied. First, a description of the primary imputation approach to address the primary estimand for the primary endpoints is given followed by a description of the sensitivity analyses used to assess the robustness of the primary analysis conclusions. The sensitivity analyses investigate how assumptions on body weight development after discontinuation of randomised study treatment impact the estimated treatment contrasts between oral semaglutide 25 mg once daily and placebo.

Primary imputation approach for the primary estimand

Multiple imputation approach using retrieved drop-outs (RD-MI): The primary imputation approach for the primary estimand is a multiple imputation similar to the one described by McEvoy.[60] Missing body weight measurement at week 64 for non-retrieved participants (MD) are imputed using assessments from retrieved participants (AD) in each randomised treatment arm. This will be done according to the timing of last available observation (LAO) of body weight. Missing body weight measurements at week 64 for participants on randomised treatment (MT) are imputed by sampling from available measurements at week 64 from participants on randomised treatment (AT) in the relevant randomised treatment arm. The multiple imputation approach is done in three steps:

1. **Imputation:** Defines an imputation model using retrieved participants (AD) from FAS and done within groups defined by randomised treatment. The model will be a linear regression of body weight (kg) at week 64 with gender (male/female), as factors and baseline body weight (kg), timing of LAO and LAO of body weight (kg) as covariates. No interactions will be included. If any participants are MT, an imputation model for missing body weight measurements at week 64 for MT participants will also be defined using AT participants in a similar way. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 64 body weight

values for each randomised treatment arm. This will be done 1,000 times and results in 1,000 complete data sets.

2. **Analysis**: Analysis of each of the 1,000 complete data sets, using the analysis models (ANCOVA) results in 1,000 estimations.

3. **Pooling**: The results obtained from analysing the datasets will be combined using Rubin's formula. When applying multiple imputation to the analysis of a binary endpoint Rubin's rule is applied on the logit scale.[61]

The multiple imputations will be generated using Novo Nordisk study number 99324954 as seed number.

Sensitivity analyses

Jump to reference multiple imputation approach (J2R-MI): Missing values of body weight at week 64 (MT and MD) for all treatment groups are imputed by sampling among all available assessments at week 64 in the placebo group (AT and AD). This approach is based on 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.[62] The multiple imputation approach is done as above with the first imputation step replaced by the following:

1. **Imputation**: Defines an imputation model using semaglutide placebo participants from FAS with a week 64 measurement (AT and AD). The model will be a linear regression of body weight (kg) at week 64 with gender (male/female), BMI (kg/m^2) (in categories 27-<35, 35-<40, ≥40 as factors and baseline body weight (kg) as covariate. No interactions will be included. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 64 body weight values for each randomised treatment arm. This will be done 1,000 times and results in 1,000 complete data sets.

The jump to reference approach is the basis for the sample size calculations.

Tipping-point multiple imputation analysis (TP-MI): This sensitivity analysis evaluates the robustness of the superiority conclusions to violations of the MAR assumption. First, missing body weight data are imputed according to the primary multiple imputation approach. Then, a penalty is added to the imputed values at week 64. The approach is to explore a range of penalties for both treatment groups, and the impact these would have on the study conclusions. A 2-dimensional space of penalties will be explored for the two treatment groups.

Analysis addressing the additional estimand

The additional estimand for % weight change addresses the efficacy of semaglutide 25 mg once daily and will be assessed using a 'MMRM for IMP estimand'. Week 64 assessments for retrieved drop-outs (AD) are not used in this analysis. The MMRM for IMP estimand will use assessments only from participants who are taking the randomised treatment until end-of-treatment or until first discontinuing of randomised treatment. The date of the last dose before first discontinuation of randomised treatment plus 3 days will be used as the latest date for using assessments in this

MMRM. The assessment closest in time and before the date of the last dose before first discontinuation of randomised treatment plus 3 days will be used as last assessment on randomised treatment.

For participants who initiate rescue interventions before completion or first discontinuation of randomised treatment, the date of starting weight management drugs or undergoing bariatric surgery will be used as latest date for using assessments in this MMRM. Similarly, the assessment closest in time and before the date of starting weight management drugs or undergoing bariatric surgery will be used as last assessment on randomised treatment. The MMRM for IMP estimand will be fitted using % weight change and the same factor and covariate as for the primary analyses 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.

Achievement of body weight reduction ≥ 5%

A body weight reduction of at least X% from baseline (week 0) to week 64 is defined as

$$\text{X\% responder} = \begin{cases} 1 \text{ if } \% \text{ weight change} \leq -\text{X\%} \\ 0 \text{ if } \% \text{ weight change} > -\text{X\%} \end{cases}$$

The analysis model for the 5% responder endpoint is a logistic regression using randomised treatment as a factor and baseline body weight (kg) as covariate. The estimated odds ratios (OR) between oral semaglutide 25 mg once daily and placebo will be reported together with the associated two-sided 95% CIs and corresponding two-sided p-values.

For missing body weight measurements at week 64 the 5% responder variable is derived based on imputed values using the methods specified above.

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.

9.3.3 Secondary endpoint(s) analysis

Confirmatory secondary endpoint

The continuous confirmatory secondary endpoints will be analysed using the same analysis and imputation models as used to address the primary estimand for the primary continuous endpoint and also the same sensitivity analyses will be done.

The binary confirmatory secondary endpoint will be analysed using the same analysis and imputation models as used to address the primary estimand for the primary binary endpoint and also the same sensitivity analyses will be done.

Supportive secondary endpoints

Details on the statistical analyses of the supportive secondary endpoints will be available in the SAP, which will be completed prior to the partial DBL.

9.3.4 Exploratory endpoint(s)/estimand(s) analysis

Details on the statistical analyses of the exploratory endpoints will be available in the SAP, which will be completed prior to the partial data base lock.

9.3.5 Other safety analyses

All safety analyses will be made on the safety analysis set.

9.3.6 Other analyses

For other analyses, please refer to the SAP.

9.3.6.1 Pharmacokinetic modelling

Population PK modelling and exposure-response analyses may be included to support dose selection and to explore the benefits of high versus lower doses of semaglutide in adults with overweight and obesity.

The modelling will include data from all randomised participants that were exposed to semaglutide in this study and might be performed as a meta-analysis including data from historical studies. Actual dose and date of administration of last dose before PK sampling will be registered in the eCRF and used in the analysis, together with actual time point for PK sampling.

A modelling analysis plan will be prepared before partial DBL for the study, outlining details of the analysis. The results will be reported separately from the CSR.

9.4 Interim analysis

Not applicable for this study.

9.5 Sample size determination

The sample size has been determined to ensure adequate statistical power to confirm superiority of oral semaglutide 25 mg once daily to placebo with respect to the co-primary endpoints as well as to enable evaluation of safety, tolerability and ensure sufficient exposure.

Given that semaglutide has been investigated in several large clinical programmes for obesity (s.c. - NN9536 (STEP)) and diabetes (oral – NN9924 (PIONEER) - and s.c. - NN9535 (SUSTAIN)) 300 participants are considered sufficient to evaluate the efficacy of oral semaglutide for weight management.

In the analysis approach addressing the primary estimand, week 64 assessments from retrieved participants (AD) are used. These data are also used to impute missing week 64 measurements for non-retrieved participants (MD). The imputation is done separately within each treatment arm (see description below). However, for the power calculations missing values (MT and MD), regardless of treatment arm, are assumed to be similar to placebo participants. These assumptions are likely conservative with respect to the power and correspond to the jump to reference sensitivity analysis planned below.

The following assumptions have been used for the power calculations:

- 5% significance level
- 2:1 randomisation
- For continuous endpoints the t-test on the mean difference assuming equal variances is used
- For binary endpoints the Pearson chi-square test for two independent proportions is used
- Based on data from STEP 1
- 20% of participants discontinue treatment permanently (18.9% in STEP 1) and
- 70% of these are retrieved (AD) at week 64 (69.3% in STEP 1)
- All participants in the placebo arm are assumed to have same effect as participants who complete the study on placebo (AT)
- Retrieved participants (AD) in the active arm are assumed to have an effect corresponding to half the treatment difference (compared to placebo) of participants who complete the study on treatment (AT)
- Non-retrieved participants (MD) in the active arms are assumed to have an effect corresponding to placebo
- Further assumptions made to calculate the power for the co-primary endpoints are based on findings from other projects conducted by Novo Nordisk (NN8022 (SCALE), NN9535 (SUSTAIN), NN9924 (PIONEER)), and NN9536-4153. The below assumptions have been used in the power calculations. The treatment differences for change in body weight are estimated by exposure-response modelling.

    - Mean relative change from baseline (week 0) to week 64 in body weight (%) for completers: -15% for semaglutide, -2% for placebo. Assumed common standard deviation of 10%.
    - When accounting for discontinuation the expected treatment difference is 11.3% with standard deviation of 10.6%. Further, the expected proportion of participants achieving at least 5% weight loss is 79% and 38% for semaglutide and placebo, respectively. The expected proportion of participants achieving at least 10% weight loss is 63% and 21% for semaglutide and placebo, respectively. The expected proportion of participants achieving at least 15% weight loss is 44% and 10% for semaglutide and placebo, respectively. The expected proportion of participants achieving at least 20% weight loss is 27% and 4% for semaglutide and placebo, respectively.
    - Mean change in IWQOL-Lite Physical Functioning domain score from baseline (week 0) to week 64 for completers: 14 for semaglutide (15.6 for semaglutide in STEP 1), 6.5 for placebo (6.5 in STEP 1), SD=21 (21.1 in STEP 1).

When accounting for discontinuation the expected treatment difference is 6.5 with standard deviation of 21.1.

Given these assumptions, a sample size of 300 participants (200 randomised to 25 mg semaglutide and 100 randomised to placebo), provides more than 99% power for confirming superiority for both co-primary endpoints, and 71% power for confirming superiority for all confirmatory endpoints.

The power is considered acceptable and the number of participants is adequate for evaluating safety, tolerability and ensure sufficient exposure. The marginal power for each hypothesis is listed in Table 9-4.

Table 9-4 Marginal power

Test order	Endpoint	Marginal power	Effective power
1	Relative change in body weight	> 99%	> 99%
2	Achievement of body weight reduction ≥ 5% (Yes/No)	> 99%	> 99%
3	Achievement of body weight reduction ≥ 10% (Yes/No)	> 99%	> 99%
4	Achievement of body weight reduction ≥ 15% (Yes/No)	> 99%	> 99%
5	Achievement of body weight reduction ≥ 20% (Yes/No)	> 99%	> 99%
6	Change in IWQOL-Lite for CT Physical Function Score	71%	71%

A number of alternative assumptions for the primary endpoints are considered (Table 9-5). Scenario 1 is the baseline case presented above. Scenarios 2 and 4 assume a 25% higher standard deviation compared to the baseline case. Scenarios 3 and 4 assume a 20% reduction in the treatment difference compared to the baseline case.

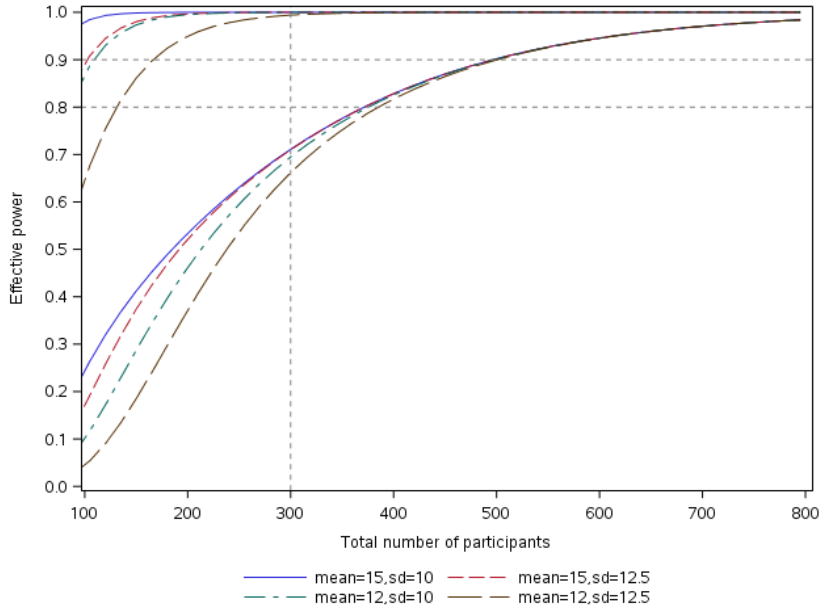
Table 9-5 Alternative assumptions for the primary endpoints

Scenario	Mean weight loss on sema (%)	Standard deviation for weight loss (%)	Power for confirming co-primary endpoints	Power for confirming all confirmatory endpoints
1	15	10	> 99%	71%
2	15	12.5	> 99%	71%
3	12	10	> 99%	69%
4	12	12.5	> 99%	66%

Power for confirming co-primary and all confirmatory endpoints as function of sample size are illustrated in Figure 9-1 for each the four scenarios in Table 9-5. The four upper curves are the power for confirming superiority for both co-primary endpoints as a function of total number of participants. Each curve corresponds to a set of assumptions for mean and standard deviation for percent weight loss for completers. Similarly, the four lower curves are power for confirming superiority for all confirmatory endpoints.

In conclusion the chosen sample size the power is considered robust towards deviation from assumed treatment differences and standard deviation for percent weight loss.

Figure 9-1 Power curves



9.6 Reporting of the main part of the trial

A partial DBL may be performed at the end of the treatment period for all participants, i.e., after the date of the last participant last treatment (LPLT) visit. The database will be updated after the partial DBL to include remaining data. The full DBL will be performed after the date of the last participant last visit (LPLV). A detailed plan for data handling, blinding, data analysis, and operational aspects of the partial DBL and the database update will be finalised before the partial DBL.

Novo Nordisk may decide to opt out of the partial DBL. In such case, the SAP will be finalised before the DBL.

10 Supporting documentation and operational considerations

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

Mexico and United States of America: For country-specific requirements, please refer to Appendix 8 (Section 10.8).

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[63] and applicable ICH Good Clinical Practice (GCP) Guideline[64]
- Applicable laws and regulations

The protocol, informed consent form, IB (as applicable) and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.

Regulatory authorities will receive the clinical study 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.

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

10.1.3 Informed consent process

The investigator or his/her representative will explain the nature of the 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 guidelines[65], Declaration of Helsinki[63] 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.

Participants must be informed about their privacy rights.

10.1.4 Information to participants during the study

The site will be offered a communication package for the participants 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 “welcome to the study letter” and a “thank you for your participation letter” after completion of the study. Further, the participant may receive other written information during the study.

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.

Different initiatives for participant retention will be implemented throughout this study. Site retention activities may include cooking classes, group meetings, fitness memberships and others. Materials and items will be supplied if locally acceptable. The retention items will be relevant for

the participants' participation in the study and/or their obesity and will not exceed local fair market value.

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 CSR. 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. The safety committee may recommend unblinding of any data for further analysis, and in this case an internal study independent *ad hoc* group will be established in order to maintain the blinding of the study personnel.

10.1.7 Dissemination of clinical study data

Study information will be disclosed at clinicaltrials.gov and novonordisk-trials.com and, if applicable, also other national or regional study registries. It will also be disclosed according to other applicable requirements, relevant recommendations or regulations, such as the Declaration of Helsinki,[63] the International Committee of Medical Journal Editors (ICMJE),[66] the Food and Drug Administration Amendment Act (FDAAA),[67] European Commission Requirements[68-70] and 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.

The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

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

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

All participant data relating to the study will be recorded on eCRFs 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 eCRF.

The following will be provided as paper CRFs:
- Pregnancy forms

The following will be provided as paper CRFs to be used when access to the eCRF is revoked or the eCRF is temporarily unavailable:
- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints on IMP not yet allocated to a participant)

Corrections to the eCRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF 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 eCRF, the eCRF must be signed and dated again by the investigator.

The investigator must ensure that data is recorded in the eCRF 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). During the COVID-19 pandemic, site visits and audits may be conducted remotely, if local regulations permit. 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 eCRF 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,[64] 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.

Monitors will review the participants' medical records and other source data, e.g., the diaries and eCOAs, to ensure consistency and/or identify omissions compared to the eCRF.

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 CSR.

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 or via listings from the study database.

10.1.9 Source documents

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

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 eCRF and a copy is kept at the site.

For ePROs, data in the service providers' database is considered source data.

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 25 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, 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.

Canada and US: For country-specific requirements, please refer to Appendix 8, Section 10.8.

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.

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 IMP. 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 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 disease and/or study intervention investigated in this study.

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

One (or two) investigator(s) will be appointed by Novo Nordisk to review and sign the CSR (signatory investigator(s)) on behalf of all participating investigators. The signatory investigator(s) will be appointed based upon criteria defined by the ICMJE for research publication.[71]

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 Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the ICMJE.[71]

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 and Table 10-2 will be performed by the central laboratory, with the exception of:

- Urine pregnancy testing, which will be performed locally at site or at home.
- Semaglutide plasma concentration testing, which will be performed at a specialised laboratory. Semaglutide plasma concentrations collected at end-of-study visit (V20) will only be analysed if anti-semaglutide antibodies are requested to be analysed.
- Anti-semaglutide antibody testing will only be analysed if deemed necessary for clarification of unexpected drug exposure or other safety issues that may be related to antibody formation, or if deemed relevant for other reasons. Analysis will be performed by Novo Nordisk or at a special laboratory appointed by Novo Nordisk.

Laboratory results will be made available to the investigator on an on-going basis. Laboratory results that could unblind the study or that will not be used for clinical evaluation will not be reported to the sites (anti-semaglutide antibody, PK and human biosamples for future research).

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 laboratory will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their 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.

Anti-semaglutide antibody samples and human biosamples for future research will be stored as described in Appendix 7 (Section 10.7).

For haematology samples (different counts) where the test result is not normal, then a part of the sample may be kept for up to two years according to local regulations.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters	Visit												
		V1	V2	V4	V5	V6	V7	V9	V11	V13	V15	V17	V19	V20
		Timing of Visit (Weeks)												
		-1	0	4	8	12	16	24	32	40	48	56	64	71
Glucose metabolism	Fasting plasma glucose[1]		x				x				x		x	
	HbA_{1c}	x	x				x				x		x	
	Insulin serum-fasting		x				x				x		x	
Lipids	Free fatty acids		x				x				x		x	
	High density lipoprotein (HDL) cholesterol		x				x				x		x	
	Low density lipoprotein (LDL) cholesterol		x				x				x		x	
	Very-low density lipoprotein (VLDL) cholesterol		x				x				x		x	
	Total cholesterol		x				x				x		x	
	Triglycerides		x				x				x		x	
Biomarker	High sensitive c-reactive protein		x				x				x		x	

NOTES:
[1]An FPG result < 3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as an AE at the discretion of the investigator (see Appendix 3, Section 10.3).

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters	Visit												
		V1	V2	V4	V5	V6	V7	V9	V11	V13	V15	V17	V19	V20
		Timing of Visit (Weeks)												
		-1	0	4	8	12	16	24	32	40	48	56	64	71
Haematology	Erythrocytes	x					x				x		x	
	Haematocrit	x					x				x		x	
	Haemoglobin	x					x				x		x	
	Leucocytes	x					x				x		x	
	Thrombocytes	x					x				x		x	
	Basophils	x					x				x		x	
	Eosinophils	x					x				x		x	
	Lymphocytes	x					x				x		x	

	Monocytes	x					x				x		x	
	Neutrophils	x					x				x		x	
Biochemistry[1]	Alanine Aminotransferase (ALT)	x					x				x		x	
	Alkaline phosphatase	x					x				x		x	
	Aspartate Aminotransferase (AST)	x					x				x		x	
	Bilirubin	x					x				x		x	
	Creatinine	x					x				x		x	
	Potassium	x					x				x		x	
	Sodium	x					x				x		x	
Hormones	Thyroid Stimulating Hormone (TSH)	x					x				x		x	
Pregnancy Testing	Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]	x	x	x	x	x	x	x	x	x	x	x	x	x
Other tests	Semaglutide plasma concentration			x		x	x		x		x		x	x[3]
	Anti-semaglutide antibodies		x[3,4]	x[3]		x[3]	x[3]		x[3]		x[3]		x[3]	x[3]
	eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation	x					x				x		x	
	Serum tryptase, in case of systemic hypersensitivity reaction (see Section 8.7)													
	Biosamples for future analysis	x					x						x	
	Biosamples for genetic analysis	x												

NOTES:
[1]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. If ALT or AST >3 upper normal limit (UNL), additional blood sample should be taken from the subject to analyse international normalised ratio (INR) by central laboratory (except at screening visit). Repeat testing of the abnormal laboratory assessment should be performed via central laboratory for the subject until abnormalities return to normal or baseline state.
[2]Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC (see Appendix 4, Section 10.4).
[3]Samples will only be analysed upon request. See Appendix 2, Section 10.2 for full details.
[4]Must be taken prior to first dose

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

10.3.1 Definitions 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
- Obesity-related surgical procedures where both the event leading up to the AE and the procedure (e.g., knee surgery, bariatric and metabolic surgery) should be reported as an AE.

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.
- In general, medical or surgical procedures (e.g., endoscopy, appendectomy) should not be reported as an AE. The condition (new or worsening) that leads to the procedure is the AE. Exceptions include obesity-related surgical procedures where both the surgical procedure and the condition (new or worsening) that leads to the procedure should be reported as AEs.

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. The selection of these events is based on the non-clinical and clinical data with semaglutide, knowledge from the GLP-1 RA drug class as well as regulatory requirements.

Acute gallbladder disease
Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis).

Hepatic event

Hepatic event defined as:

- disorders of the liver including cholestatic conditions and liver related signs and symptoms
- ALT or AST > 3x UNL and total bilirubin > 2x UNL or INR > 1.5*
- ALT or AST > 3x UNL with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

* Please note that in case of a hepatic event defined as ALT or AST > 3 x 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 (Section 10.3.2) if no other serious criteria are applicable.

Neoplasms

All confirmed neoplasm (both malignant and non-malignant) by histology or other substantial clinical evidence.

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 imaging

Medication error

A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the 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
- accidental administration of a lower or 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.

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 eCRF.

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 paper CRF" later in this section.

Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the 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 IB 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.

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

New or updated information should be recorded in the eCRF.

10.3.5 Reporting of SAEs

SAE reporting via electronic CRF

Relevant forms must be completed in the eCRF.

For reporting and sign-off timelines, see Figure 10-1 below.

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):

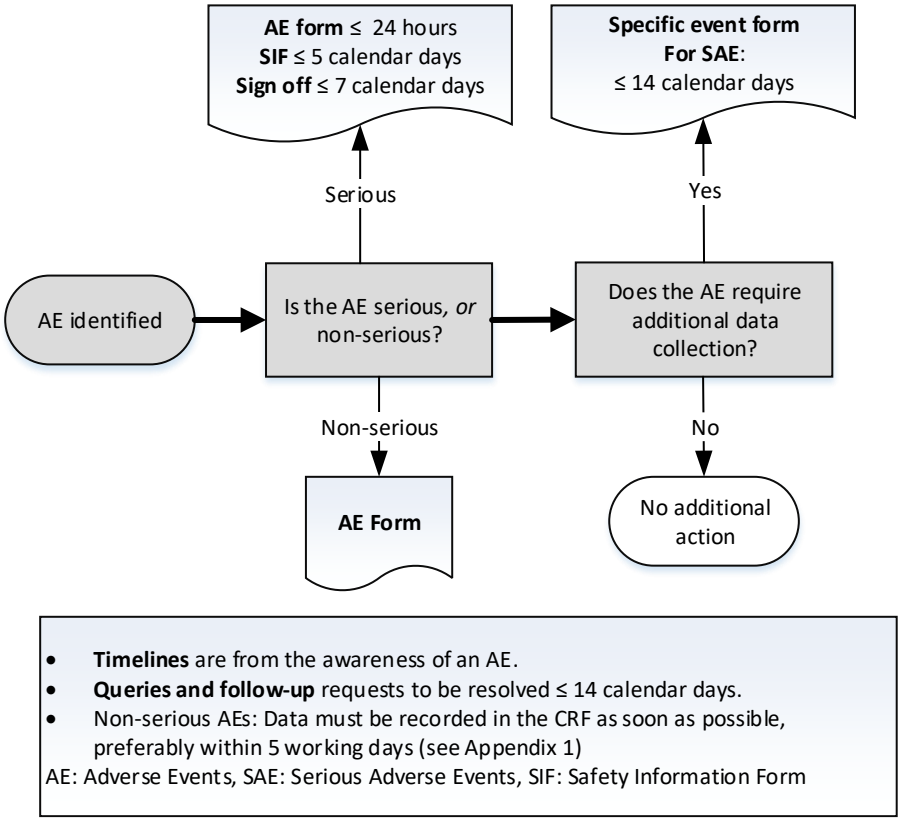
- AE form within 24 hours
- Safety information form within 5 calendar days
- Both forms must be signed within 7 calendar days after first knowledge by the investigator
- Specific event form within 14 calendar days

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



Note: The collection of AEs includes the collection of COVID-19 or suspected COVID-19 AEs.

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 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 because the risk of teratogenicity/fetotoxicity caused by transfer of semaglutide in seminal fluid is unlikely.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly. Table 10-3 lists the highly effective methods of contraception allowed.

Highly effective contraception should be utilised for a least 7 weeks (49 days) after last dose of IMP (corresponding to time during treatment and until the end of relevant systemic exposure).

Table 10-3 Highly effective contraceptive methods allowed

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, 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).

In addition, a combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered highly effective methods of contraception.

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 Table 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.

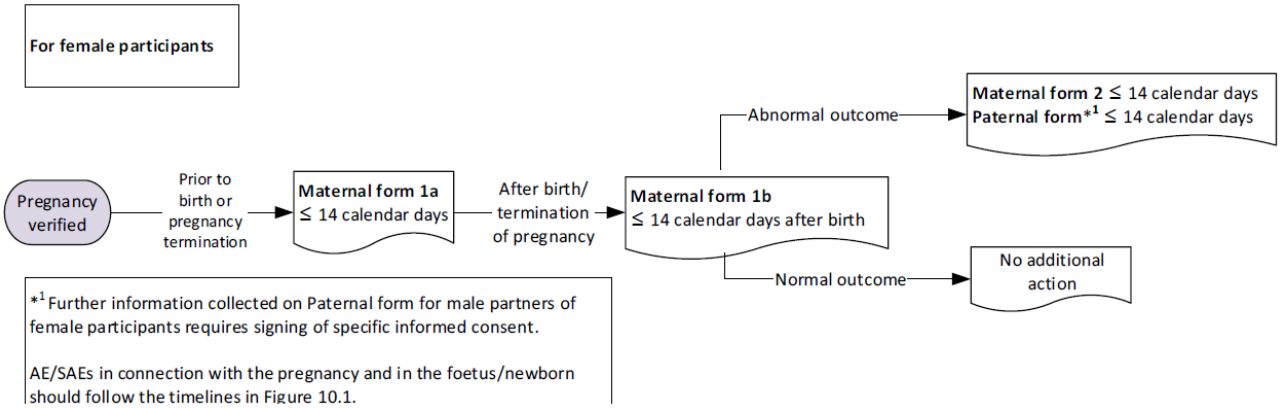
Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

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.

Germany: For country-specific requirements, please see Appendix 8, Section 10.8.

10.5 Appendix 5: Genetics

Use/analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism and excretion, mechanism of action of the drug, disease aetiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for future research related to study intervention or indication and related diseases. Genetic research may consist of the analysis of one or more candidate genes, or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

Additional analyses may be conducted if it is hypothesised that this may help further understand the clinical data.

The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to study intervention or product treatments of this class to understand study disease or related conditions.

Novo Nordisk will store the DNA samples in a secure storage space with adequate measures to protect confidentiality, as described in Appendix 7 (Section 10.7).

The samples will be retained while research on study intervention(s) of this class or indication continues, but no longer than 15 years.

10.6 Appendix 6: Technical complaints: Definitions and procedures for recording, evaluation, follow-up and reporting

10.6.1 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

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.

10.6.2 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:

- For products with DUN: One technical complaint form must be completed for each affected DUN

Timelines for reporting technical complaints to Novo Nordisk

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

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

If the eCRF 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.

10.7 Appendix 7: Retention of human biosamples for future research

Antibody samples

Antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug, if required by health authorities or for safety reasons.

- Only Novo Nordisk staff and personnel from the specialised laboratory will have access to the stored specimens.
- The samples will be stored at Novo Nordisk or a biorepository assigned by Novo Nordisk after end of study and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from the end of the study after which they will be destroyed.
- Samples might be transferred to other countries, to a laboratory assigned by Novo Nordisk, if not prohibited by local regulations.
- The retained samples may be used to:
    - evaluate safety or efficacy aspects that address concerns arising during or after the study.
    - further characterise the antibody responses towards the drug, if required by health authorities or for safety reasons.
    - conduct further analytical method development and validation of antibody assays.
- The participant's identity will remain confidential and the samples will be identified only by participant number, visit number and study identification number. No direct identification of the participant will be stored together with the samples. The analyses will not have any medical consequences for the participants or their relatives.

Biosamples for future research

In countries where applicable, the study will involve collection of human biosamples (also in some cases known as human biospecimen or human biological materials) to be stored in a central archive for future use. See Section 8.8.

- Participants must sign and date a separate informed consent form before biosamples are collected to be stored for future analysis.
- Human biosamples include:
    - Primary cells containing fluids of human origin (whole blood)
    - Cell free fluids of primary human origin (serum and plasma)
    - Extracts or derivatives of the above, when derived by purification (DNA, RNA, proteins, membranes, microsomes and other cellular substructures)

The material will be collected according to the flowchart (Section 1.2).

- As new biomarkers related to the disease and/or safety, efficacy or mechanism of action of semaglutide may evolve during the conduct of the study, the analyses of the stored biosamples may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the study.
- The biosamples will be stored at a central laboratory, at a central storage facility or an analysing laboratory contracted by Novo Nordisk for up to 15 years from the end of the study after which they will be destroyed.
- Only Novo Nordisk and storage facility employees will be able to access the stored biosamples.

- In case the participant withdraws his/her informed consent for biosamples for future analysis and genetics, the monitor must contact the trial manager at Novo Nordisk as soon as possible in order to have the samples withdrawn from storage.

The analyses of the biosamples for future research are not intended to identify participant-specific findings, but to understand and predict response to semaglutide and related conditions on a population level.

Analysis will be done on the biosamples and associated data (data relating to the test results or results from the main study).

Novo Nordisk will ensure that third party collaborators live up to the regulations on data protection, see Appendix 1 (Section 10.1.5).

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

10.8 Appendix 8: Country-specific requirements

Canada

Section 5.1: Inclusion criteria: PK studies: Males must not have donated blood (450 mL) within 56 days of PK draws totalling 450 mL; Females 84 days.

Germany

Section 5.1: Inclusion criteria: Date of Birth: participant's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth.

Section 5.2 Exclusion criterion no. 28: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

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

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

Section 8.3.1 Time period and frequency for collecting AE information

All SAEs must be recorded and reported to Novo Nordisk immediately, without undue delay, and the investigator must submit any updated SAE data to Novo Nordisk immediately, without undue delay.

South Korea

Section 8.8: Human biosamples for future research: According to IRB/EC policy, IRB/EC could request not to store the biosamples after study completion or to use additional local IC named "Informed Consent Form for Research of Human Biospecimen."

Mexico

Section 7.2: Participant discontinuation/withdrawal from the study: Should the subject his/her family members parents or legal representative decide to withdraw the consent for participation in the study, the subject will be entitled to receive appropriate, free of charge medical care and/or IMP during the follow up period of the protocol when it will be established with certainty that no untoward medical consequences of the subject´s participation in the research occurred.

Section 10.1: Regulatory, ethical and study oversight considerations: The protocol must be submitted to authorities in the official language (Spanish).

Section 10.1.1: Regulatory and ethical considerations: The following responsibilities for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility:

- Investigation follow-up
- Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the participant;
- Timely compliance of the terms in which the authorisation of a research for health in human beings had been issued;
- To present in a timely manner the information required by the Health Authority.

Section 10.1.13: Indemnity statement:

a) Novo Nordisk carries product liability for its products assumed under the special laws, acts/and/or guidelines for conducting studies in any country, including those applicable provisions on the Mexican United States. If the participant feels that something goes wrong during the course of this trial, the participant should contact the study staff in the first instance.

b) If during their participation in the trial the participant experiences a disease or injury that, according to the study doctor and the sponsor, is directly caused by the study medication and/or a study procedure that otherwise would not have been part of his/her regular medical care, the participant will receive from the institution or medical care establishment and free of charge, the appropriate medical treatment as required. In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by the study sponsor in accordance with the terms provided by all applicable regulations; even if the participant discontinues his/her participation in the study by his own will or by a decision from the investigator.

c) By signing the informed consent, the participant will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the trial; any additional expense resulting from the participant's participation in the study will be covered by the study sponsor.

United States of America

Section 10.1: Regulatory, ethical, and study oversight considerations:
FDA form 1572:
For US sites:

- Intended for US sites
- Conducted under the IND
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND

- All investigators outside of the US will not sign FDA form 1572
- Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

Section 10.1.10: Retention of clinical trial documentation: In the United States, 21 CFR 312.62(c) and 21 CFR 812.140(d) require 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified'.

10.9 Appendix 9: Abbreviations

AD	available but discontinued
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	available on randomised treatment
BMI	body mass index
BMR	basal metabolic rate
BG	blood glucose
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COEQ	Control of Eating Questionnaire
COVID-19	Coronavirus disease 2019
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	clinical study report
CV	cardiovascular
CVOT	cardiovascular outcome trial
DBL	database lock
DNA	deoxyribonucleic acid
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HbA_{1c}	glycated haemoglobin
HDL	high density lipoprotein
HDPE	high density polyethylene
HRT	hormone replacement therapy
IB	investigator's brochure
ICH	International Council for Harmonisation

ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalised ratio
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWDAQ	Impact of Weight on Daily Activities Questionnaire
IWQOL	Impact of Weight on Quality of Life
KDIGO	Kidney Disease: Improving Global Outcomes
LAO	last available observation
LAM	lactational amenorrhoea method
LC-MS/MS	Liquid Chromatography with tandem mass spectrometry
LDL	low-density lipoprotein
LPFT	last participant first treatment
LPLV	last participant last visit
LPLT	last participant last treatment
MD	missing and discontinued
MHP	mental health professional
MMRM	mixed model for repeated measurements
MT	missing on randomised treatment
PGI-C	Patient Global Impression of Change
PCD	Primary completion date
PGI-S	Patient Global Impression of Status
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic
PRO	patient-reported outcome
PYE	patient years of exposure
PYO	patient years of observation
QTL	quality tolerance limits
RA	Receptor agonist
RNA	ribonucleic acid
RTSM/IWRS	randomisation and trial supplies management system/interactive web response system
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
SD	standard deviation

SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TEE	total energy expenditure
TMM	trial materials manual
UNL	upper normal limit
US	United States
VLDL	very-low density lipoprotein
WOCBP	woman of childbearing potential

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