Cover Page for Protocol

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NCT number	NCT05035095
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Protocol

Protocol title: Efficacy and safety of oral semaglutide 50 mg once daily in subjects with overweight or obesity (OASIS 1)

Substance: Semaglutide

Universal Trial Number: U1111-1253-1670

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Trial phase: 3a

In the following, Novo Nordisk A/S and its affiliates will be stated as "Novo Nordisk".

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
Protocol version 3.0	25 November 2021	Global
Protocol version 2.0	20 April 2021	Global
Protocol version 1.0		Not applicable

Protocol version 3.0 (25 November 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union[1].

Overall rationale for preparing protocol, version 3.0:

Section # and name	Description of change	Brief rationale
Section 2.3.1 Risk Assessment	Table of Risks has been corrected.	For clarity
Section 3.2.1 Secondary Endpoints and Section 9.1 Statistical Hypotheses	Addition of Confirmatory Secondary Endpoints to table	Supportive secondary endpoints have been moved to confirmatory in the test hierarchy.
Section 4.4 End of trial definition	Addition of visit number	For clarity
Section 5.3.1 Dosing instructions	Dosing instructions have been corrected	To ensure the dosing instructions are followed the text has been revised for clarity.
Section 6.2 Preparation/handling/storage/accountability	Drug accountability has been corrected	To ensure the correct trial products are provided for drug accountability
Section 8 Trial assessments and procedures	Text regarding paper diaries and eCOA has been corrected	To reflect the correct data collected in the paper diaries and the correct number of questions in the eCOA.
Section 8.5 Pharmacodynamics	Fasting requirements updated	To reflect the correct fasting requirements (withholding of trial product), the test has been revised
Section 8.8 Biomarkers and biosamples for future analysis and Appendix 6 Section 10.6	Irrelevant text has been removed	To ensure section regarding biomarkers and biosamples for future analysis is correct the text has been revised
Section 8.9 Immunogenicity assessments	Antibody collection for subjects who test positive for antibodies against semaglutide has been added	As per FDA request.
Section 9.4.3 Secondary endpoints	Additional text added	Description of analysis has been added.
Appendix 1, Section 10.1.8 Data quality assurance	Text regarding protocol deviations has been corrected.	Correction
Appendix 2, Section 10.2 Clinical laboratory tests	Corrections to Table 10-1 and 10-2 and removal of text related to antibody sampling	Revised to reflect correct fasting plasma glucose values and to clarify need for additional blood samples for ALT or AST if greater than 3 the upper normal limit. Antibody sampling text has been revised to align with Section 8.9.

Section # and name	Description of change	Brief rationale
Section 8.3 & Appendix 3, Section 10.3.1 Adverse Events	Texts describing events not meeting Adverse Event definition has been revised for clarity and COVID-19 related text has been removed	For clarification and to avoid confusion regarding events which meet the definition of an Adverse Event.

Table of Contents

1 Protocol summary

1.1 Synopsis

Rationale:

Oral semaglutide in a tablet formulation has the potential of becoming a new preferable 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 and HbA_{1c} have been demonstrated with oral semaglutide, at dose levels up to 40 mg (trial NN9924-3790). Similarly, dose-dependent effects on body weight reduction were seen for once daily s.c. semaglutide (NN9536-4153). 2.4 mg s.c. semaglutide, corresponding to 50 mg oral semaglutide, has shown clinically meaningful reductions in body weight with acceptable safety and tolerability (NN9536, STEP programme). Therefore, 50 mg oral semaglutide is expected to enable subjects with obesity to achieve body weight reductions beyond those demonstrated with 40 mg oral semaglutide and with improvement in obesity-related complications.

The present randomised placebo-controlled trial has been designed to support the approval of oral semaglutide for weight management, by comparing the efficacy, safety and tolerability of 50 mg oral semaglutide versus placebo in subjects with overweight or obesity.

Objectives and endpoints:

Primary objective	To confirm superior efficacy on body weight reduction of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity.
Secondary objectives	To confirm superior efficacy on physical function of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity.
	To estimate the efficacy on cardio-metabolic parameters of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity.
	To compare the safety and tolerability of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity.
Exploratory objective	To estimate the efficacy on clinical outcome assessments of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity.

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 50 mg (vs placebo) on body weight.

The primary estimand addresses the main clinical question of interest: What is the efficacy of oral semaglutide 50 mg on body weight in subjects with overweight or obesity regardless of premature randomised treatment discontinuation and initiation of rescue intervention?

The additional estimand addresses an additional question of interest: What is the efficacy of oral semaglutide 50 mg on body weight in subjects with overweight or obesity if all subjects remained on randomised treatment and did not initiate rescue intervention?

Primary endpoints

Endpoint title	Time frame	Unit
Relative change in body weight	From baseline (week 0) to end-of-treatment (week 68)	%
Achievement of body weight reduction ≥ 5% (Yes/No)	At end-of-treatment (week 68)	Count of subjects

Confirmatory secondary endpoint

Endpoint title	Time frame	Unit
Achievement of body weight reduction ≥ 10% (Yes/No)	At end-of-treatment (week 68)	Count of subjects
Achievement of body weight reduction ≥ 15% (Yes/No)	At end-of-treatment (week 68)	Count of subjects
Achievement of body weight reduction ≥20% (Yes/No)	At end-of-treatment (week 68)	Count of subjects
Change in IWQOL-Lite-CT Physical Function	From baseline (week 0) to end-of-treatment (week 68)	Score points
Change in Short Form-36 (SF-36) Physical Function	From baseline (week 0) to end-of-treatment (week 68)	Score points

Supportive secondary endpoints

Endpoint title	Time frame	Unit
Change in waist circumference	From baseline (week 0) to end-of-treatment (week 68)	cm

In addition to above-mentioned supportive secondary endpoints, change in glycaemic parameters, lipid profile, markers of cardiovascular risk and inflammation, and physical functioning scores will also be evaluated.

Overall design:

This is a 68-week, randomised, placebo-controlled, double-blind, two-armed, multi-centre, multinational clinical trial comparing the efficacy, safety and tolerability of once daily oral semaglutide 50 mg versus placebo once daily as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity.

Subjects will be randomised to receive either oral semaglutide or placebo.

Key inclusion criteria:

- Male or female, age ≥ 18 years at the time of signing informed consent
- Body mass index (BMI):
    - ≥ 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 disease
      OR
    - ≥ 30.0 kg/m^2
- History of at least one self-reported unsuccessful dietary effort to lose body weight

Key exclusion criteria:

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

Number of subjects:

660 subjects will be assigned to randomised trial treatment.

Treatment groups and duration:

The planned total trial duration for the individual subject is approximately 76 weeks. The trial comprises a screening period of approximately one week followed by randomisation. The 68-week treatment period is divided into a dose escalation period of 16 weeks and a maintenance period of 52 weeks. All subjects will enter a 7-week follow-up period after the end-of treatment visit.

Tablets of oral semaglutide (3 mg, 7 mg, 14 mg, 25 mg, 50 mg) and semaglutide placebo in dose packs and/or HDPE (high density polyethylene) bottles will be provided by Novo Nordisk.

The trial products will not be available to the subjects after the end of the trial.

Data monitoring committee:

No data monitoring committee.

1.2 Flowchart

	Protocol Sections	Screening	Randomisation	Dose escalation period					Treatment period											End of treatment	End of trial
Visit		V1	V2	P3	V4	V5	V6	V7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	V21
Timing of Visit (Weeks)		-1	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)		-7	0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	+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	X	
Concomitant Medication	6.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical Historv/Concomitant Illness	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	X
Height	8.2.1	X																				
Waist Circumference	8.1.3		X										X								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	X
Laboratory Assessments	10.2	X	X		X		X	X	X		X						X				X	X
Childbearing Potential[b]	10.4	X																				
Pregnancy Test	8.3.5, 10.4	X	X		X	X	X	X	X		X		X		X		X		X		X	X
Biosamples for Future Analysis	8.7, 8.8, 10.2	X							X												X	
Biosamples for Genetic Analysis	8.7, 8.8, 10.2	X																				
Attend Visit Fasting	5.3.1		X						X								X				X	
ECG	8.2.3		X						X												X	

	Protocol Sections	Screening	Randomisation	Dose escalation period					Treatment period												End of treatment	End of trial
Visit		V1	V2	P3	V4	V5	V6	V7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	V21
Timing of Visit (Weeks)		-1	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)		-7	0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	+5
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	X
Clinical outcome assessments	8.1.4, 8.2.4	X	X				X		X				X				X				X	
Drug Dispensing	6.1		X		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		X	
Hand Out ID Card		X																				
Hand Out and Instruct in Diary	8		X		X	X	X	X	X		X		X		X		X		X			
Collect, Review and Transcribe Diary					X	X	X	X	X		X		X		X		X		X		X	
Diet and Physical Activity Counselling	5.3.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Breast and Colon Neoplasms Follow-up																					X	X
Evaluation of Antihypertensive and Lipid-lowering treatment	6.5																				X	

a: Demography consists of date of birth, sex, race and ethnicity (according to local regulation). France and Germany: For country-specific requirements, please refer to Appendix 7, Section 10.7.

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 trial 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.[2-8] 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 diseases.[9-23] Moreover, obesity adversely affects physical and mental health and reduces health-related quality-of-life (HRQoL).[24, 25]

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,[26-29] and improves physical symptoms, HRQoL and other obesity-related complications. Finally, studies suggest a beneficial impact of weight loss on cardiovascular risk and mortality in both people with diabetes and people with obesity.[30-32]

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.[33-42] 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.[33-38, 43, 44] 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.[45] In addition, the blood glucose-lowering effect of GLP-1 can provide glycaemic control.

Once-weekly s.c. semaglutide 2.4 mg is being developed for weight management in a global development programme (project number NN9536), which includes the phase 3a programme, STEP.

Oral semaglutide (7 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, Rybelsus® also meaningfully reduces body weight. Semaglutide is also approved as a subcutaneous (s.c.) formulation (0.5 mg and 1 mg Ozempic®, NN9535, based on the global clinical programme SUSTAIN) for once-weekly administration for the treatment of T2D and reduction of CV risk in adults with established CV disease.

2.1 Trial rationale

Oral semaglutide is the first approved GLP-1 receptor agonist (RA) in a tablet formulation for glycaemic control in adults with T2D, and has the potential of becoming a new preferable 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 and HbA_{1c} have been demonstrated with oral semaglutide, at dose levels up to 40 mg (trial NN9924-3790), i.e. above the current maximum Rybelsus® maintenance dose (14 mg). Similarly, dose-dependent effects on body weight reduction were seen for once daily s.c. semaglutide (NN9536-4153). Semaglutide 2.4 mg s.c, corresponding to 50 mg oral semaglutide, has shown clinically meaningful reductions in body weight with acceptable safety and tolerability (NN9536, STEP programme). Therefore, 50 mg oral semaglutide is expected to enable subjects with obesity to achieve body weight reductions beyond those demonstrated with 40 mg oral semaglutide, and with improvement in obesity-related complications. See Section 4.3 for details on the justification of dose.

The present randomised placebo-controlled trial has been designed to support the approval of oral semaglutide for weight management, by comparing the efficacy, safety and tolerability of 50 mg oral semaglutide versus placebo in subjects with overweight or obesity.

2.2 Background

Semaglutide has demonstrated dose-dependent reductions in body weight independent of administration route in doses exceeding the currently maximum approved doses of 1 mg once weekly (s.c. semaglutide, NN9535-4191) and 14 mg once daily (oral semaglutide, NN9924-3790) for improvement of glycaemic control in adults with T2D. 40 mg once daily oral semaglutide reduced body weight by 7.6% by week 26 in subjects with T2D (NN9924-3790), and once-weekly s.c. semaglutide 2.4 mg reduced body weight up to 14.9% by week 68 in subjects with overweight or obesity (NN9536-4373, STEP 1). Please see Section 4.3 regarding correlation of oral and s.c. semaglutide doses.

5,707 subjects 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 subjects with T2D. Superior, clinically relevant and sustained reductions in HbA_{1c} and body weight were demonstrated with the approved maintenance doses (7 and 14 mg), and the safety and tolerability profiles of oral semaglutide were consistent with those of other GLP-1 RAs.[46]

The number of adverse events (AEs) has been observed to increase with increasing oral and s.c semaglutide dose in trials NN9924-3790 and NN9536-4153, respectively, and the AEs were mainly gastrointestinal (GI) related. The proportion of subjects 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 trials with semaglutide. No apparent dose-dependency was seen for SAEs across oral and s.c. semaglutide groups, and no fatal events related to treatment with semaglutide were reported in any treatment group. Thus, all dose levels investigated in trial NN9924-3790 (including once daily 40 mg oral semaglutide) and NN9536-4153 (including

once daily 0.4 mg s.c. semaglutide) 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 IB,[47] and any updates hereof.

2.3 Benefit-risk assessment

Main benefits and risks are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of oral semaglutide may be found in the current edition of the investigator's brochure[47] 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[47] or any updates hereof. The risks are based on findings in non-clinical studies and clinical trials 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 subjects enrolled in this trial.

Identified/Potential risks of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Trial treatment (oral semaglutide)		
Identified risks		
Gastrointestinal adverse events	Consistent with findings for other GLP-1 RAs, the most frequently reported AEs in clinical trials with semaglutide were gastrointestinal (GI) disorders, including nausea, diarrhoea, and vomiting. In general, these reactions were mild or moderate in severity and of short duration. In subjects treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating subjects with impaired renal function as it may cause a deterioration of renal function.	Clinical trials have shown that a low starting dose and gradual dose escalation mitigates the risk of developing GI symptoms. A low starting dose and dose escalation steps has been implemented in the trial to mitigate the risk of GI AEs. Subjects with GI symptoms are recommended to drink plenty of fluids to avoid volume depletion.
Cholelithiasis	Events of cholelithiasis were reported more frequently with semaglutide than with placebo in the clinical development programme for s.c. semaglutide 2.4 mg for weight management (NN9536). The increased risk of cholelithiasis with s.c. semaglutide 2.4 mg 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 trials was 0.2% for s.c. semaglutide 2.4 mg and <0.1% for placebo.	Subjects with a history of chronic pancreatitis or recent acute pancreatitis will not be enrolled in the trial (see Section 5.2). Subjects should be informed of the characteristic symptoms of acute pancreatitis. In addition, in case of suspicion of acute pancreatitis, trial product

Identified/Potential risks of clinical significance	Summary of data/rationale for risk	Mitigation strategy
		should be promptly interrupted in accordance to 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.	Subjects with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this trial (see Section 5.2). In addition, subjects will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the trial product occurs.
Neoplasms (*malignant and non-malignant)*	Patients with overweight or obesity as well as patients with T2D, have an increased risk of certain types of cancer. There is no evidence from clinical trials that GLP-1-based therapies increase the risk of neoplasms. However, in the s.c. semaglutide as well as oral semaglutide phase 3a trials for T2D, the proportion of subjects with neoplasms (malignant and non-malignant) were slightly higher with semaglutide than with comparator. The number of subjects exposed to s.c. semaglutide or oral semaglutide for a longer period is considered insufficient for a thorough assessment of the risk of neoplasms.	Subjects with presence or history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this trial. 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 trials or post-marketing data that GLP-1 RA based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies based on the unknown long-term effects on β-cell stimulation and α-cell suppression.	Subjects with presence or history of malignant neoplasm within 5 years prior to screening will not be enrolled in this trial (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,[48] and therefore the clinical relevance of the findings is considered to be low.	Subjects with a family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2) are excluded from the trial (see Section 5.2).
Trial procedures		
Risk of COVID-19 infection in relation to participation in trial.	Subjects 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 minimize the risk of COVID-19 transmission as much as possible, local guidelines must be followed.

Identified/Potential risks of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Risk of externally induced unforeseen events with a global impact (e.g global pandemic)	Sites and subjects 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 must be performed as on-site visits, please refer to Section 7.1.
Other		
Risk of COVID-19 infection in relation to trial 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 or any updates hereof.
Pregnancy (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 trial. Women of childbearing potential are required to use highly effective contraceptive methods when participating in this trial (Appendix 4, Section 10.4, Table 10-3). If a subject wish 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 50 mg will provide clinically meaningful body weight reduction in subjects with overweight or obesity.

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

It is expected that all subjects will benefit from participation through close contact with the trial site and counselling by a dietician or a similar qualified healthcare professional, all of which will optimise retention and likely result in intensified weight management.

All subjects in this trial will receive trial product, 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 trial in order to minimise the risks and inconveniences of participation in the trial. The safety profile for

semaglutide generated from the clinical and non-clinical development programme has not revealed any safety issues that would prohibit administration of oral semaglutide up to 50 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 trials (see Section 2.2) indicate that treatment with oral semaglutide 50 mg will provide clinically meaningful reduction of body weight.

In conclusion, the potential benefits of the trial 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 Investigator's Brochure,[47] and any updates hereof.

3 Objectives and endpoints

3.1 Primary, secondary and exploratory objectives and estimands

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

Primary objective	To confirm superior efficacy on body weight reduction of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity.
Secondary objectives	To confirm superior efficacy on physical function of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity.
	To estimate the efficacy on cardio-metabolic parameters of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity.
	To compare the safety and tolerability of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity.
Exploratory objective	To estimate the efficacy on clinical outcome assessments of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity.

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 50 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 subjects). 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 3-1. Additional details are available in Section 9.

Similar estimands are applied to the secondary efficacy-related objectives (Section 9.4.3).

The primary estimand addresses the main clinical question of interest: What is the efficacy of oral semaglutide 50 mg on body weight in subjects 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 Rybelsus® and is being applied as the primary estimand in the development programme for s.c. semaglutide 2.4 mg in weight management (STEP, NN9536).

The additional estimand addresses an additional question of interest: What is the efficacy of oral semaglutide 50 mg on body weight in subjects with overweight or obesity if all subjects 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 3-1 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 of oral semaglutide 50 mg once daily versus placebo as adjuncts to reduced-calorie diet and increased physical activity in subjects 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 to week 68: • relative change in body weight • Achievement of body weight reduction ≥ 5% (yes/no)	Subjects 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 subjects achieving body weight reduction ≥ 5%
	Additional*	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	

* Not related to the confirmatory hypotheses

3.2 Primary, secondary and exploratory endpoints

3.2.1 Primary endpoints

Endpoint title	Time frame	Unit
Relative change in body weight	From baseline (week 0) to end-of-treatment (week 68)	%
Achievement of body weight reduction ≥ 5% (Yes/No)	At end-of-treatment (week 68)	Count of subjects

3.2.2 Secondary endpoints

3.2.2.1 Confirmatory secondary endpoint

Endpoint title	Time frame	Unit
Achievement of body weight reduction ≥ 10% (Yes/No)	At end-of-treatment (week 68)	Count of subjects
Achievement of body weight reduction ≥ 15% (Yes/No)	At end-of-treatment (week 68)	Count of subjects
Achievement of body weight reduction ≥ 20% (Yes/No)	At end-of-treatment (week 68)	Count of subjects
Change in IWQOL-Lite-CT Physical Function	From baseline (week 0) to end-of-treatment (week 68)	Score points
Change in Short Form-36 (SF-36) Physical Function	From baseline (week 0) to end-of-treatment (week 68)	Score points

3.2.2.2 Supportive secondary endpoints

Endpoint title	Time frame	Unit
Cardio-metabolic parameters		
Change in waist circumference	From baseline (week 0) to end-of-treatment (week 68)	cm
Change in body mass index (BMI)	From baseline (week 0) to end-of-treatment (week 68)	kg/m^2
Change in systolic blood pressure	From baseline (week 0) to end-of-treatment (week 68)	mmHg
Change in diastolic blood pressure	From randomisation (week 0) to end-of-treatment (week 68)	mmHg
Change in HbA_{1c}	From baseline (week 0) to end-of-treatment (week 68)	%-point
Change in fasting plasma glucose (FPG)	From baseline (week 0) to end-of-treatment (week 68)	mg/dL
Change in fasting serum insulin	From baseline (week 0) to end-of-treatment (week 68)	Ratio to baseline
Change in lipids: • Total cholesterol • HDL cholesterol • LDL cholesterol • VLDL cholesterol • Triglycerides • Free fatty acids	From baseline (week 0) to end-of-treatment (week 68)	Ratio to baseline
Change in high sensitivity C-Reactive Protein	From baseline (week 0) to end-of-treatment (week 68)	Ratio to baseline
Safety and tolerability		
Number of treatment emergent adverse events	From baseline (week 0) to end-of-trial (week 75)	Count of events
Number of serious adverse events	From baseline (week 0) to end-of-trial (week 75)	Count of events

3.2.3 Exploratory endpoints

Endpoint title	Time frame	Unit
Clinical outcome assessments		
Change in IWQoL-Lite-CT • Pain/discomfort domain score • Psychosocial domain score • Total score	From baseline (week 0) to end-of-treatment (week 68)	Score points
Change in Impact of Weight on Daily Activities total score	From randomisation (week 0) to end-of-treatment (week 68)	Score points
Change in Short Form-36 (SF-36) • Role-physical score • Bodily pain score • General health score • Vitality score • Social functioning score • Role-emotional score • Mental health score • Physical component summary • Mental component summary	From baseline (week 0) to end-of-treatment (week 68)	Score points

4 Trial design

4.1 Overall design

This is a 68-week, randomised, placebo-controlled, double-blind, two-armed, multi-centre, multinational clinical trial.

Eligible subjects will be randomised 1:1 to receive either:

- oral semaglutide 50 mg once daily
- oral semaglutide placebo once daily

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

The trial comprises a 1-week screening period to assess the subject's eligibility followed by a randomisation visit and a 68-week treatment period. The treatment period is divided into a dose escalation period of 16 weeks and a maintenance period of 52 weeks. After the end-of-treatment visit (V20), all subjects will enter a follow-up period of 7 weeks, ended by a follow-up visit (V21, end-of-trial). The planned total trial duration for the individual subject is approximately 76 weeks (including screening).

In total, 660 subjects will be randomised in a 1:1 ratio.

The trial design is illustrated in Figure 4-1.

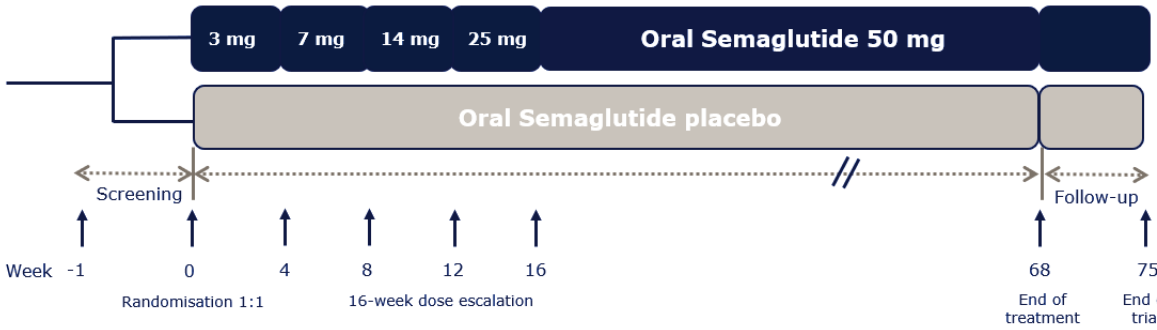


Figure 4-1 Trial design

4.2 Scientific rationale for trial design

The trial population will consist of subjects with obesity (BMI ≥ 30.0 kg/m^2) or with overweight (BMI ≥ 27.0 kg/m^2) and at least one weight-related complication. These subjects 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 subjects who have tried but failed a dietary weight loss intervention will be included in accordance with regulatory guidelines.[49, 50]

The trial has been designed as a parallel, two-armed, placebo-controlled trial to compare once daily oral semaglutide 50 mg versus placebo to support the objective of the trial. To mitigate potential bias, the trial is randomised, and the active treatment arm is controlled against placebo in a double-blinded design.

The planned treatment duration will be 68 weeks, including 16 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 68-week treatment duration is considered sufficient to assess weight loss, safety and tolerability in accordance with regulatory guidelines.[49, 50]

4.3 Justification for dose

The 50 mg oral dose of semaglutide has been chosen based on pharmacokinetic (PK) modelling demonstrating that exposures at this dose are expected to correspond to the 2.4 mg s.c semaglutide dose level tested in the STEP programme. The PK simulations assume dose proportionality and are based on a population PK model developed on a trial population matching subjects on 14 mg oral semaglutide from the PIONEER trials NN9924-4233, -4223 and -4280 and T2D vs. non-T2D differences obtained from s.c. semaglutide NN9536-4153 and NN9535-4191.

It is expected that oral dosing of semaglutide leads to higher variability in exposure compared to s.c dosing. However, based on exposure-response modelling on oral semaglutide in subjects with T2D, the variability in exposure leads to very small increases (approximately 6%) in the variability in response.

Based on prior experience with semaglutide (NN9924-3790, the PIONEER programme, NN9536-4153 and the SUSTAIN programme) and other GLP-1 RAs, 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 6.6).

4.4 End of trial definition

A subject is considered to have completed the trial if he/she has completed all phases of the trial including the last visit (V21).

The end of the trial is defined as the date of the last visit (V21) of the last subject in the trial globally.

5 Trial population

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

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

5.1 Inclusion criteria

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

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

Japan: For country-specific requirements, please refer to Appendix 7, Section 10.7.

5.2 Exclusion criteria

Subjects are excluded from the trial 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 trial period) obesity treatment with surgery or a weight loss device. However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed >1 year 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 investigators 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[51] 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 the day of screenings.
20. Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina or transient ischaemic attack within 60 days prior to screening
21. Subject presently classified as being in New York Heart Association (NYHA) Class IV
22. Surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator
23. Known or suspected abuse of alcohol or recreational drugs
24. Known or suspected hypersensitivity to trial product or related products
25. Previous participation in this trial. Participation is defined as signed informed consent.
26. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days prior to screening
27. Other subject(s) from the same household participating in any oral semaglutide trial
28. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method
29. Any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the subject's safety or compliance with the protocol

Denmark, Finland, Japan and Germany: For country-specific requirements, please refer to Appendix 7, Section 10.7.

5.3 Lifestyle considerations

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

5.3.1 Dosing instructions, meals and dietary restrictions

- The trial product 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.
- Subjects 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.
    - Trial product and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood samples have been obtained.
    - If the subject is not fasting as required, the subject 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.

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

5.3.3 Diet and physical activity counselling

All subjects 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 (Section 1.2). Subjects 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) (Table 5-1) with a Physical Activity Level value of 1.3.[52]

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

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 trial. If deemed necessary, the investigator could consult Novo Nordisk to discuss when maintenance diet can be initiated.

5.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

A screen failure must be made in the interactive web response system (IWRS/RTSM).

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

However, if a subject is inadvertently randomised in violation of the inclusion and exclusion criteria the following procedure must be performed:

- Temporary discontinuation of randomised treatment
    - treatment discontinuation should be made in the IWRS/RTSM
- 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 IWRS/RTSM
- 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 trial.

6 Treatments

6.1 Treatments administered

Investigational medicinal products

The investigational medicinal products (IMP, trial products) provided by Novo Nordisk are listed in Table 6-1.

Table 6-1 Investigational medicinal product provided by Novo Nordisk

Description	Trial product (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
Semaglutide	Semaglutide C 50 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.

Directions for use

The investigator must document that directions for use are given to the subject verbally at the first dispensing visit. The investigator should remind subjects of dosing instruction (as described in Section 5.3.1) regularly during dose escalation and afterwards ongoing throughout the trial, as applicable.

Dose escalation

Dose escalation should take place during the first 16 weeks after randomisation as illustrated in Table 6-2. All subjects should aim at reaching the recommended maintenance dose of 50 mg semaglutide once daily or the corresponding placebo.

Table 6-2 Dose escalation and maintenance of oral semaglutide/semaglutide placebo

		Dose escalation				Maintenance	Follow-up
Trial periods	**Screening**	**Randomisation/ Treatment-period 1**	**Treatment-period 2**	**Treatment-period 3**	**Treatment-period 4**	**Treatment-period 5**	**End-of-treatment**
Duration of each period	1 week	4 weeks	4 weeks	4 weeks	4 weeks	52 weeks	7 weeks
Treatment arm							
Oral semaglutide 50 mg	Screening	Oral semaglutide 3 mg Dose pack	Oral semaglutide 7 mg Dose pack	Oral semaglutide 14 mg Dose pack	Oral semaglutide 25 mg HDPE bottle	Oral semaglutide 50 mg HDPE bottle	Follow-up
Semaglutide placebo	Screening	Placebo Dose pack	Placebo Dose pack	Placebo Dose pack	Placebo HDPE bottle	Placebo HDPE bottle	Follow-up

If a subject does not tolerate the current dose during dose escalation, the subject may prolong the dose escalation phase. If a subject does not tolerate the recommended maintenance dose of 50 mg, the subject may stay at a lower dose level as per the investigator's discretion. However, it is recommended that the subject makes at least one attempt to re-escalate to the recommended maintenance dose of 50 mg as per the investigator's discretion. 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 trial product are missed, and the subject does not meet any of the discontinuation criteria, the subject should be encouraged to re-commence the treatment if considered safe as per the investigator's discretion (Section 7.1). The trial product should be continued as early as the situation allows. In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk.

Shipment of trial product to subject's home

For selected countries and if permitted by local regulations, the investigator may offer to send trial product and auxiliaries from the trial site or pharmacy to the subject's home by courier service.

The process for sending trial product from the trial site or pharmacy to a subject's home is described in the "Trial site/pharmacy instruction for shipment of trial product to patients' homes" document. This document contains detailed instructions for preparing packaging and setting up the pick-up of trial product, handover of trial product from the trial site or pharmacy staff to the courier, required temperature monitoring of trial product, delivery to and receipt of trial product by the

subject. The process for returning trial product to the trial site or pharmacy by courier is also described in this document.

Investigators, trial site/pharmacy staff and subjects who will be involved in shipment of trial product to the subject's home will be adequately trained in this process.

6.2 Preparation/handling/storage/accountability

Only subjects randomised to treatment may use trial product and only delegated site staff may supply trial product.

- Each site will be supplied with sufficient trial products for the trial on an ongoing basis. Trial products will be distributed to the sites according to number of subjects screened and randomised.
- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the trial materials manual (TMM).
- The investigator or designee is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- The investigator or designee must instruct the subject in what to return at next visit.
- The investigator or delegated site staff must ensure the participant is aware of the in-use time for the dispensed trial products (25 mg and 50 mg)
- Drug accountability must be performed in the IWRS/RTSM by registering tablets as either returned, unused or as lost.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- All returned, opened, un-used, expired or damaged trial products (for technical complaint samples, see Section 10.5) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the site.

Japan: For country-specific requirements, please refer to Appendix 7, Section 10.7.

6.3 Measures to minimise bias: Randomisation and blinding

All subjects will be centrally screened and randomised using an IWRS/RTSM and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed/allocated at the trial visits summarised in the flowchart (Section 1.2).

At screening, each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. 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 trial.

The IWRS/RTSM is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subjects' treatment is warranted. Subject safety must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Novo Nordisk prior to unblinding a subjects' treatment unless this could delay emergency treatment of the subject. If a subject's treatment is unblinded, Novo Nordisk (Global Safety department) must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

The person breaking the blind must print the "code break confirmation" notification generated by the IWRS/RTSM, sign and date the document. If IWRS/RTSM is not accessible at the time of blind break, the IWRS/RTSM helpdesk should be contacted. Contact details are listed in Attachment I.

6.4 Treatment compliance

Drug treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to encourage subject compliance.

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

- Drug accountability information; counting returned trial product.
- Review of dosing diaries
- Questioning of subjects about missed doses

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

6.5 Concomitant medication

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) and vaccines other than the trial product that the subject is receiving at the time of the first visit or receives during the trial must be recorded along with:

- Trade name or generic name

- Indication
- Dates of administration including start and stop dates
- Dose (only to be recorded for 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 (V20) in the relevant forms.

During the trial, subjects should not initiate any anti-obesity medication or treatment which is not part of the trial procedures. If such treatment is initiated, the subjects 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.

6.6 Dose modification

Not applicable for this trial. Please refer to Section 6.1 for description of missed dose(s).

6.7 Treatment after end of trial

After the end of the trial the subject should be treated 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 (V20) and the end-of-trial visit (V21).

7 Discontinuation of randomised treatment and subject discontinuation/withdrawal

Treatment of a subject may be discontinued at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Efforts must be made to have subjects who discontinue randomised treatment attend and complete all scheduled visit procedures. Subjects must be informed about the continued scientific importance of their data, even if they discontinue trial product. Only subjects who withdraw consent will be considered as withdrawn from the trial.

7.1 Discontinuation of randomised treatment

Discontinuation of randomised treatment can be decided by both the investigator and the subject.

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

Subjects meeting discontinuation of treatment criterion no. 1, 2, 3 and 4 are allowed to resume trial product if the criteria are no longer met.

Subjects who discontinue randomised treatment should be encouraged to continue with the scheduled visits and assessments until the time of the originally scheduled end-of-treatment visit (V20) and end-of-trial visit (V21) to ensure continued counselling and data collection.

The screening visit (V1) and the randomisation visit (V2) should always be performed as on-site visits. All efforts should be made to have the subject attend at least the following visits on-site:
- V8 (week 20)
- V16 (week 52)
- V20 (end-of-treatment visit, week 68)
- V21 (end-of-trial visit, week 75)

A visit window of ±2 days is allowed for visits V8, V16 and V20. For the end-of-trial visit (V21), the visit window is +5 days.

For subjects who have discontinued treatment >7 weeks prior to the end-of-treatment visit (V20) and under no circumstances are willing to attend the scheduled end-of-trial visit (V21), the site can suggest to combine the two visits. If the subject does not wish to attend the scheduled clinic visits, efforts should be made to have the remaining visits converted to phone contacts. If a subject is unwilling to attend the remaining visits, information about the attempts to follow up with the subject must be documented in the subject's medical record.

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

The primary reason for discontinuation of randomised treatment must be specified in the end-of-treatment form in the eCRF at the end-of-treatment visit, and final drug accountability must be performed. Treatment discontinuation must be made in the IWRS/RTSM.

7.1.1 Temporary discontinuation of randomised treatment

If a subject has discontinued randomised treatment due to a temporary safety concern not related to trial product, and treatment with trial product is allowed to be resumed, the guide for missed doses (see Section 6.1) should be followed. Similarly, a subject who discontinues trial product on their own initiative should be encouraged to resume the trial product (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 trial product should not be resumed. If the Atlanta criteria[53] are not fulfilled, and thus, the suspicion of acute pancreatitis is not confirmed, treatment with trial product can be resumed. Trial product may be resumed for subjects with a gallstone-induced pancreatitis in case of cholecystectomy.

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

Missed doses are recorded in the diary by the subject. At each visit, the investigator should evaluate if the subject is still taking the medicine, e.g. by reviewing the diary. If a dose has 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 IWRS/RTSM to indicate discontinuation of trial product, a new treatment resumption must be made to resume trial product.

7.2 Subject discontinuation/withdrawal from the trial

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

If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessments performed according to the end-of-treatment visit (V20). See the flowchart for data to be collected.

Final drug accountability must be performed even if the subject is not able to come to the site. A treatment discontinuation must be made in the IWRS/RTSM.

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

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

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

7.2.1 Replacement of subjects

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

7.3 Lost to follow-up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.
- Should the subject continue to be unreachable at the end-of-trial visit (V21), he/she will be considered to have withdrawn from the trial with a primary reason of `lost to follow-up'.

8 Trial assessments and procedures

- The following sections describe the assessments and procedures, while their timing is summarised in the flowchart (Section 1.2) and Appendix 2, Section 10.2.
- Informed consent must be obtained before any trial related activity, see Section 10.1.3.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all inclusion criteria and none of the exclusion criteria.
- The investigator must maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant site staff that can be contacted in case of emergency.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- The investigator must ensure to keep regular contact with each subject throughout the entire trial, 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 subjects 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) and vital signs
    2. Blood samples
    3. Patient reported outcome questionnaires (see Section 8.1.4) and mental health assessments instruments (see Section 8.2.4)
    4. Other assessments
- Paper diaries will include the following in relation to the visit they support:
    - Reminders:
        - to return diary at next site visit
    - Instruction on how to use the diary
    - Information to be recorded:
        - date of first dose of trial product
        - date and time of last dose prior to PK visit
- Subjects must receive training in how to record dosing information in the designated paper diary.
- Only the subject 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 subject'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, and laboratory reports, etc., must be documented either on the documents or in the subject's source documents. If

clarification of entries or discrepancies in the diary is needed, the subject must be questioned, and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.

- Repeat 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 (Section 1.2) 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 trial. 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 trial.

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).

BMI will be calculated in the eCRF from 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 their side and feet together while the subject 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

Subjects 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 patient reported outcome questionnaires will be used:

- Impact of Weight on Quality of Life-Lite Clinical Trials Version (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.[54]

  IWQOL-Lite-CT must be completed at V2, V6, V8, V12, V16 and at end-of-treatment (V20).

- Short Form 36 v2.0 acute (SF-36)

  SF-36 measures the subject's overall health related quality of life. It is a 36-item generic measure of health status that yields 2 summary scores for physical health and mental health, and 8 domain scores.[55]

  SF-36 must be completed at V2, V6, V8, V12, V16 and V20 and at end-of-treatment (V20).

- Impact of Weight on Daily Activities Questionnaire (IWDAQ) version 1.0

  IWDAQ is a 18-item obesity-specific PRO measure developed to evaluate daily activity limitations associated with excess weight. It uses an adaptive questionnaire design where the subjects choose 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.[56]

  IWDAQ must be completed at V2, V6, V8, V12, V16 and at end-of-treatment (V20).

- 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 Feel Mentally
  - PGI-C Feel Mentally
  - PGI-S Ability to do things needed
  - PGI-C Ability to 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, V8, V16 and at end-of-treatment (V20).
  PGI-C must be completed at V8, V16 and at end-of-treatment (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.

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

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

Only relevant and 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
- Cardiovascular 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 subjects 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, 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 subject 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 trial and any clinically significant worsening from baseline must be reported as an AE (see Section 10.3).

8.2.1 Physical examinations

- A physical examination will include assessments of the following:
    - general appearance
    - thyroid gland
    - breasts (females only)
    - abdomen
    - cardiovascular system
    - respiratory system
    - central and peripheral nervous system
- 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 ½cm 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 subject in a quiet setting without distractions (e.g. no use of television, cell phones).
- Blood pressure and pulse measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

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

- C-SSRS Baseline and C-SSRS Since Last Visit [57]

  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 V2, V6, V8, V12, V16 and at end-of-treatment (V20).

- Patient Health Questionnaire-9 (PHQ-9) [58]

PHQ-9 is a 9-item depression module of the subject 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.

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

If a subject has a PHQ-9 score of 10-14 both inclusive the subject 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 subject's medical records.

A subject must be referred to an MHP if:

- the subject has a PHQ-9 score ≥15 or
- the subject has any suicidal behaviour or
- the subject 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 subject

If one or more of the referral criteria are met, the investigator should explain to the subject why the referral and psychiatric evaluation by an MHP is needed. If the subject refuses to be referred to an MHP, the subject's decision should be documented in the subject's medical record and the investigator must assess if it is safe for the subject to continue in the trial or if the subject should be discontinued from randomised treatment.

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

PHQ-9 must be completed at screening (V1), V2, V6, V8, V12, V16 and at end-of-treatment (V20).

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 flowchart (Section 1.2).

8.3 Adverse events and serious adverse events

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 trial product
Acute pancreatitis
Acute gallbladder disease
Neoplasms
Hepatic events

A detailed description of the events mentioned in the above table can be found in Appendix 3, Section 10.3.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs must be collected from the screening visit and until the end-of-trial visit (V21) at the time points specified in the flowchart (Section 1.2).

Medical occurrences that take place or have onset prior to the time point from which AEs are collected will be recorded as concomitant illness/medical history. AE and SAE reporting timelines can be found in Appendix 3, Section 10.3. All SAEs must be recorded and reported to Novo Nordisk within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former trial subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related to the trial product or related to trial participation, the investigator must promptly notify Novo Nordisk.

8.3.2 Method of detecting AEs and SAEs

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

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

8.3.3 Follow-up of AEs and SAEs

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

8.3.4 Regulatory reporting requirements for SAEs

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

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR).

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

8.3.5 Pregnancy

Details of pregnancies in female subjects will be collected after first exposure to trial product and until pregnancy outcome.

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

Subject must discontinue randomised treatment 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 5, Section 10.5.

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

8.4 Treatment of overdose

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

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE(s) and laboratory abnormalities, and appropriate supportive treatment should be initiated according to the subjects' 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.

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.

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the subject.

For more information on overdose, also consult the current version of the oral semaglutide current edition of the investigator's brochure[47] and any updates hereof.

8.5 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 trial. 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 subjects on visits specified in the flowchart (Section 1.2) and in Appendix 2, Section 10.2. The PK sample taken at V21 (end of trial) will not be included in the Clinical Trial Report and instead provided together in a separate analytical report.

- Subjects must be instructed to withhold their trial product dose in the morning of the clinic visit where fasting is required see Section 5.3.1.

- The exact timing (date and time) of last trial product dose prior to PK sampling must be recorded in the diary by the subject 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 Clinical Trial Report (CTR) 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.

8.6 Pharmacodynamics

Not applicable for this trial.

8.7 Genetics

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 trial. A blood sample for DNA analysis will only be collected from subjects who have consented to participate in the genetic analysis.

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 subject.

8.8 Biomarkers and biosamples for future analysis

Biomarkers

Collection of samples for biomarker research is part of this trial. The following sample is required and will be collected from all subjects in this trial on visits specified in Appendix 2, Section 10.2:

- Biomarker linked to cardiovascular risk:
    - High sensitive C-reactive protein (hs-CRP)

Biosamples for future research

Participation in the future research is optional. Subjects who do not wish to participate in the future research may still participate in the trial. Biosamples will be collected according to Appendix 2, Section 10.2, and stored for future use in a biobank.

The samples are collected for the purpose of future analyses of biomarkers, both genetic and circulating. The analyses may include biomarkers currently known or discovered in the future.

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 diseases.

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 diseases.

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

Refer to Appendix 6, Section 10.6.

Finland: For country-specific requirements, please refer to Appendix 7, Section 10.7.

8.9 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 the sample collected at V2 must be taken prior to the first dose of trial product.

All serum samples from oral semaglutide treated subjects will be analysed for anti-semaglutide antibodies following a tiered approach. Samples positive for anti-semaglutide antibodies will be titrated and analysed for *in vitro* neutralising effect towards semaglutide. In addition, confirmed antibody positive samples will be further characterised for cross reactivity in native GLP-1 and if positive for cross reactivity the sample will be analysed for *in vitro* neutralising effect towards native GLP-1.

The analysis will be performed by Novo Nordisk or a special lab appointed by Novo Nordisk.

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 (Appendix 6, Section 10.6).

Subjects who test positive for antibodies against semaglutide (high titre antibodies and/or *in vitro* neutralising antibody response) at the end of trial visit (V21) will be requested to have a follow-up analysis performed 3 months after V21. If the follow-up analysis is positive for antibodies against semaglutide, the subject will be requested to have an additional follow-up analysis performed 6 months after V21.

The results from the potential additional follow-up analysis(es) will be reported in a separate analytical report. Thus, the results will not be part of the CTR for this trial.

Hypersensitivity

In the event of a systemic hypersensitivity reaction, as judged by the investigator, the subject 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 trial product. Analysis of anti-semaglutide IgE, anti-semaglutide binding antibodies and Tryptase will be performed at Novo Nordisk.

8.10 Health economics

Not applicable for this trial.

9 Statistical considerations

Taxonomy of week 68 assessments

For each subject, a given week-68 assessment may be available or missing as specified in Table 9-1. The assessment availability is defined by subject and by assessment; thus, for body weight at week 68, a subject may be characterised as 'available on randomised treatment (AT)', whereas for waist circumference, the subject may be characterised as 'missing on randomised treatment (MT)'.

Table 9-1 Taxonomy for subjects based on week 68 assessments

Availability	Subjects on randomised treatment at week 68	Description	Abbreviation
Available	Yes	**Available on randomised treatment**: Subjects who complete the trial on randomised treatment with an assessment at week 68: Includes those that stop and restart trial product.	AT
	No	**Available but discontinued** Subjects who discontinued randomised treatment prematurely but returned to have an assessment at week 68. These are also called retrieved subjects	AD
Missing	Yes	**Missing on randomised treatment**: Subjects who complete the trial on randomised treatment without an assessment at week 68: Includes those that stop and restart trial product.	MT
	No	**Missing and discontinued**: Subjects who discontinued randomised treatment prematurely and did not return to have an assessment at week 68. These are also called non-retrieved subjects	MD

9.1 Statistical hypotheses

The confirmatory hypotheses to be tested are superiority of oral semaglutide 50 mg once daily vs placebo for the co-primary endpoints, as well as superiority of oral semaglutide 50 mg once daily vs placebo for the confirmatory secondary endpoint. All tests are done on a 5% level of significance in a pre-defined fixed-sequence hierarchical order (Table 9-2), i.e. all previous hypotheses must be rejected in order to proceed to the next hypothesis test thereby preserving the type I error rate. More details on the statistical models and testing are given in Section 9.4.

Table 9-2 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
7	Change in SF-36 Physical Function Score	Semaglutide	Placebo

9.2 Sample size determination

The sample size has been determined to ensure adequate statistical power to confirm superiority of oral semaglutide 50 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 the 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)) 660 subjects are considered sufficient to evaluate the safety and tolerability of oral semaglutide for weight management.

In the analysis approach addressing the primary estimand, week 68 assessments from retrieved subjects (AD) are used. These data are also used to impute missing week 68 measurements for non-retrieved subjects (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 subjects. 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
- 1:1 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 NN9536-4153
  - 25% of subjects discontinue treatment permanently and
  - 60% of these are retrieved (AD) at week 68
- All subjects in the placebo arm are assumed to have same effect as subjects who complete the trial on placebo (AT)
- Retrieved subjects (AD) in the active arm are assumed to have an effect corresponding to half the treatment difference (compared to placebo) of subjects who complete the trial on treatment (AT)
- Non-retrieved subjects (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 trial NN9536-4153. The below assumptions have been used in the power calculations. The treatment differences are estimated by exposure-response modelling.

    - Mean relative change from baseline (week 0) to week 68 in body weight (%) for completers: -17% for semaglutide, -2% for placebo. Assumed common standard deviation of 10%.
    - When accounting for discontinuation the expected treatment difference is 12.4% with standard deviation of 11.1%. Further, the expected proportion of subjects achieving at least 5% weight loss is 80% and 38% for semaglutide and placebo, respectively. The expected proportion of subjects achieving at least 10% weight loss is 66% and 21% for

semaglutide and placebo, respectively. The expected proportion of subjects achieving at least 15% weight loss is 49% and 10% for semaglutide and placebo, respectively. The expected proportion of subjects achieving at least 20% weight loss is 31% and 4% for semaglutide and placebo, respectively.

- Mean change in IWQoL-Lite Physical Functioning domain score from baseline (week 0) to week 68 for completers: 14 for semaglutide (14.7 for semaglutide in STEP 1), 5 for placebo (5.3 in STEP 1), SD=21 (21.1 in STEP 1).
- When accounting for discontinuation the expected treatment difference is 7.4 with standard deviation of 21.2.
- Mean change in SF-36 Physical Functioning score from baseline (week 0) to week 68 for completers: 2.2 for semaglutide (2.2 for semaglutide in STEP 1), 0.4 for placebo (0.4 in STEP 1), SD=8 (7.4 in STEP 1).
- When accounting for discontinuation the expected treatment difference is 1.5 with standard deviation of 8.0.

Given these assumptions, a sample size of 660 subjects (330 in each arm), provides more than 99% power for confirming superiority for both co-primary endpoints, and 66% power for confirming superiority for all confirmatory endpoints.

The power is considered acceptable and the number of subjects are adequate for evaluating safety, tolerability and ensure sufficient exposure.

9.3 Populations for analyses

The following populations are defined:

Population	Description
Full analysis set (FAS)	All subjects randomised. Subjects will be analysed according to the randomised treatment
Safety analysis set (SAS)	All subjects randomly assigned to trial treatment and who take at least 1 dose of trial product. Subjects are analysed according to the treatment they actually received.

Two observation periods are defined for each subject:

- In-trial: The in-trial period is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site.
- On-treatment (with trial product): In general, the on-treatment period will be from the date of first trial product administration to date of last trial product 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 trial product administration to date of last trial product 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-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

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

9.4 Statistical analyses

A statistical analysis plan (SAP) will be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before the partial DBL.

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 p-values. Superiority will be claimed if p-values are less than 5% and the estimated treatment contrasts favours oral semaglutide 50 mg once daily.

9.4.1 General considerations

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 subjects is used as the baseline value.

9.4.2 Primary endpoint(s)

Relative change from baseline (week 0) to week 68 in body weight (%)

Relative change from baseline (week 0) to week 68 in body weight (%) is defined as:

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

Analyses addressing the primary estimand

The 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. The estimated treatment differences between oral semaglutide 50 mg once daily and placebo will be reported together with the associated two-sided 95% confidence intervals (CI) and corresponding p-values.

The superiority tests of oral semaglutide 50 mg once daily vs. placebo will be carried out as follows:

Let $\mu_{\text{semaglutide}}$ and μ_{placebo} denote the true mean of % weight change for oral semaglutide 50 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 is below 0.

Handling of missing week 68 values for the primary estimand

All available data at week 68 (AT and AD) are used and missing values (MT and MD) at week 68 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 trial treatment impact the estimated treatment contrasts between oral semaglutide 50 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.[59] Missing body weight measurement at week 68 for non-retrieved subjects (MD) are imputed using assessments from retrieved subjects (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 68 for subjects on randomised treatment (MT) are imputed by sampling from available measurements at week 68 from subjects 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 subjects (AD) from FAS and done within groups defined by randomised treatment. The model will be a linear regression of body weight (kg) at week 68 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 subjects are MT, an imputation model for missing body weight measurements at week 68 for MT subjects will also be defined using AT subjects 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 68 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.[60]

The multiple imputations will be generated using Novo Nordisk trial number 99324737 as seed number.

Sensitivity analyses

Jump to reference multiple imputation approach (J2R-MI): Missing values of body weight at week 68 (MT and MD) for all treatment groups are imputed by sampling among all available assessments at week 68 in the placebo group (AT and AD). This approach is based on the assumption that subjects 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.[61] 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 subjects from FAS with a week 68 measurement (AT and AD). The model will be a linear regression of body weight (kg) at week 68 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 68 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 68. 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.

Mixed model for repeated measurements (MMRM): This 'MMRM for treatment policy estimand' will use all assessments regardless of adherence to randomised treatment, including assessments at week 68 for retrieved drop-outs (AD). The MMRM for treatment policy estimand will be fitted using the same factor and covariate as for the primary analyses all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

Analysis addressing the additional estimand

The additional estimand for % weight change addresses the efficacy of semaglutide 50 mg once daily and will be assessed using a 'MMRM for trial product estimand'. Week 68 assessments for retrieved drop-outs (AD) are not used in this analysis. The MMRM for trial product estimand will use assessments only from subjects 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 subjects 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 trial product 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 subject will be employed, assuming that measurements for different subjects are independent.

Achievement of body weight reduction ≥ 5%

A body weight reduction of at least X% from baseline (week 0) to week 68 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 50 mg once daily and placebo will be reported together with the associated two-sided 95% CIs and corresponding p-values.

Let $OR_{semaglutide/placebo}$ denote the true odds ratio between oral semaglutide 50 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.

For missing body weight measurements at week 68 the 5% responder variable is derived based on imputed values using the methods specified above.

Non-retrieved subjects as non-responders:

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

9.4.3 Secondary endpoints

9.4.3.1 Confirmatory secondary endpoints

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.

9.4.3.2 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.

9.4.4 Exploratory endpoints

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

9.4.5 Other safety analyses

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

9.4.6 Other analyses

For other analyses, please refer to the SAP.

9.4.6.1 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 subjects with overweight and obesity.

The modelling will include data from all randomised subjects that were exposed to semaglutide in this trial and might be performed as a meta-analysis including data from historical trials. 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 DBL for the trial, outlining details of the analysis. The results will be reported separately from the CTR.

9.5 Interim analyses

Not applicable for this trial.

9.6 Data monitoring committee

Not applicable for this trial

9.7 Reporting of the main part of the trial

A partial DBL may be performed at the end of the treatment period for all subjects, i.e. after the date of the last subject last treatment (LSLT) 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 subject last visit (LSLV). 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 trial oversight considerations

10.1.1 Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[62] and applicable ICH Good Clinical Practice (GCP) Guideline[63]
- Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
    - providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
    - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
    - ensuring submission of the CTR synopsis to the IRB/IEC
    - reporting any potential serious breaches to the sponsor immediately after discovery

Japan: For country-specific requirements, please refer to Appendix 7, Section 10.7.

10.1.2 Financial disclosure

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

- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.
- Subjects must be informed about their privacy rights.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[63], Declaration of Helsinki[62] and the IRB/IEC or site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the trial.
- A copy of the informed consent form(s) must be provided to the subject.

10.1.4 Information to subjects during trial

The site will be offered a communication package for the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the subjects. The written information will be translated and adjusted to local requirements and distributed to the subject at the discretion of the investigator. The subject may receive a “welcome to the trial letter” and a “thank you for your participation letter” after completion of the trial. Further, the subject may receive other written information during the trial.

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

Different initiatives for subject retention will be implemented throughout this trial. 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 subjects’ participation in the trial and/or their obesity and will not exceed local fair market value.

10.1.5 Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the subject are transferred to Novo Nordisk.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.

- The subject must be informed about his/her privacy rights, including that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law in the given country of data handling. The disclosure of the data must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee. The safety committee may recommend unblinding of any data for further analysis, and in this case an internal trial independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

10.1.7 Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements, such as those of the International Committee of Medical Journal Editors (ICMJE)[64], the Food and Drug Administration Amendment Act (FDAAA)[65], European Commission Requirements[1, 66, 67] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The primary completion date (PCD) is the last assessment of the primary endpoint, and is for this trial last subject first treatment (LSFT) + 68 weeks corresponding to visit V20. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit V20. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on eCRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The following will be provided as paper CRFs:
    - Pregnancy forms
- The following will be provided as paper CRFs to be used when access to the eCRF is revoked or the CRF is temporarily unavailable:
    - AE forms
    - Safety information forms

- Technical complaint forms (also to be used to report complaints on trial product not yet allocated to a subject)

- Corrections to the 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 trial-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 trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.
- Monitors will review the subject's medical records and other source data, e.g. the diaries and eCOAs, to ensure consistency and/or identify omissions compared to the eCRF.

10.1.8.3 Protocol compliance

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

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

10.1.9 Source documents

- All data entered in the eCRF must be verifiable in source documentation other than the 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 trial 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 subject and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data reported on the paper CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify subject's medical history in source documents, such as subject's medical record.
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, eCRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by Novo Nordisk. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.
- Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

Canada and United States of America: For country-specific requirements, please refer to Appendix 7, Section 10.7.

10.1.11 Trial and site closure

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

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

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

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

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

10.1.12 Responsibilities

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

A qualified physician, who is an investigator or a sub investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents, including the subject identification code list must be kept in a secure locked facility so that no unauthorized persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. 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 subjects to a specific qualified physician who will be readily available to subjects during that time.

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

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

10.1.13 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the trial or by persons for whom the said site or investigator are responsible.

Novo Nordisk accepts liability in accordance with country-specific requirements of France and Russia. Please refer to Appendix 7, Section 10.7.

10.1.14 Publication policy

The information obtained during the conduct of this trial is considered confidential and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial.

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

Novo Nordisk may publish on its clinical trials website a redacted CTR for this trial.

One (or two) investigator(s) will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator(s)) on behalf of all participating investigators. The signatory investigator(s) will be appointed based upon criteria defined by the International Committee of Medical Journal Editors for research publication.[68]

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

At the end of the trial, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

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

10.1.14.2 Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the trial concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[68]

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

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

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

For a multicentre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the trial.

10.1.14.4 Investigator access to data and review of results

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

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

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10-1 and Table 10-2 will be performed by the central laboratory, unless otherwise specified.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.
- The central laboratory will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their laboratory SOPs. These data will not be transferred to the trial database. The investigator should review such values for AEs and report these according to this protocol.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- 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.
- All laboratory samples, with the exception of anti-semaglutide antibody samples and biosamples for future research (see Appendix 6, Section 10.6), will be destroyed no later than at finalisation of the CTR.
- For haematology samples (differential count) where the test result is not normal, then a part of the sample may be kept for up to two years or according to local regulations.
- Biosamples for retention will be stored as described in Appendix 6, Section 10.6.

All trial-required laboratory assessments will be performed by a central laboratory, with the exception of:

- urine pregnancy testing, which will be performed locally at site or at home
- Semaglutide plasma concentration, which will be performed at a specialised laboratory
- Anti-semaglutide antibodies which will be performed by Novo Nordisk or at a special lab appointed by Novo Nordisk
- Laboratory results will be made available to the investigator on an on-going basis. Laboratory results that could unblind the trial or that will not be used for clinical evaluation will not be reported to the sites (anti-semaglutide antibody, PK and biosamples for future research results).

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters	Visit													
		V1	V2	V4	V5	V6	V7	V8	V10	V12	V14	V16	V18	V20	V21
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 chloesterol		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	V8	V10	V12	V14	V16	V18	V20	V21
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	

Laboratory assessments	Parameters	Visit													
		V1	V2	V4	V5	V6	V7	V8	V10	V12	V14	V16	V18	V20	V21
	Alkaline phosphatase	x						x				x		x	
	Aspartate Aminotransferase (AST)	x						x				x		x	
	Total 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	x
Other tests	Semaglutide plasma concentration			x		x	x	x	x			x		x	x
	Anti-semaglutide antibodies		x[3]	x		x	x	x	x			x		x	x
	eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation France: For country-specific requirements, please refer to Appendix 7, Section 10.7	x						x				x		x	
	Serum tryptase, in case of systemic hypersensitivity reaction (see Section 8.9)														
	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 (Section 10.3.3) 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.
[3]Must be taken prior to first dose

10.3 Appendix 3: Adverse events: Definitions and procedures for recording, evaluation, follow-up, and reporting

10.3.1 Definition of AE

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

Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected • Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected • Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent • Obesity-related surgical procedures 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 meeting the AE definition
• Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or other trial procedures performed before exposure to IMP. Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history. • In general, medical or surgical procedures (e.g. endoscopy, appendectomy) should not be reported as AE The condition that leads to the procedure is the AE. Exceptions include obesity-related surgical procedures. In these cases, both the surgical procedure and the condition that leads to the procedure should be reported as AEs. • Medical or surgical procedures not preceded by an AE or worsening of a known condition. Exceptions include obesity-related surgical procedures, which for this trial should be reported as individual AEs.

10.3.2 Definition of an SAE

An SAE is an AE that fulfils at least one of the following criteria:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

- Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.
- Hospitalisation for elective treatment (e.g. elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE.
  Note:
  - Hospitalisations for administrative, trial related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs.
  - Hospital admissions for medical or surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Important medical event:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
- The following adverse events must always be reported as SAEs using the important medical event criterion if no other seriousness criteria are applicable:
  - Suspicion of transmission of infectious agents via the IMP
  - Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of AEs requiring additional data collection

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

Adverse events requiring additional data collection
AEs requiring additional data collection (Table 8-1) are AEs where the additional data will benefit the evaluation of the safety of the trial product. 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 seriousness 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 subject, such as:

- administration of wrong drug
  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- wrong route of administration, such as intramuscular instead of subcutaneous
- accidental administration of higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

Misuse and abuse

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

Medication error, misuse and abuse must always be reported as an AE (e.g. accidental overdose, intentional overdose or other) on a separate AE form, and a medication error, misuse and abuse form must be completed. In case of a medication error and/or misuse and abuse resulting in a clinical consequence (e.g. hypoglycaemia or other), this must be reported on an additional AE form.

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

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the CRF.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.*8.3*
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
- For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE related forms, refer to "AE and SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

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

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

Assessment of causality

• The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE.
• Relationship between an AE/SAE and the relevant IMP(s) should be assessed as:
  • Probable - Good reason and sufficient documentation to assume a causal relationship.
  • Possible - A causal relationship is conceivable and cannot be dismissed.
  • Unlikely - The event is most likely related to aetiology other than the IMP.
• Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
• The investigator should use the investigator's brochure for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.
• There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.**
• The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.
• The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

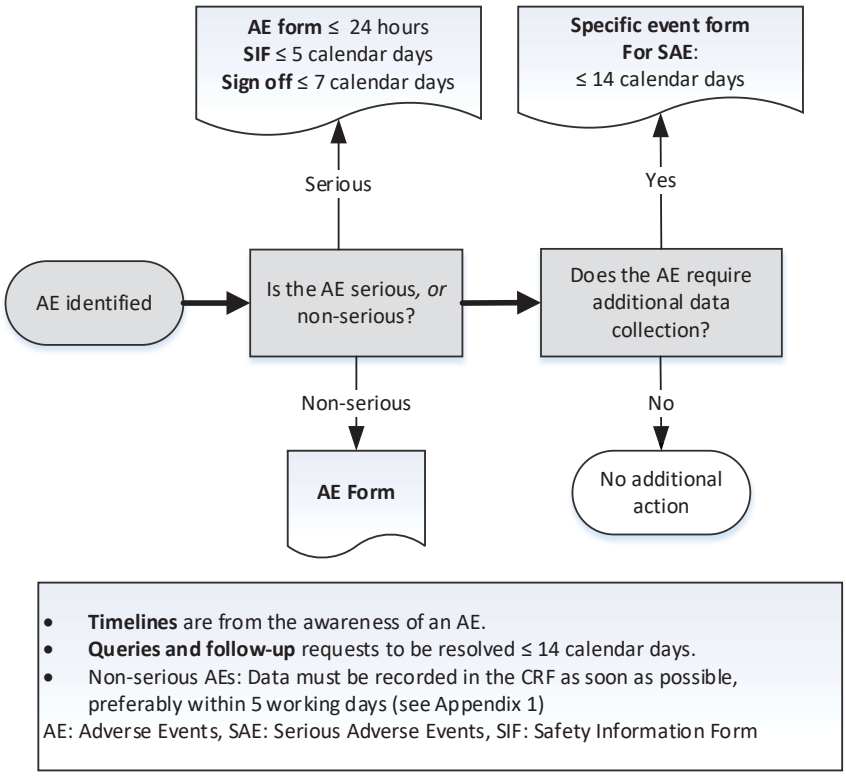
Follow-up of AE and SAE
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals. If a subject dies during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology, if available. New or updated information will be recorded in the eCRF.

10.3.5 Reporting of SAEs

SAE reporting via electronic CRF
• Relevant forms (AE and safety information form) must be completed in the CRF. • For reporting and sign-off timelines, see Figure 10-1 below. • If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the CRF is unavailable for more than 5 calendar days, then the site will use the safety information form (see box below). • The site will enter the SAE data into the CRF as soon as it becomes available. • After the trial is completed, the trial database will be locked, and the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after CRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

AE and SAE reporting via paper CRF

• Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk in accordance with Section 10.1.5.
• For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting timelines (as illustrated in the figure below):
  • AE form within 24 hours
  • Safety information form within 5 calendar days
  • Both forms must be signed within 7 calendar days after first knowledge by the investigator.
• The specific event form for AEs requiring additional data collection within 14 calendar days



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

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

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

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of childbearing potential (WOCBP)

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

Females in the following categories are not considered WOCBP

1. Premenarcheal
5. 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 trial enrolment.

6. Postmenopausal female:

- A postmenopausal state is defined as amenorrhoea for 12 months without an alternative medical cause.
- Females ≥ 50 years of age can be considered postmenopausal (irrespective of treatment with a hormonal contraception or hormone replacement therapy (HRT)) if they have both:
    - Amenorrhoea and
    - Documentation of 2 high follicle stimulating hormone (FSH) measurements in the postmenopausal range and one of these was observed ≥1 year prior to screening.
- Females ≥ 60 years of age can be considered postmenopausal.

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

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

Contraception guidance

<u>Male subjects</u>
No contraception measures are required for male subjects, because the risk of teratogenicity/fetotoxicity caused by transfer of semaglutide in seminal fluid is unlikely.

<u>Female subjects</u>
Female subjects of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly as described in table(s) below:

Table 10-3 Highly effective contraceptive methods

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:

• **Highly effective methods[b, d] that have low user dependency** (Failure rate of <1% per year when used consistently and correctly):
  • Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
  • Intrauterine device (IUD)
  • Intrauterine hormone-releasing system (IUS)[b]
  • Bilateral tubal occlusion
  • Vasectomized partner
  Vasectomised partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
 	
• **Highly effective methods[b,d] that are user dependent** (Failure rate of <1% per year when used consistently and correctly):
  • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  o oral
  o intravaginal
  o transdermal
  o injectable
  • Sexual abstinence
  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the randomised treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.
 	
NOTES
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical trials.
b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
d) Contraception should be utilised during the treatment period and for at least 7 weeks (49 days) after the last dose of trial product.

Pregnancy testing

- WOCBP should only be included after a 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 treatment.

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

Collection of pregnancy information

Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy (see Figure 10-2).
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate which will be forwarded to Novo Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding 'gestational', 'pregnancy related' or a similar term when reporting the AE/SAE.
- Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the IMP by the investigator will be reported to Novo Nordisk as described in Section 10.3. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

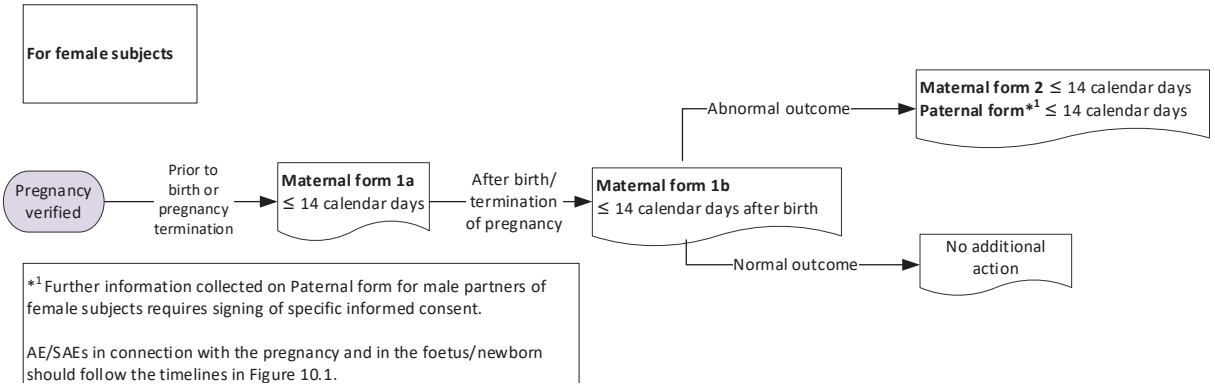


Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy

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

Denmark, Finland and Germany : For country-specific requirements, please see Appendix 7, Section 10.7.

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

10.5.1 Definition of technical complaint

Technical complaint definition
• A technical complaint is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself.

Examples of technical complaints:

- Problems with the physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- Problems with packaging material including labelling

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

10.5.2 Recording and follow-up of technical complaints

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

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the eCRF within: • 24 hours if related to an SAE • 5 days calendar for all other technical complaints If the eCRF is unavailable, or when reporting a technical complaint on a trial product that is not yet allocated to subject, the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

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

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

10.6 Appendix 6: Retention of human biosamples

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 trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from the end of the trial 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 trial.
    - 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 subject's identity will remain confidential and the samples will be identified only by subject number, visit number and trial identification number. No direct identification of the subject will be stored together with the samples. The analyses will not have any medical consequences for the subjects or their relatives.

Biosamples for future research

In countries where applicable, the trial 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.

- Subjects 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 trial, 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 trial.
- 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 trial after which they will be destroyed.
- Only Novo Nordisk and storage facility employees will be able to access the stored biosamples.

- In case the subject 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

Finland: For country-specific requirements, please refer to Appendix 7, Section 10.7.

10.7 Appendix 7: Country-specific requirements

Canada

Section 10.1.10: Retention of clinical trial documentation: Part C, Division 5 of the Food and Drug Regulations [C.05.012] requires a 25-year retention period.

Denmark

Section 5.2 Exclusion criterion no. 27: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

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

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

Finland

Section 5.2 Exclusion criterion no. 27: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

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

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

Sections 8.8 and 10.6: No subjects from Finland will take part in the optional biobank component of the trial where collected samples will be used for future research.

France

Section 1.2: Date of Birth: subject's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth.

Section 1.2 and Table 10-2: Race and ethnic origin can only be collected if purpose of the research is justified. Therefore, in this trial for the central laboratory calculation of the eGFR, information on race (black/white/other) and year of birth will be collected on the laboratory requisition form only.

Section 10.1.13: Indemnity statement: Novo Nordisk is responsible for identification of the harmful consequences of the biomedical research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without Novo Nordisk being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research (according to The French Public Health Code Article L.1121-10 [law n° 2004-806 of 9 August 2004 art. 88 I, IX Journal Official of 11 August 2004]).

Germany

Section 1.2: Date of Birth: subject's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth.

The approval of the Federal Office for Radiation Protection may not be available at the start of the trial in Germany.

Section 5.2 Exclusion criterion no. 27: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group). Such methods include:

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

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

Japan

Section 5.1 Inclusion criterion no. 2: Age ≥ 20 years at the time of signing informed consent.

Section 6.2: Preparation/Handling/Storage/Accountability: The head of the trial site or the trial product storage manager assigned by the head of the trial site (a pharmacist in principle) is responsible for control and accountability of the trial products.

Section 10.1.1: Regulatory and ethical considerations: A name or a seal is accepted as a signature.

Russia

Section 10.1.13: Indemnity statement: The trial should be conducted in compliance with the protocol and Ministry of Healthcare of Russian Federation order #200H from 01 April 2016 "Approval of rules of good clinical practice and legal requirements of Russian Federation regulating circulation of medicines."

United States of America

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

10.8 Appendix 8: Abbreviations

AD	available but discontinued
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	available on randomised treatment
BMI	body mass index
BG	blood glucose
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Corona virus disease 2019
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTR	clinical trial 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	gastro intestinal
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
IEC	independent ethics committee
IMP	investigational medicinal product

IRB	institutional review board
IWDAQ	Impact of Weight on Daily Activities Questionnaire
IWRS/RTSM	interactive web response system/randomisation and trial supplies management system
IWQoL	Impact of Weight on Quality of Life
KDIGO	Kidney Disease: Improving Global Outcomes
LAO	last available observation
LC-MS/MS	Liquid Chromatography with tandem mass spectrometry
LDL	low-density lipoprotein
LSFT	last subject first treatment
LSLT	last subject last treatment
LSLV	last subject last visit
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
PGI-S	Patient Global Impression of Status
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic
PRO	patient-reported outcome
RA	Receptor agonist
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
SD	standard deviation
SF-36	Short Form-36
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 child bearing potential

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