Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03574597
Sponsor trial ID:	EX9536-4388
Official title of study:	SELECT - Semaglutide effects on cardiovascular outcomes in people with overweight or obesity
Document date:	06 June 2023

16.1.1 Protocol and protocol amendments

List of contents

Protocol

Including:

Amendment 1, dated 27-November-2018
Amendment 2, dated 15-October-2018
Amendment 3, dated 12-December-2018
Amendment 4, dated 07-March-2019
Amendment 5, dated 12-June-2019
Amendment 6, dated 23-August-2019
Amendment 7, dated 23-October-2019
Amendment 8, dated 04-January-2021
Amendment 9, dated 09-February-2022

Protocol title: SELECT - Semaglutide effects on cardiovascular outcomes in people with overweight or obesity

Substance name: Semaglutide

Universal Trial Number: U1111-1200-5564

EUdraCT Number: 2017-003380-35

Trial phase: 3b

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

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document	Date	Protocol version
Updated protocol including amendment 9 (Global)	09-February-2022	7.0
Updated protocol including the local amendments 6 and 7 and the global amendment 8.	04-January-2021	6.0
Updated protocol including amendment 7 (only applicable for countries involved in the VHP and Netherlands)	23-October-2019	5.0
Updated protocol including amendment 6 (only applicable for countries involved in the VHP and Netherlands)	23-August-2019	4.0
Amendment 5 (Greece)	12-June-2019	The amendment was due to local changes required for translation and lead to no changes to the protocol and no changes in protocol version number.
Updated protocol including amendment 2 (Russia), 3 (France) and 4 (all countries, except for countries involved in the VHP and Netherlands)	07-March-2019	3.0
Updated protocol including amendment 1 Only applicable for countries involved in the VHP and Netherlands	27-November-2018	2.0
Original protocol	15-May-2018	1.0

Protocol amendment no. 9 (protocol version 7.0 dated 09 February 2022)

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

Overall rationale for preparing protocol, version 7:

A benefit of GLP-1RA in preventing heart failure hospitalizations (HHF) has emerged with a growing body of scientific evidence in recent years. Across CVOTs with GLP-1RA in T2D patients, the overall data indicates a beneficial effect of GLP-1 RA. Inclusion of HF composite

endpoint in the testing hierarchy is an opportunity to increase the level of evidence for semaglutide and HF.

For Algeria and Germany, co-participation in COVID-19 trials is not allowed due to local requirements, and not allowing co-participation in COVID-19 trials does not affect patient safety.

Section # and name	**Description of change**	**Rationale**
Section 4.2.2 Objectives and endpoints Secondary endpoints	HF composite endpoint moved from supportive secondary endpoints to confirmatory secondary endpoints	See overall rationale
Section 8.1 Discontinuation/Withdrawal criteria	Sentence related to discontinuation/withdrawal criterion#3 'Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator's discretion without discontinuing trial treatment.' is not applicable for Algeria and Germany.	Co-participation in COVID-19 trials is not allowed in Algeria and Germany due to local requirements
Section 10.3.2 Statistical considerations Secondary endpoints	HF composite endpoint moved from supportive secondary endpoints to confirmatory secondary endpoints	See overall rationale
Appendix 9 Country-specific requirements for Algeria and Germany	Section 8.1, Sentence related to discontinuation/withdrawal criterion#3 'Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator's discretion without discontinuing trial treatment.' is not applicable for Algeria and Germany.	Co-participation in COVID-19 trials is not allowed in Algeria and Germany due to local requirements

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1 Synopsis

Rationale:

People with overweight or obesity are at high risk for cardiovascular (CV) disease. Semaglutide has shown CV risk reduction and impact on CV risk factors including overweight, dysglycaemia and increased blood pressure in subjects with type 2 diabetes (T2D). Whether semaglutide will reduce CVD risk and mortality in subjects with established CV disease and overweight or obesity is not known.

Objectives and endpoints:

The primary objective

To demonstrate that semaglutide subcutaneously (s.c) 2.4 mg once-weekly lowers the incidence of major adverse cardiovascular events (MACE) versus semaglutide placebo, both added to standard of care in subjects with established CV disease and overweight or obesity.

Key secondary objectives

To compare the effect of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo, both added to standard of care in subjects with established CV disease and overweight or obesity with regards to:

- Mortality
- CV risk factors

The primary estimand

The primary estimand for all objectives is the intention-to-treat estimand evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment and changes to background medication.

Primary endpoint

The primary endpoint is time from randomisation to first occurrence of a composite endpoint consisting of: CV death, non-fatal myocardial infarction, or non-fatal stroke

Key secondary endpoints

Confirmatory secondary endpoints
Time from randomisation to:

- CV death
- First occurrence of a composite heart failure endpoint consisting of: heart failure hospitalisation, urgent heart failure visit or CV death
- All-cause death

Overall design:

This is a randomised, double-blind, parallel group, placebo-controlled trial comparing semaglutide 2.4 mg with semaglutide placebo both administered subcutaneously (s.c.) once-weekly in subjects

with established CV disease and overweight or obesity. Subjects will be randomised in a 1:1 ratio to receive either semaglutide 2.4 mg or semaglutide placebo as an adjunct to standard of care.

Key inclusion criteria

- Male or female, age ≥ 45 years at the time of signing informed consent
- Body mass index (BMI) ≥ 27 kg/m^2
- Have established CV disease as evidenced by at least one of the following:
  - prior myocardial infarction
  - prior stroke (ischemic or haemorrhagic stroke) or
  - symptomatic peripheral arterial disease (PAD), as evidenced by intermittent claudication with ankle-brachial index (ABI) < 0.85 (at rest), or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease

Key exclusion criteria

- Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within the past 60 days prior to the day of screening
- HbA_{1c} ≥ 48 mmol/mol (6.5 %) as measured by the central laboratory at screening
- History of type 1 or type 2 diabetes (history of gestational diabetes is allowed)

Number of subjects:

In this trial approximately 17,500 subjects will be randomly assigned to trial products.

Treatment groups and duration:

The trial is event driven; therefore, end of trial will be scheduled according to projected trial closure. Trial duration is expected to be up to 59 months following randomisation of the first subject.

Trial products:

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

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

2 Flowchart

	Screening	Randomisation	Dose escalation period				Maintenance period																		End of treatment	End of trial
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V-EOT[a]	P-FU[a]
Timing of Visit (Weeks)	Up to -3[b]	0	4	8	12	16	20	26	39	52	65	78	91	104	117	130	143	156	169	182	195	208	221	234	End of treatment	V-EOT + 5 weeks
Visit Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Informed consent Appendix 3	X																									
Demography[c]	X																									
Barriers and motivation interview (9)	X																									
Childbearing potential	X																									
In/exclusion criteria (6.1)(6.2)	X																									
Hand out ID card	X																									
Randomisation criteria(6.4)		X																								
Medical history/ Concomitant illness (9.4)		X																								
Tobacco Use[d]		X								X				X				X				X			X	
Concomitant medication (7.8)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-questionnaire (9.1.3)		X					X			X				X				X				X			X	
Weight related sign and symptom measure (9.1.3)		X					X			X				X				X				X			X	

[a] End of treatment and End of trial visits will be scheduled according to trial completion
[b] It can take up to 3 weeks from screening of first subject to delivery of trial product
[c] Demography consists of date of birth, sex, ethnicity and race (according to local regulation)
[d] Tobacco use/smoking is defined as smoking at least one cigarette or equivalent daily

	Screening	Randomisation	Dose escalation period				Maintenance period																	End of treatment	End of trial
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V-EOT[a]	P-FU[a]
Timing of Visit (Weeks)	Up to -3[b]	0	4	8	12	16	20	26	39	52	65	78	91	104	117	130	143	156	169	182	195	208	221	234	End of treatment	V-EOT + 5 weeks
Visit Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Subject engagement assessment[e] (9.1.3)							X			X				X				X				X				
Height (9.1.1)	X																									
Body Weight (9.1.1)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Waist Circumference (9.1.1)		X					X			X				X				X				X			X	
Vital Signs (9.4.3)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[f] (Appendix 2)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (9.4.2)	X																								X	
Central laboratory assessments																										
HbA_{1c} (Appendix 2)	X						X			X				X				X				X			X	
Haematology[g] (Appendix 2)		X					X			X				X				X				X			X	
Biochemistry[g,h] (Appendix 2)		X					X			X				X				X				X			X	
Lipids[g] (Appendix 2)		X					X			X				X				X				X			X	

[e] Only for a sub-set of subjects

[f] Only applicable for women of childbearing potential; urine HCG. For country specific requirements, please see Appendix 9: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden, United Kingdom.

[g] Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden, United Kingdom: For country specific requirements, please see Appendix 9

[h] Calcitonin ≥ 100 ng/L must lead to discontinuation of study drug

	Screening	Randomisation	Dose escalation period				Maintenance period																	End of treatment	End of trial
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V-EOT[a]	P-FU[a]
Timing of Visit (Weeks)	Up to -3[b]	0	4	8	12	16	20	26	39	52	65	78	91	104	117	130	143	156	169	182	195	208	221	234	End of treatment	V-EOT + 5 weeks
Visit Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
High sensitive C-reactive protein[g] (Appendix 2)		X					X			X				X				X				X			X	
Urinalysis[g] (Appendix 2)		X					X			X				X				X				X			X	
Biosamples for future analysis (biobank, genetics)[i] (Appendix 2)		X																								
Biosamples for future analysis (biobank, biomarkers)[i] (Appendix 2)		X					X							X												
Non-SAE hospitalisation (9.1.4.1)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events[j] (9.2)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaints (9.2.8, Appendix 6)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Evaluation of glycaemic status (9)		X						X			X				X				X				X			X
Trial product dose (7.1)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IWRS session	X	X		X		X		X		X		X		X		X		X		X		X		X	X	
Dispensing visit		X		X		X		X		X		X		X		X		X		X		X		X		
Drug accountability (7.5)				X		X		X		X		X		X		X		X		X		X		X	X	
Healthy lifestyle counselling session (7.7)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

[i] Only applicable for subjects that have provided informed consent for genetics and biomarkers

[j] Only serious adverse events and selected other adverse events are required to be reported

	Screening	Randomisation	Dose escalation period				Maintenance period																		End of treatment	End of trial
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V-EOT[a]	P-FU[a]
Timing of Visit (Weeks)	Up to -3[b]	0	4	8	12	16	20	26	39	52	65	78	91	104	117	130	143	156	169	182	195	208	221	234	End of treatment	V-EOT + 5 weeks
Visit Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Hand out directions for use[k] (7.1.1)		X		X		X		X		X		X		X		X		X		X		X		X		
Hand out dose reminder card		X	X	X	X	X																				
Training in trial product, pen-handling[l] (7.1.1)		X	X	X	X	X				X				X				X				X				
Ensure updated contact persons list (9)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Breast neoplasms follow-up[m] (9.4)																									X	X
Colon neoplasms follow-up (9.4)																									X	X
End of trial																										X

[k] Mandatory at the randomisation visit and then "as needed" at subsequent visits

[l] Training must be repeated at the yearly visits, i.e. visit 10, visit 14, visit 18 and visit 22 and as needed

[m] For all female subjects

3 Introduction

3.1 Trial rationale

People with overweight or obesity are at high risk for cardiovascular (CV) disease. In spite of advances in improving CV risk factors, these people continue to be at considerable increased risk of adverse cardiovascular events[2, 3].The cardiovascular (CV) safety of semaglutide s.c. 0.5 and 1.0 mg once-weekly was assessed in a phase 3a CV outcomes trial (NN9535-3744, SUSTAIN 6) designed to rule out an 80% increased CV risk in subjects with type 2 diabetes and high CV risk. The trial, however indicated a statistically significant 26% risk reduction with semaglutide compared with placebo for the major adverse CV event (MACE) primary endpoint (time from randomisation to first occurrence of a composite endpoint consisting of: CV death, non-fatal myocardial infarction or non-fatal stroke)[4]. The current trial is designed to evaluate the hypothesis of CV risk reduction for semaglutide 2.4 mg once-weekly versus semaglutide placebo both added to standard of care in subjects with established CV disease and overweight or obesity and without diabetes.

3.2 Background

Glucagon-like peptide-1 (GLP-1) is a physiological regulator of appetite[5] and pharmacological levels of GLP-1 receptor agonists (RAs) have been shown to induce weight loss. Semaglutide is a next generation long-acting GLP-1 RA currently under development by Novo Nordisk.

Besides effects on appetite, GLP-1 regulates blood glucose by a glucose-dependent stimulatory effect on insulin and inhibitory effect on glucagon secretion (i.e. when plasma glucose levels are above normal)[6, 7]. GLP-1 has also several effects in the CV system. In the T2D development programme, the CV safety of semaglutide s.c. 0.5 mg and 1.0 mg once-weekly was assessed in a pre-approval CV outcomes trial (SUSTAIN 6; NN9535-3744) in subjects with T2D and high CV risk. Semaglutide-treated subjects (0.5 and 1.0 mg dose groups combined) had a significant 26% lower risk of the primary composite outcome of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke than did those receiving placebo (hazard ratio (HR): 0.74 [0.58; 0.95] 95% CI)[4]. The exact mechanism behind the CV effect of semaglutide is not known. However, both pre-clinical and clinical studies suggest that GLP-1 RAs, including semaglutide[4], have direct and beneficial effects on the CV system (including reductions in lipid levels and blood pressure as well as anti-inflammatory effects) resulting in attenuation of atherosclerosis[8-10]. Weight loss of the magnitude seen in the recent phase 2 dose-finding trial in subjects with obesity (BMI ≥ 30 kg/m2) (trial NN9536-4153) might also lower CV risk independently. Specifically, semaglutide s.c. in doses of 0.05 to 0.4 mg once-daily was accompanied by an improvement in CV risk factors[11]. Semaglutide s.c. 2.4 mg once-weekly is currently also in phase 3a development for weight management.

In summary, these data indicate that semaglutide s.c. has beneficial effects on the CV system. Accordingly, semaglutide s.c. may target an unmet medical need in subjects with established CV disease and overweight or obesity.

Detailed information for semaglutide s.c. is available in the current edition and any updates of the Investigator's Brochure[12].

3.3 Benefit-risk assessment

3.3.1 Risks and precautions

The sections below describe the risks associated with semaglutide s.c. treatment. Risks are included if there is evidence or suspicion of an association, mainly from clinical data with semaglutide s.c. but also based on findings in non-clinical studies and data with other GLP-1 RA. For details please refer to the current version of the IB[12] or any updates hereof.

Based on clinical trials a causal relationship with semaglutide was suggested for the following risks.

- Gastrointestinal disorders

For semaglutide as for other glucagon-like peptide-1 (GLP-1) receptor agonists, the most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting. In general, these reactions were mild or moderate in severity and of short duration. The gastrointestinal adverse reactions should be considered when treating subjects with impaired renal function as nausea, vomiting, and diarrhoea may cause dehydration which could cause a deterioration of renal function. A low starting dose and dose escalation steps will be implemented in the trial to mitigate the risk of gastrointestinal AEs.

- Cholelithiasis

Events of cholelithiasis were reported more frequently with semaglutide than with comparator products in the semaglutide clinical development programme. In the phase 2 weight management trial (NN9536-4153), events of cholelithiasis were the most frequently reported gallbladder events and were in a few instances co-reported with acute pancreatitis (data on file).

Risks for subjects with type 2 diabetes

Below risks only applies to subjects who develop diabetes during the trial.

- Hypoglycaemia (identified for T2D subjects)

Subjects with T2D treated with semaglutide in combination with a sulfonylurea (SU) or insulin may have an increased risk of hypoglycaemia. There is a low risk of hypoglycaemic episodes when semaglutide is used as monotherapy. Subjects initiating SU or insulin should perform adequate frequent blood glucose monitoring to ensure patient safety.

Russia: For country specific requirement, please see Appendix 9.

- Diabetic retinopathy complication (identified for T2D subjects)

The cardiovascular outcome trial in the semaglutide T2D development programme showed an increased risk of events related to diabetic retinopathy complications in subjects treated with semaglutide compared to placebo, albeit the proportion of subjects with an event of diabetic retinopathy complications was low. The imbalance was driven by subjects with a history of diabetic retinopathy at baseline and subjects who were treated with insulin[13]. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded[14]. Long-term improved glycaemic control has been shown to decrease the risk of progression of diabetic retinopathy[15]. Subjects developing T2D during the trial should be treated according to local clinical guidelines including ophthalmologic care.

In addition, for the risks below, there is some basis for suspicion of an association with semaglutide, however, the relationship has not been confirmed.

- Medullary thyroid cancer (MTC)

Expected proliferative thyroid C-cell changes were seen in the mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. No hyperplasia was observed in monkeys after 52 weeks exposure up to 13-fold above the clinical plasma exposure at 2.4 mg/week. The C-cell changes in rodents are mediated by the GLP-1 receptor, which is not expressed in the normal human thyroid. Accordingly, the risk of GLP-1 receptor-mediated C-cell changes in humans is considered to be low. As a precaution, exclusion and discontinuation criteria related to medical history of multiple endocrine neoplasia type2 (MEN 2) or MTC and elevated plasma levels of calcitonin (biomarker for MTC) have been implemented in the trial.

- Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 RA drug class. As a precaution, subjects with a history of chronic pancreatitis or recent acute pancreatitis will not be enrolled in the trial. In addition, trial product should be discontinued in case of suspicion of acute pancreatitis in accordance to section 8.1.

- Pancreatic cancer

Subjects with T2D have an increased risk of certain types of cancer such as pancreatic cancer. In the development programme for the T2D indication, rates of pancreatic cancer do not support a causal association with semaglutide, and no safety concerns related to the pancreas were identified in the nonclinical programme with semaglutide. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 receptor agonists.

- Allergic reactions

As is the case with all protein-based pharmaceuticals, subjects treated with semaglutide are at risk of developing immunogenic and allergic reactions.

- Pregnancy and fertility (based on non-clinical data)

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

3.3.2 Benefits

In clinical trials semaglutide has provided clinically relevant reductions in body weight as compared to placebo. The CV safety of semaglutide has been established in subjects with T2D in a CV outcomes trial (SUSTAIN-6)[4] and the trial suggested a clinically relevant CV risk reduction with semaglutide compared to placebo.

During this trial it is expected that all subjects, including those randomised to placebo will benefit from participation through frequent contact with the trial site, where CV diseases and risk factors are monitored and treated following careful medical examinations. To ensure all subjects, including those receiving placebo have an adequate CV risk factor management, investigators are encouraged

to optimise treatment with medications affecting CV risk factors throughout the trial in accordance with treatment guidelines or local clinical practice. In addition, all subjects will be offered healthy lifestyle counselling. All subjects in this trial will receive trial product and auxiliary supplies free of charge.

3.3.3 Risk-benefit conclusion

Data from the development programme for semaglutide for the T2D indication has not revealed any safety issues that would outweigh the benefits. The recently completed phase 2 programme with semaglutide s.c. in obesity did not reveal any new safety issues either[11]. The trial population will consist of subjects with established CV disease and overweight or obesity. Assessment and treatment of the subjects' CV risk factors, including overweight or obesity, and with appropriate attention to the standard of care treatment will be provided throughout the trial. It is therefore concluded that the potential benefits from the trial will outweigh the potential risks for the semaglutide as well as the placebo treated subjects.

More detailed information about the known and expected benefits and risks and expected AEs of semaglutide s.c. may be found in the current edition of the Investigator's Brochure (IB)[12] and any updates hereof.

4 Objectives and endpoints

All time to event endpoints will be assessed within the interval from time of randomisation (visit 2) to the follow-up visit (up to 59 months or longer) and reported in months.

4.1 Primary, secondary and exploratory objective(s)

The primary objective

To demonstrate that semaglutide s.c. 2.4 mg once-weekly lowers the incidence of major adverse cardiovascular events (MACE) versus semaglutide placebo both added to standard of care in subjects with established CV disease and overweight or obesity.

The secondary objectives

To compare the effect of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo both added to standard of care in subjects with established CV disease and overweight or obesity with regards to:

- Mortality
- CV risk factors
- Glucose metabolism
- Body weight
- Renal function

The exploratory objectives

To compare the effect of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo as an adjunct to standard of care in subjects with established CV disease and overweight or obesity with regards to:

- Smoking status
- Hospitalisations

The primary estimand

The primary estimand for all objectives is the intention-to-treat estimand evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment and changes to background medication.

4.2 Primary endpoint and secondary endpoint(s)

4.2.1 Primary endpoint

The primary endpoint is time from randomisation to first occurrence of a composite endpoint consisting of: CV death, non-fatal myocardial infarction, or non-fatal stroke

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

Time from randomisation to:

- CV death
- First occurrence of a composite heart failure endpoint consisting of: heart failure hospitalisation, urgent heart failure visit or CV death
- All-cause death

4.2.2.2 Supportive secondary endpoints

Time from randomisation to first occurrence of:

- An expanded composite CV endpoint consisting of: CV death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation or unstable angina requiring hospitalisation
- A composite endpoint consisting of: all-cause death, non-fatal myocardial infarction, or non-fatal stroke
- Non-fatal myocardial infarction
- Non-fatal stroke
- Coronary revascularisation
- Unstable angina requiring hospitalisation
- Heart failure hospitalisation or urgent heart failure visit
- $HbA_{1c} \geq 48$ mmol/mol (6.5%)
- A 5-component composite nephropathy endpoint consisting of: onset of persistent macroalbuminuria (UACR >300 mg/g), persistent 50% reduction in eGFR compared with baseline (randomisation), onset of persistent eGFR < 15 ml/min/1.73m^2, initiation of chronic renal replacement therapy (dialysis or transplantation) or renal death*

For subjects with a screening $HbA_{1c} < 39$ mmol/mol (5.7%):

- Time from randomisation to $HbA_{1c} \geq 39$ mmol/mol (5.7%)

For subjects with a screening $HbA_{1c} \geq 39$ mmol/mol (5.7%):

- Proportion of subjects with $HbA_{1c} < 39$ mmol/mol (5.7%) at each visit where HbA_{1c} is assessed

*This component consists of events from central laboratory and outcome from event adjudication. UACR: urinary albumin-to-creatinine ratio. A persistent change in estimated glomerular filtration rate (eGFR) is defined as having 2 consecutive samples meeting the criteria. The 2 samples must be at least 4 weeks apart. A persistent change in macroalbuminuria is defined as having 2 out of 3 consecutive post-baseline samples above the limit for macroalbuminuria. The 2 samples above the limit must be at least 4 weeks apart.

Change from randomisation to year 2 (visit14) in:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse (bpm)
- High sensitivity C-Reactive Protein (hsCRP) (mg/L)
- Lipids (mg/dL)
    - Total cholesterol
    - High density lipoprotein (HDL) cholesterol
    - Low density lipoprotein (LDL) cholesterol
    - Triglycerides
- Body weight (%)
- Waist circumference (cm)
- Patient reported outcomes:
    - EuroQol five dimensions five level (EQ-5D-5L) questionnaire (EQ-5D index score (range 0 to 1) and EQ-5D-VAS (range 0 to 100). A higher score indicates better self-reported health status.)
- HbA_{1c} (%, mmol /mol) change from screening (visit 1) to year 2 (visit 14)

4.2.2.3 Exploratory endpoints

- Being current smoker at year 2 (visit 14) (yes/no)
- Total number of hospitalised days from randomisation and to end of trial
- Total number of hospitalisations from randomisation and to end of trial

Change from randomisation to week 117 in:

- Glycaemic status (normoglycaemia, pre-diabetes or type 2 diabetes)

Change from randomisation to year 2 (visit 14) in:

- Patient reported outcomes:
    - Total score weight related sign and symptom measure (WRSSM)

5 Trial design

5.1 Overall design

This is a randomised, double-blind, parallel group, placebo-controlled trial comparing semaglutide 2.4 mg with semaglutide placebo both administered s.c. once-weekly in subjects with established CV disease and overweight or obesity. Subjects will be randomised in a 1:1 ratio to receive either semaglutide 2.4 mg or semaglutide placebo as an adjunct to standard-of-care.

The trial is event driven with trial closure being performed when the targeted number of primary endpoint events has been reached. An independent Data Monitoring Committee (DMC) will oversee efficacy and subject safety and may recommend stopping the trial early (see section 8.4, 10.3.5, Appendix 3, Appendix 4). The trial will employ a group sequential design and interim testing for efficacy will be performed by the DMC.

With the assumed event rate (see section 10.1) and a recruitment period of 28 months, the estimated trial duration will be 59 months from start of randomisation to end of follow-up of the last subject, including 28 months of recruitment and 5 weeks of follow-up. Estimated trial duration for an individual subject is from 31 to 59 months.

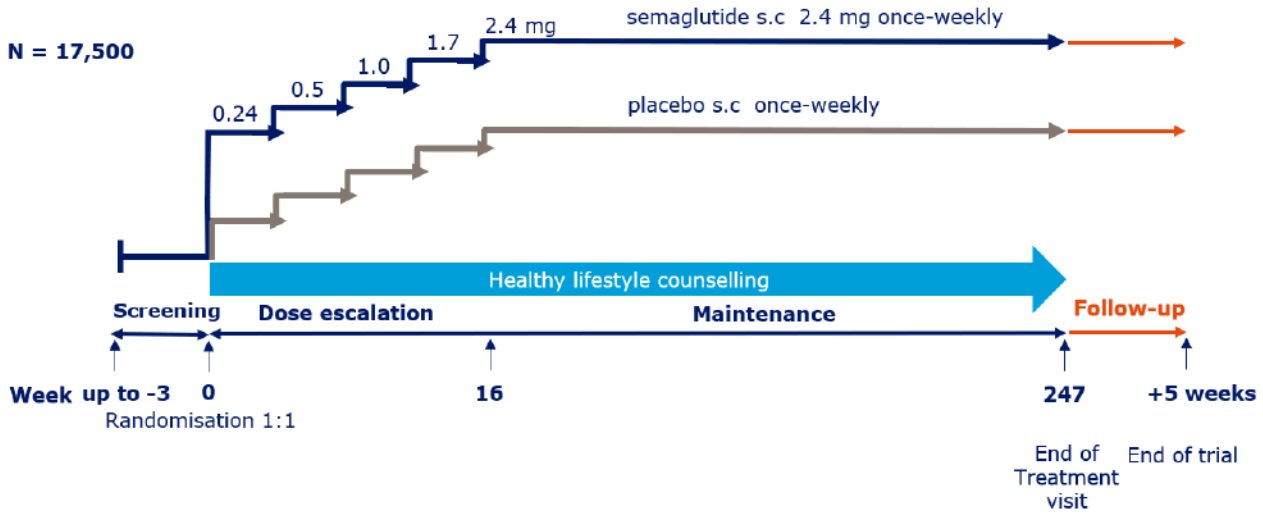

Figure 5-1 Trial design

5.2 Subject and trial completion

In this trial approximately 17,500 subjects will be randomly assigned to trial product. The recruitment period is expected to be 28 months.

Trial period completion for a subject:

Trial period completion is defined as:

- when the randomised subject has completed the final scheduled visit ('end of trial' (P-FU) according to the flowchart).

-or-

- when the randomised subject has died during trial.

The trial is event driven; therefore, end of treatment visit (V-EOT) and end of trial visit (P-FU) will be scheduled according to projected trial closure. If the event rate is lower than anticipated, then visits and related assessments will be repeated every 13 weeks beyond V24 until the necessary number of primary outcome events have been accrued. When the trial is approaching the end investigators will be notified and instructed by Novo Nordisk regarding the visit schedules for their subjects. When the trial comes to an end, the investigator must make every effort to ascertain endpoint data and AEs with a focus on those related to the primary objective for all subjects. This should be done by direct contact to the subject whenever possible. If a subject proves difficult to reach for the FU visit, all attempts to re-establish direct contact must be made as noted below. If establishing direct contact is not possible, AE status should be obtained from any available source including electronic health records, the subjects' primary physician or other health care professionals and, as a last resort, vital status (dead or alive) should be obtained. Public available data sources should also be searched. A search agency may be used to facilitate identifying updated contact details for a missing subject or provide vital status (date of death or last alive date). The above suggestions should be followed unless prohibited by local regulation and may be modified according to practical aspects.

In case several attempts are required to establish direct contact to a subject, exceeding the visit window of the follow-up visit may be needed. In order for the data set to be as complete as possible, end of trial follow-up information can be collected until the randomisation codes are broken.

As a minimum the following contact attempts should be made and also documented in the source documents:

- To subjects: three phone calls and one written contact
- To primary physician and/or other health care professionals: calls until contact is established
- To relatives or other(s) on the contact persons list: three phone calls and one written contact
- Search/contact publicly available data sources, if available and unless prohibited by local regulation

If contact to a subject is lost during the trial but contact is re-established at the end of trial efforts must be made to undertake the same procedures as those for the end of trial visit with special focus on AE status.

Publically available data sources should also be searched for withdrawn subjects to establish vital status (unless prohibited by local regulation).

5.3 End of trial definition

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

5.4 Scientific rationale for trial design

To minimise bias the trial is randomised, double-blind and placebo-controlled. Blinded treatment with semaglutide 2.4 mg or semaglutide placebo offers a robust method for assessment of semaglutide's effects. A broad spectrum of treatments for co-morbidities and CV risk factors should be introduced or adjusted throughout the trial based on standard of care and at investigator's discretion. This is in accordance with a pragmatic approach to compare two treatments: one where semaglutide is available and another where it is not.

To support the subject during the dose escalation period, site visits will occur more frequently during the first months of the trial. To maximise retention and compliance, and to optimise treatment, the subject is in contact with the investigator every 13th week throughout the trial. A multinational design has been chosen to ensure a sufficient screening pool of subjects and to reflect the anticipated subject population. The long half-life of semaglutide supports once-weekly administration and the 5-week follow-up is considered appropriate for end of systemic exposure.

The trial population will consist of subjects with established CV disease and overweight or obesity. This population represents a clinically relevant population as they are likely to benefit both from the reduction of their risk of a CV event as well as weight reduction. Subjects with diabetes are excluded from this trial to eliminate any confounding that a diabetes diagnosis could have on CV risk.

5.5 Justification for dose

In the trial, a target dose of semaglutide s.c. 2.4 mg once-weekly will be investigated. The dose selection is based on an integrated evaluation of existing efficacy and safety data as well as exposure considerations (C_{avg} and C_{max}) from the phase 2 dose-finding trial in weight management (NN9536-4153), in addition to the development programme of semaglutide s.c. in T2D.

The phase 2 trial (NN9536-4153) investigated semaglutide s.c. doses of 0.05-0.4 mg once-daily, and showed that semaglutide s.c. 0.4 mg once-daily was most effective in terms of weight loss while displaying an acceptable tolerability profile. However, since a once-weekly administration is preferred to ease the burden of drug administration in clinical practice and since data from the semaglutide s.c. T2D development programme (SUSTAIN trials with once-weekly dosing and trial NN9535-4191 with once-daily s.c. dosing of up to 0.3 mg/day) did not support the hypothesis that daily dosing provides better gastrointestinal tolerability as compared to weekly dosing, once-weekly dosing is investigated in the phase 3a confirmatory programme and in SELECT.

Population pharmacokinetic modelling was used to select the weekly target dose, based on data from the phase 2 trial (NN9536-4153). Using this, it was estimated that a once-weekly maintenance dose of 2.4 mg semaglutide s.c. will not exceed the C_{max} at steady-state that was obtained with the once-daily 0.4 mg semaglutide s.c. dose investigated in trial NN9536-4153. A weekly dose of 2.8 mg semaglutide (i.e., 7 daily doses of 0.4 mg semaglutide) was found to exceed this C_{max}. Further, when comparing the simulated human exposure at 2.4 mg/week to the animal exposures at the no-observed-adverse-effect-level (NOAEL), exposure ratios are above 1, indicating that exposure at 2.4 mg is supported by the nonclinical studies. Consequently, the proposed semaglutide s.c. target dose for the phase 3 weight management development programme is 2.4 mg once-weekly. SELECT will include subjects with a BMI $\geq$ 27 kg/m2 with established CV disease (i.e. a subgroup of those

eligible to be included in the weight management development programme), consequentially, the same dose of semaglutide s.c. 2.4 mg once-weekly will also be used in SELECT.

Further, it is well known that to mitigate gastrointestinal side effects with GLP-1 RA treatment, dose escalation to the target dose is required. Based on experience from the semaglutide s.c. T2D development programme, and similar to the phase 3a programme, subjects will be initiated on a low dose and follow a fixed-dose escalation regimen, with dose escalation every 4 weeks until the target dose of 2.4 mg is reached after 16 weeks.

The dosing regimen, route and administration form are described in section 7 of the protocol. Please refer to section 7.1 for more details on treatment doses.

6 Trial population

Prospective approval of protocol deviations to inclusion, exclusion and randomisation criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion criteria

All inclusion criteria are based on the subjects' medical records, except for #1 and #3 (screening assessment). Subjects are eligible to be included in the trial only if all of the following criteria apply:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male or female, age ≥ 45 years at the time of signing informed consent
3. Body mass index (BMI) ≥ 27 kg/m^2
4. Have established CV disease as evidenced by at least one of the following:
    a. prior myocardial infarction
    b. prior stroke (ischemic or hemorrhagic stroke)
    c. symptomatic peripheral arterial disease (PAD), as evidenced by intermittent claudication with ankle-brachial index (ABI) < 0.85 (at rest), or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease

6.2 Exclusion criteria

All exclusion criteria are based on the subjects' medical records, except for #4 (HbA_{1c}, central laboratory) and the urine pregnancy test (#17). Subjects are excluded from the trial if any of the following criteria apply:

Cardiovascular-related:

1. Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within the past 60 days prior to the day of screening
2. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening
3. Presently classified as being in New York Heart Association (NYHA) Class IV heart failure

Glycaemia-related:

4. HbA_{1c} ≥ 48 mmol/mol (6.5%) as measured by the central laboratory at screening
5. History of type 1 or type 2 diabetes (history of gestational diabetes is allowed)
6. Treatment with glucose-lowering agent(s) within 90 days before screening
7. Treatment with any GLP-1 RA within 90 days before screening

General safety[a]:

8. History or presence of chronic pancreatitis
9. Presence of acute pancreatitis within the past 180 days prior to the day of screening
10. Personal or first degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
11. End stage renal disease or chronic or intermittent haemodialysis or peritoneal dialysis

12. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening Basal and squamous cell skin cancer and any carcinoma in-situ are allowed
13. Severe psychiatric disorder which in the investigator's opinion could compromise compliance with the protocol
14. Known or suspected hypersensitivity to trial product(s) or related products
15. Previous participation in this trial. Participation is defined as randomisation
16. Receipt of any investigational medicinal product within 30 days before screening
17. 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
18. Any disorder, unwillingness or inability, which in the investigator's opinion, might jeopardise the subject's safety or compliance with the protocol

[a]For country specific requirements, please refer to Appendix 9.

6.3 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to in/exclusion criteria and randomisation 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 demography, screen failure details, and eligibility criteria. A screen failure session must be made in the interactive web response system (IWRS). The reason for failure will be captured in the case electronic report form (eCRF). Due to the long recruitment period re-screening is allowed for all inclusion and exclusion criteria. A new subject number must be assigned in the IWRS.

6.4 Randomisation criteria

To be randomised, the randomisation criterion must be answered "yes". The IWRS randomisation session should only occur after evaluation of the randomisation criteria.

1. None of the following: myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack has occurred and no revascularisation has been planned between screening and randomisation

6.4.1 Assessment of eligibility

It is the responsibility of the investigator to have sufficient evidence to ensure eligibility. If a subject is not from the investigators practice; reasonable efforts must be made to obtain a copy of subjects' medical records from relevant party e.g. the primary physician and hospitals. It is at the investigator's discretion on a case by case basis to decide if the complete medical records are needed or if the available documentation is enough to determine whether a subject is eligible. The values used to assess eligibility must reflect the subjects' current health status.

7 Treatments

7.1 Treatments administered

All trial products listed in Table 7-1 are considered investigational medicinal products (IMP) Trial product must only be used, if it appears clear and colourless.

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

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

All baseline assessments must be done prior to administration of the first dose of trial product.

Dose escalation of semaglutide/semaglutide placebo should take place during the first 16 weeks after randomisation as described in Table 7-2. All subjects should aim at reaching the recommended target dose of 2.4 mg semaglutide once-weekly or the corresponding volume of placebo. If a subject does not tolerate the recommended target dose of 2.4 mg once-weekly, the subject may stay at the lower dose level, preferably1.7 mg once-weekly, but efforts should be made to minimise these instances.

Extension of dose escalation intervals and treatment pauses may be considered if treatment with the trial product is associated with unacceptable AEs or due to other circumstances.

It is recommended to re-escalate to the target dose if considered safe to continue on trial product, as per the investigator's discretion.

Date and dose need to be recorded in the eCRF when trial product dose is initiated and changed.

If trial product is discontinued, subjects should continue to follow the trial schedule. Treatment with trial product should be resumed if deemed safe at the discretion of the investigator.

A dose reminder card should be handed out to the subjects at each site visit during the dose escalation period. This is to remind the subjects of the dose to be taken until next site visit and provide a conversion of the dose to value shown in the dose counter. Once the target dose has been reached, the dose reminder card is only handed out as needed.

Table 7-2 Dose escalation and maintenance of semaglutide/semaglutide placebo

IMP	Dose	Volume	Value shown in the dose counter	Duration
Dose escalation period				
Semaglutide B 3.0 mg/mL PDS290 or	0.24 mg	0.08 mL	8	4 weeks

semaglutide placebo				
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	0.5 mg	0.17 mL	17	4 weeks
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	1.0 mg	0.34 mL	34	4 weeks
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	1.7 mg	0.57 mL	57	4 weeks
Maintenance period				
Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo	2.4 mg	0.80 mL	80	Up to ~231 (53 months)

Subjects will be instructed to inject semaglutide/semaglutide placebo once-weekly at the same day of the week (to the extent possible) throughout the trial.

Injections may be administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. The injections should be administered on the same day of the week during the trial. Subjects should be encouraged to inject in the same area throughout the trial, meaning keeping to thigh, abdomen or upper arm but changing between left and right side is allowed.

If a single dose of trial product is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 2 days (48 hours). If a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the subject should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week.

If ≥ 2 consecutive doses of trial product are missed, the subject should be encouraged to re-commence the treatment if considered safe as per the investigator's discretion and if the subject does not meet any of the discontinuation criteria (section 8.1). The trial product should be continued as early as the situation allows. The missed doses should not affect the scheduled dosing day of the week. The start dose for re-initiation of trial product is at the investigator's discretion but the following guidance can be used:

- If ≤3 consecutive doses are missed, once-weekly regimen can be resumed as prescribed without dose reduction
- If 4-5 consecutive doses are missed, it is recommended to resume treatment at 1.0 mg for 4 weeks, and then escalate to 2.4mg, using 1.7mg as the intermediate dose for 4 weeks
- If ≥6 consecutive doses are missed, it is recommended to restart treatment at 0.24 mg semaglutide and escalate to 2.4mg, using the standard dose escalation regimen

In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk.

Auxiliary supplies will be provided in accordance with the trial materials manual (TMM) please see Table 7-3.

Table 7-3 Auxiliary supplies provided by Novo Nordisk A/S

Auxiliary supply	Details
Needles	Needles for pre-filled pen system. Details provided in the TMM. Only needles provided and approved by Novo Nordisk must be used for administration of trial product.
Direction for use (DFU)	DFU for 3 mL PDS290 pre-filled pen-injector. Not included in the dispensing unit and to be handed out separately.

7.1.1 Medical devices

Information about the PDS290 pre-filled pen-injector may be found in the IB[12] and any updates hereof.

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

Training in the PDS290 pre-filled pen-injector

The investigator must document that DFU are given to the subjects orally and in writing at the first dispensing visit (as specified in the flowchart). Training must be repeated as specified in the flowchart and, if needed, during the trial at regular intervals in order to ensure correct use of the medical device. Training is the responsibility of the investigator or delegate.

7.2 Dose modification

Please refer to section 7.1 for description of missed doses.

7.3 Method of treatment assignment

All subjects will be centrally randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed at the trial visits summarised in the flowchart, section 2.

At screening, each subject will be assigned a unique 6-digit number which will remain the same throughout the trial. For re-screened subjects please see section 6.3.

7.4 Blinding

The trial products containing the active drug and the placebo drug are visually identical and will be packed in a manner that maintains blinding.

The IWRS is used for blind-breaking instructions. The blind may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Novo Nordisk will be notified immediately after breaking the blind. The date when and reason why the blind was broken must be recorded in the source documentation.

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

When the blind is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IWRS is not accessible at the time of blind break, the IWRS helpdesk should be contacted. Contact details are listed in Attachment I. Treatment with trial product can be resumed if there are no safety concerns at the discretion of the investigator.

7.5 Preparation/Handling/Storage/Accountability

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

Table 7-4 Trial product storage conditions

Trial product name	Storage conditions (not-in-use)	In-use conditions	In-use time[a]
Semaglutide B 3.0 mg/ml PDS290	Store in refrigerator (2°C-8°C/36°F-46°F) Do not freeze Protect from light	In-use conditions will be available on the trial product label	In-use conditions will be available on the trial product label
Semaglutide placebo PDS290			

[a] In-use time starts when the product is taken out of the refrigerator in the subject's home.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to screening and randomisation. The first shipment will be triggered by first subject screened.

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

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

The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the TMM.

Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. Subjects must return all used, partly used and unused trial product as instructed by the investigator.

The investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records). Drug accountability should be performed at pen level for semaglutide/placebo.

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

All returned, expired or damaged trial products (for technical complaint samples see Appendix 6) must be stored separately from non-allocated trial products. No temperature monitoring is required.

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

7.5.1 Shipment of trial product to subject's home

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

The process for sending trial product from the trial site or pharmacy to a subject's home must be described in an instruction document. The instruction document must contain 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 must also be described in the instruction.

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

7.6 Treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed. The measures that will be taken to ensure and document treatment compliance also include reporting of changes in the dose taken (see section 7.1).

7.7 Standard of care

Subjects will be treated with semaglutide s.c. 2.4 mg once-weekly or placebo on top of standard of care, which covers management of CV risk factors including medical treatment and healthy lifestyle counselling. Throughout this trial investigators are encouraged to optimise treatment with medications affecting CV risk in accordance with treatment guidelines or local clinical practice. At every visit subjects should be offered individualised healthy lifestyle counselling (including diet and physical activity). It will be documented in the eCRF whether the subject received the healthy lifestyle counselling. Recommendations for management of CV risk factors and the healthy lifestyle counselling will be provided in guidance documents from the steering committee or global expert panel during trial conduct.

7.8 Concomitant medication

Only medication, other than trial product, that the subject is receiving at the time of screening or receives during the trial for the following reasons must be recorded in the eCRF:

- To treat or prevent CV diseases (for example anti-hypertensives, lipid-lowering agents, anticoagulants, aspirin and other antiplatelet agents)
- To treat overweight or obesity
- To treat diabetes and diabetes complications (for subjects who develop diabetes during the trial)
- To treat an SAE or medication which may provide further information on the SAE i.e. alternative aetiology.
- in relation to a clinical trial for COVID-19 prevention or treatment
- in relation to an approved COVID-19 vaccine

The information collected for each concomitant medication includes medication, start date and stop date or continuation, dose (only to be collected for diabetes medication) and related AE number when applicable.

Changes in concomitant medication listed above must be recorded at each visit. If a change is due to a SAE, then this must be reported if required according to section 9.2.

Initiating other GLP-1 receptor agonists are not permitted during the entire trial. Other changes to background medications can take place during the trial. Importantly, investigators should ensure that subjects are treated according to recommended standard of care for CV risk management. If allowed according to local regulation, Novo Nordisk may compensate for new concomitant medications prescribed during the trial for CV disease management.

For subjects who develop diabetes during the trial or who are started on another glucose lowering drug:

For glucose-lowering medication, the total daily dose on the day preceding the visit (if available) should be recorded in the eCRF. Stable dose changes (2 weeks or more) should be captured as new concomitant medication with the relevant start and stop date. Hypoglycaemic episodes have mainly been observed when semaglutide is combined with sulphonylurea or insulin. It is therefore recommended that the investigator ensures that subjects initiating sulphonylurea or insulin perform adequately frequent blood glucose monitoring to ensure subject safety during initiation.

If initiating glucose-lowering treatment after the discontinuation of trial product, the long semaglutide half-life of approximately one week should be kept in mind.

7.9 Treatment after the end of the trial

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

8 Discontinuation/Withdrawal criteria

8.1 Discontinuation of trial treatment

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

1. Pregnancy
2. Intention of becoming pregnant
3. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product
4. If pancreatitis is suspected, trial product must be discontinued; if confirmed, trial product shall not be restarted
5. Calcitonin ≥ 100 ng/L (see Appendix 8)
6. Treatment with another GLP-1 RA
7. Other safety concerns, at the discretion of the investigator

Ad 1 and 2: If a subject intends to become pregnant, trial product must be discontinued at least 5 weeks before the contraceptive method is stopped. If a subject becomes pregnant unintentionally, trial product must be discontinued immediately during pregnancy, and during breast feeding. The subject will continue the other trial procedures or will be followed-up via phone contacts.

Ad 3: Subjects must not receive investigational medical product from another clinical trial, while participating in this trial. If done, treatment with trial product should be discontinued. If the use of investigational medical product in the other trial is discontinued, treatment with trial product can be resumed if there are no safety concerns at the discretion of the investigator. The subject may be discontinued from trial product at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. The subject should continue the other trial procedures. Treatment with trial product can be resumed later if it is evaluated as being safe by the investigator. Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator's discretion without discontinuing trial treatment.

Algeria and Germany: For country specific requirement, please see Appendix 9.

Subjects who do not fully meet eligibility (inclusion/exclusion/randomisation) criteria must not be randomised. If a subject is randomised in error this will be handled as an important protocol deviation and the IRB/IEC and regulatory authorities must be notified according to local requirements. If there are no safety concerns, treatment with trial product can be continued or resumed at the discretion of the investigator after a discussion with a Novo Nordisk medical expert.

Temporary or permanent discontinuation of treatment with trial product will not lead to withdrawal from the trial.

The primary reason for discontinuation of trial product must be specified in the eCRF, and drug accountability must be performed.

8.1.1 Temporary discontinuation of trial treatment

Temporary treatment discontinuation is allowed at the discretion of the investigator and the reason for discontinuation must be recorded in the eCRF. Treatment with trial product should be resumed if the circumstances later allow (section 7.1). Similarly subjects who discontinue trial product on their own initiative should be encouraged to resume the treatment (section 7.1). At both instances dose escalation may be necessary (section 7.1). Date and trial product dose should be recorded in eCRF. A treatment status session in the IWRS should be performed when a subject is on treatment pause or resumes treatment.

8.2 Withdrawal from the trial

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

If considering withdrawing from the trial, the subject should as an alternative, be offered flexible participation in the trial. This could be attending fewer visits (i.e. reduced visit schedule), converting site visits to phone contacts, treatment pause, or only being followed-up for AEs, especially those related to the primary objective. Another alternative could be to cease all trial related activities including trial product, and simply receive a phone call at trial end to collect AEs. It must be explained to the subject that this must include information on their AEs, especially those related to the primary objective that occurred since last contact to the subject. This is important to ensure that the information gained is complete and accurate, and that the correct conclusions are drawn. Only if the subject declines all alternatives, should the subject be recorded as withdrawn.

Final drug accountability must be performed even if the subject is not able to come to the trial site.

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

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

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

8.2.1 Replacement of subjects

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

8.3 Lost to follow-up

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

- Before a subject is deemed lost to follow-up, the investigator must make every effort to regain contact with the subject as described in section 5.2.
- A subject cannot be declared lost to follow-up before all the attempts have been repeated and the trial has come to an end

The attempts must be documented at site.

8.4 Termination or modification of the trial

The DMC will monitor accumulating efficacy and safety data at each DMC meeting and make recommendations to the internal Novo Nordisk semaglutide s.c. safety committee whether to continue, modify or terminate the trial. Recommendations to modify or stop the trial should be given if there is clear evidence of clinical harm to the patients which changes the benefit-risk evaluation to a situation where the benefit no longer outweighs the risks (see section 5.1, 10.3.5, Appendix 3, Appendix 4).

9 Trial assessments and procedures

- Trial procedures and their timing are summarised in the flowchart, see section 2.
- Informed consent must be obtained before any trial related activity, see Appendix 3.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- The investigator should inform the subjects' primary physician, if applicable, about the subjects' participation in the trial and if the subject agrees to the primary physician being informed.
- Each subject should be asked to provide contact information for persons (preferably at least 3), e.g. relatives, primary care provider or other, whom investigator can contact in case of issues when trying to contact the subject during the trial. The sites are encouraged to maintain these details as current as possible throughout the course of the trial.
- If necessary, in order to retain the subject in the trial sites visits can be replaced by phone contact. However as a minimum, subjects should be asked to attend visit 1, visit 2, visit 7, visit 10, visit 14, visit 18, visit 22 and V-EOT face to face (key assessment visits). If a site visit is changed to a phone contact the investigator needs to ensure that the subject has enough trial product within the expiry date.
- The investigator must ensure they keep regular contact with each subject throughout the entire trial, and at all times have updated contact information. Even if a visit is missed and it is not possible to re-schedule, the investigator must take every effort to have all subjects followed for MACE-related outcomes. The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to continue in the trial.
- Assessments should be carried out according to the clinic's standard of practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments (i.e. performing subject-recorded assessments before other assessments, measuring vital signs before blood draws).
- The barriers and motivation interview identify barriers to and motivation compliance with the protocol. The interview should be conducted at screening to assist in identifying subjects who are unable or unwilling to comply with protocol procedures as per the exclusion criteria. In addition, the interview will ensure that any minor barriers are addressed during site visits.
    - The results of the interview will not be entered into the CRF and will not be transferred to the trial database. It will be at the investigator's discretion to evaluate the motivation of the subject and related eligibility.
- Review of laboratory reports etc. must be documented either on the documents or in the subject's source documents.

- There are no fasting visits.
- Repeat samples may be taken for technical issues and re-rest samples or assessments may be taken for safety reasons. Please refer to Appendix 2 for further details on laboratory samples.
- The subject's glycaemic status will be categorised as normo-glycaemia, prediabetes or diagnosed with type 2 diabetes based on the investigator's evaluation of all available relevant information e.g. medical records, concomitant medication, blood glucose parameters (reference to ADA standard of care 2018)[16] (see Appendix 2) and AEs.
- The investigator may provide the subjects with a mobile phone to mediate easier contact if allowed according to local regulation and approved by IRB/IEC. The investigator should consider sending text messages to the subjects to remind them of site visits, dosing of trial product, and other trial requirements. Novo Nordisk will ensure the availability of pre-paid phone cards or similar.
- If warranted by special circumstances and if permitted by local regulations, the investigator may engage with a Health Care Professional from a third party home health care service provider to perform protocol procedures at the subject's home or other alternate location. Prior to the arrangement, the investigator must obtain the subject's consent by means of separate and locally approved consent form. The third party Health Care Professional must have a licence to practice and have received adequate protocol training. Detailed procedure and specific requirements should be available for relevant site staff in a written instruction.

9.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart section 2.

9.1.1 Body measurements

- Body weight should be measured without shoes and only wearing light clothing. It should be measured on a digital scale and recorded in kg or lb (one decimal with a precision of 0.1 kg or lb) using preferable the same scale throughout the trial. The scale must be calibrated yearly as a minimum, unless the manufacturer certifies that calibration of the weighing scales is valid for the life-time of the scale.
- Height is measured without shoes in centimetres or inches (one decimal with a precision of 0.1 centimetres or inches). At screening BMI will be calculated by the eCRF and must be in agreement with inclusion criterion #3.
- Waist circumference is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest. Measures must be obtained in standing position with a non-stretchable measuring tape and to the nearest cm or inch. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally.

9.1.2 Clinical efficacy laboratory assessments

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

9.1.3 Patient reported outcomes

Below data will not be entered into the eCRF, but will be transcribed directly into a site-pad/web-solution.

EuroQol five dimensions five level
The EQ-5D-5L questionnaire is a patient reported outcome (PRO) tool. The PRO will be used to estimate the impact on subjects' health-related quality of life and provides a description of subjects' problems by dimensions (descriptive system), a score for overall self-rated health (visual analogue scale (VAS) as well as an index score (EQ-5D-5L index)). If clarification of the test is needed, care must be taken not to bias the subject.

Weight related sign and symptom measure
The weight related sign and symptom measure assesses the presence and bother associated with weight-related symptoms using a self-rated VAS. It is a tool to assess the multifaceted aspects of obesity on symptom experience in subjects with overweight or obesity.

Subject engagement assessment
A subject engagement assessment will be performed in a subset of subjects to monitor engagement and proactively identify retention challenges. The assessment may be used for English speaking subjects in the US and UK. This data will not be transferred to the trial database.

9.1.4 Hospitalisations

Hospitalisations which are related to a SAE (see Appendix 4), including re-admissions for the same event, should be reported on the AE form.

9.1.4.1 Non-SAE hospitalisations

Hospitalisations that are not related to SAEs should be reported on the 'Non-SAE hospitalisations' form. This includes the below types of hospitalisations:

- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from randomisation
- Hospitalisations for administrative, trial related and social purposes
- Hospital admissions for surgical procedures, planned before randomisation

9.2 Adverse events

The investigator is responsible for detecting, documenting, recording and following up on:

- All SAEs
- AEs leading to discontinuation of trial product, irrespective of seriousness
- AEs of COVID-19, irrespective of seriousness.
  Note: Suspected COVID-19 should be reported if the clinical presentation is suggestive of COVID-19, even in the absence of a COVID-19 test or without a positive COVID-19 test result. In the absence of clinical symptoms, a positive COVID-19 test (antigen or antibody) should be reported, if available
- AEs requiring additional data collection (via specific event form) and events for adjudication, irrespective of seriousness, see Table 9-1

Only the above listed AEs should be recorded in the eCRF.

The definitions of AEs and SAEs can be found in Appendix 4.

For AE reporting requirements in Japan, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden and United Kingdom, please see Appendix 9.

Table 9-1 AEs requiring additional data collection (via specific event form) and events for adjudication

Event type (serious and non-serious) including description	Adjudication Outcome	Additional form required
Death: All cause death	• Cardiovascular death • Renal death • Non-cardiovascular, non-renal death	Adjudication form
Acute coronary syndrome: Conditions include all types of acute myocardial infarction and hospitalisation for unstable angina pectoris	• Acute myocardial infarction • Hospitalisation for unstable angina pectoris	Adjudication form
Stroke (Stroke and transient ischemic attack): Episode of focal or global neurological dysfunction that could be caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or ischemia, with or without infarction	• Stroke	Adjudication form
Coronary artery revascularisation: A catheter-based (percutaneous coronary intervention (PCI)) or a surgical procedure (Coronary artery bypass surgery (CABG)) designed to improve myocardial blood flow	• Coronary revascularisation procedure	Adjudication form
Heart failure hospitalisation or urgent heart failure visit: Presentation of the subject for an urgent, unscheduled hospital admission or clinic/office/emergency department visit with a primary diagnosis of heart failure (new episode or worsening of existing heart failure)	• Heart failure hospitalisation • Urgent heart failure visit	Adjudication form
Pancreatitis: Any event of pancreatitis should be reported	• Acute pancreatitis	Adjudication form Specific event form
Nephropathy (events leading to renal replacement therapy): Initiation of dialysis treatment (haemodialysis or peritoneal dialysis) or kidney transplantation Note: The underlying condition should be reported as the AE diagnosis	• Chronic renal replacement therapy	Adjudication form
Acute renal failure:	Not applicable	Specific event form

Event type (serious and non-serious) including description	Adjudication Outcome	Additional form required
Abrupt decrease in renal function, e.g. one of the following: 1) ≥ 0.3 mg/dL (≥ 26.5 µmol/l) increase in serum creatinine within 48 hours 2) ≥ 1.5 times increase in serum creatinine within 7 days 3) urine volume < 0.5mL/kg/h for 6 hours		
Gallbladder disease: Event of biliary colic, cholecystitis and other forms of gallbladder disease	Not applicable	Specific event form
Malignant neoplasm: Malignant neoplasm by histopathology or other substantial clinical evidence	Not applicable	Specific event form
Medication error (accidental errors): A medication error concerning trial products is defined as: • Administration of wrong drug. Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in a confirmed administration of wrong drug. • Wrong route of administration, such as intramuscular instead of subcutaneous. • Accidental overdose administration of more than 2.4 mg/week or a higher dose than intended during dose escalation, however, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur. Treatment pauses should not be reported as a medication error	Not applicable	Specific event form
Misuse or abuse of trial product: Misuse is when the trial product is intentionally and inappropriately used. Abuse of trial product is persistent or sporadic, intentional excessive use, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm)	Not applicable	Specific event form

Description of events is to guide investigators with regards to reporting of AEs. Event definitions for events requiring adjudication are included in the charter for the event adjudication committee (EAC).

9.2.1 Time period and frequency for collecting AE and SAE information

All events meeting the definition of an SAE (see Appendix 4), AEs leading to discontinuation of trial product, events of COVID-19 and events specified in Table 9-1 must be collected and reported. These events will be collected from the day of randomisation and until the end of trial visit, at the time points specified in the flowchart. Medical occurrences with onset between informed consent and day of randomisation need to be recorded, if applicable, on the medical history/concomitant illness form in the eCRF (see section 9.4).

All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours of investigator's knowledge of the SAE, as indicated in Appendix 4. The investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

The investigators are not obligated to actively seek for AE or SAE in former trial subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discontinued from/completed the trial, and the investigator considers the event to be

possibly/probably related to the investigational trial product or trial participation, the investigator must promptly notify Novo Nordisk.

The method of recording, evaluating and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

Timelines for reporting of AEs and events for adjudication, section 9.2.1.1, are listed in Figure 9-1.

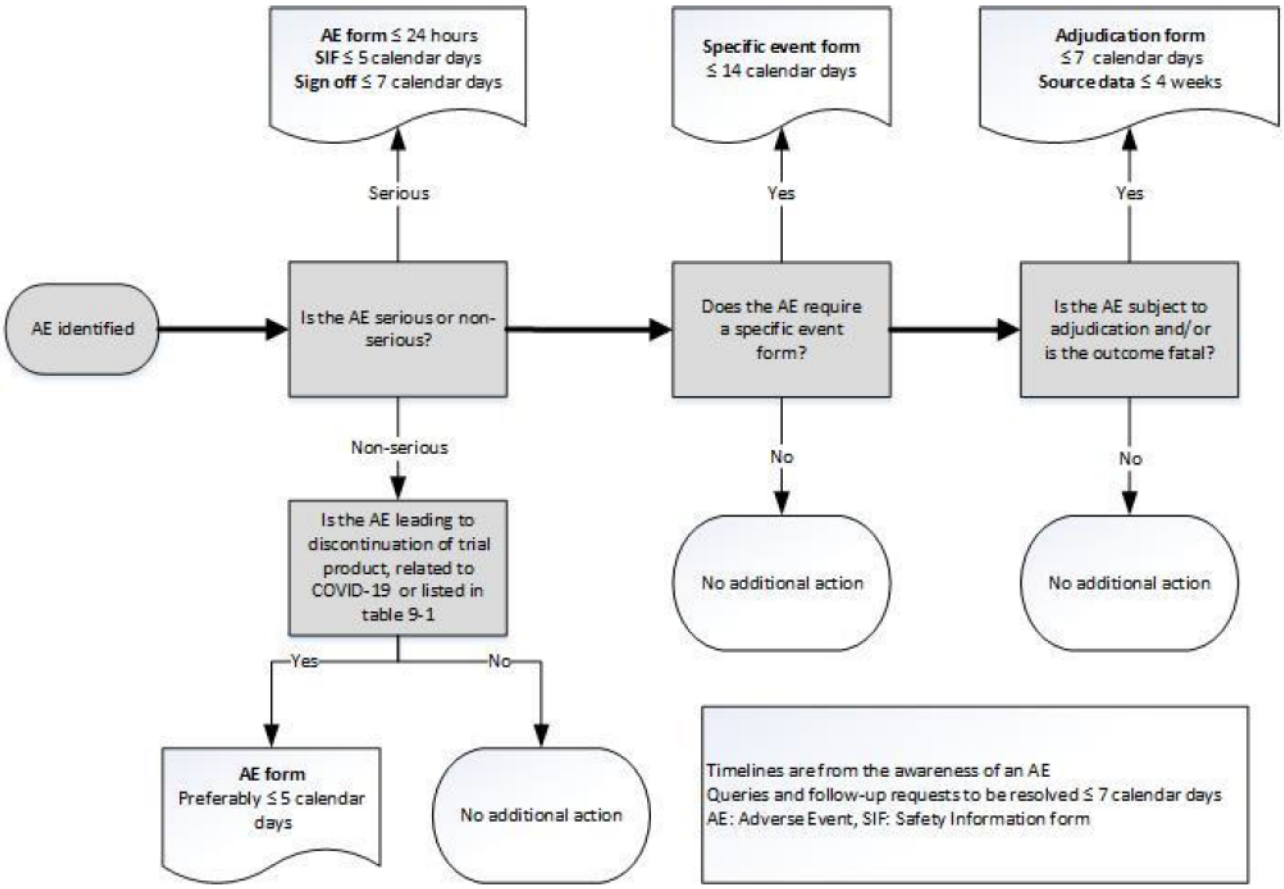

Figure 9-1 Safety reporting timelines

9.2.1.1 Events for adjudication

The list of events for adjudication can be found in Table 9-1 and the reporting timelines in Figure 9-1. Event adjudication will be performed for events in randomised subjects. These events are reviewed by an independent external event adjudication committee in a blinded manner, refer to Appendix 3 for further details.

There are four ways to identify events relevant for adjudication as described below:

1. Investigator-reported events for adjudication: When reporting AEs, the investigator must select the appropriate AE category based on pre-defined criteria (see Table 9-1). If the selected AE category is in scope for adjudication, an event specific adjudication form should be completed. Relevant source documents (as specified in the Event Adjudication Site Manual) must, if obtainable, be collected and uploaded to the Event Adjudication System (EAS).

2. Deaths (AEs reported with fatal outcome): When an AE is reported with fatal outcome, a death adjudication form will appear in the eCRF. This form must be completed and all source documents associated with the subjects' death must, if obtainable, be collected and uploaded to the EAS.

3. AE search (standardised screening): All AEs not directly reported by the investigator as requiring adjudication, will undergo screening to identify potential events for adjudication. If the AE is deemed relevant for adjudication, an event specific adjudication form will be generated in the eCRF. This form must be completed, and all predefined source documents must, if obtainable, be collected and uploaded to the EAS.

4. EAC-identified events: During review of source documents provided for another event for adjudication, the EAC may identify additional events in scope for adjudication that were not initially reported by the investigator. In these instances, the investigator will be notified of the newly identified event and has the option to report the EAC-identified event. Regardless of whether the investigator decides to report the event, it will undergo adjudication. Occasionally, EAC-identified events may require the investigator to collect additional source documents and upload these, if obtainable, to the EAS.

The specific adjudication form for the event in question should be completed in the CRF within 7 calendar days of the investigator's first knowledge of the event.

Copies of source documents should be labelled with trial ID, subject number, AE number (if applicable), redacted (anonymised of personal identifiers) and uploaded to the EAS as soon as possible and preferably within 4 weeks. If no or insufficient source documents are provided to the adjudication supplier, the investigator can be asked to complete a clinical narrative to be uploaded to the EAS.

If new information becomes available for an event sent for adjudication, it is the responsibility of the investigator to ensure the new information is uploaded to the EAS.

An Event Adjudication Site Manual will be provided to each site detailing how to provide the relevant source documents to the adjudication supplier. The anonymization and labelling requirements are also described in the site manual.

The assessments made by both the event adjudication committee and the investigator will be evaluated and included in the clinical trial report.

9.2.2 Method of detecting AEs and SAEs

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

9.2.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow all SAEs until resolution, stabilization, or if the event is otherwise explained (e.g. chronic condition). Further information on follow-up procedures is given in Appendix 4.

9.2.4 Regulatory reporting requirements for SAEs

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

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

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Novo Nordisk policy and forwarded to investigators as necessary (see Appendix 9).

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

9.2.5 Cardiovascular events and deaths

Specified in Table 9-1.

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

Not applicable for this trial.

9.2.7 Pregnancies and associated adverse events

Details of pregnancies in female subjects will be collected from the first-trial-related activity after obtaining informed consent and until pregnancy outcome.

If a pregnancy is reported in female subjects, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 5. The investigator will report information on the subject and the pregnancy outcome until the new-born infant is one month of age in accordance with European Medicines Agency (EMA)[17]. Information about the pregnancy and pregnancy outcome/health of the new-born infant has to be reported on paper pregnancy forms.

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 a SAE.

9.2.8 Technical complaints

The investigator must assess whether a technical complaint is related to an AE. The definitions and reporting process for technical complaints can be found in Appendix 6.

9.3 Treatment of overdose

There is no specific antidote for overdose with semaglutide. In the event of overdose, appropriate supportive treatment should be initiated according to the subjects' clinical signs and symptoms. Overdoses of up to 4 mg in a single dose have been reported in clinical trials. The most commonly reported adverse reaction was nausea. All subjects recovered without complications.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAEs and laboratory abnormalities. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of semaglutide of approximately one week.

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

The overdose must be reported as a medication error or abuse/misuse according to the definition in Table 9-1.

For more information on overdose, also consult the current version of the IB[12] and any updates hereof.

9.4 Safety assessments

Planned time points for all safety assessments are provided in the flowchart section 2.

A **concomitant illness** is any illness that is present at the start of the trial or found as a result of a screening procedure or other trial procedures performed up until time of randomisation.
Medical history is a medical event that the subject has experienced in the past, i.e. prior to randomisation.

The following concomitant illness/medical history should be recorded in the eCRF.
Specific Medical History forms:

- History of cardiovascular diseases. This also includes each medical condition(s) that qualified the subject for participation in the trial according to inclusion criterion #4 a-c
- Obesity comorbidities
- History of gallbladder disease
- History of pancreatitis
- History of skin cancer
- History of colon neoplasm including risk factors
- History of breast neoplasm including risk factors (for all female subjects)

Medical History/Concomitant Illness form:

- All other relevant concomitant illness/medical history that has not been recorded in Specific Medical History forms (this also includes malignant neoplasm and COVID-19)

In case of an abnormal and clinically significant finding, the investigator must record the finding on the Medical History/Concomitant Illness form if it is present before randomisation. Any new finding or worsening fulfilling the SAE definition, AEs leading to treatment discontinuation, AEs of

COVID-19 or AEs requiring additional data collection (see Appendix 4 and section 9.2) during the trial from randomisation must be reported (see section 9.2).

9.4.1 Breast neoplasms follow-up and colon neoplasms follow-up

Follow-up questions will be asked at the end of treatment (V-EOT) and end of trial (P-FU) visits related to any colonoscopy and mammography's carried out during the trial.

9.4.2 Physical examinations

A physical examination will include assessments of the:

- General appearance
- Thyroid gland
- Respiratory system
- Breast (females)
- Cardiovascular system
- Gastrointestinal system
- Central and peripheral nervous system

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

Relevant findings present at or prior to randomisation should be recorded on the concomitant illness/medical history form in the eCRF in accordance with section 9.4. Findings not present at randomisation should be reported as AEs according to section 9.2.

9.4.3 Vital signs

Blood pressure and pulse
Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. television, cell phones). The measured values should be recorded without rounding. Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

9.4.4 Clinical safety laboratory assessments

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

9.5 Pharmacokinetics

Not applicable.

9.6 Pharmacodynamics

Not applicable.

9.7 Genetics

A blood sample for DNA/RNA analysis will be collected from subjects who have consented to participate in the optional biobank component of the trial. Refer to section 9.8 and Appendix 7 for further details.

Algeria, Brazil, Israel: For country specific requirements, please see Appendix 9.

9.8 Biomarkers

Collection of blood samples for biomarker research is a component of this trial. Participation in the biobank component is optional. Subjects who do not wish to participate in the biobank component may still participate in the trial. For the biobank, samples will be collected according to the flow chart and stored for future use.

The samples are collected for the purpose of allowing future analyses of biomarkers, both genetic and circulating, at a later point in time when new knowledge or improved measurement techniques may have become available. The analyses may include biomarkers currently known or discovered in the future.

Genetic analyses will include analysis of candidate genes or genetic markers throughout the genome with the purpose of understanding and predicting response to semaglutide as well as to understand cardiometabolic diseases. Analyses of circulating biomarkers will measure hormones, metabolites or other non-genetic plasma or serum entity with the purpose of understanding and predicting response to semaglutide as well as understanding cardiometabolic diseases.

These samples need to be frozen and should be sent in batches to the central laboratory. The analyses are likely to be performed after the trial has come to an end, and results will therefore not be part of the clinical trial report. The biobank samples may be stored up to 15 years after end of trial at a central laboratory (see Appendix 7).

Algeria, Brazil, Israel: For country specific requirements, please see Appendix 9.

10 Statistical considerations

10.1 Sample size determination

This trial is designed to have 90% overall power to confirm superiority of the primary endpoint (section 10.3.1). The following information has been used to calculate the number of events that need to be accrued in this trial.

Table 10-1 Information used to calculate the number of primary endpoint events needed

Endpoint	Statistical test	Hypothesis Tested	One-sided significance level	Assumed true HR	Required power
Time to first event	Log-rank	Superiority	2.5%	0.83	90%

The assumed true HR is based on a conservative assessment of the observed point estimate for the HR in the SUSTAIN 6, which was 0.74 [CI95%: 0.58 ; 0.95] for a similar definition of MACE[4].

The number of events needed to be accrued is determined based on the log-rank test and the group sequential design allowing for interim testing. The Lan-DeMets alpha spending function, approximating the O'Brien-Fleming's stopping boundaries, is used with a study-wise (cumulative) one-sided type I error rate of 2.5%. A total of 1225 first MACEs will provide 90% power.

The power as a function of true HR is seen from the below figure:

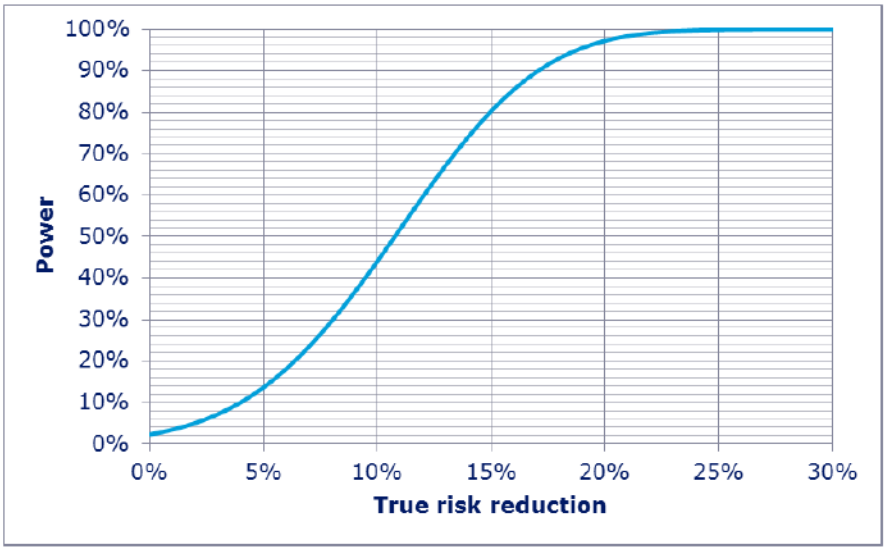

Figure 10-1 Power as a function of true risk reduction (i.e. 1- hazard ratio) with 1225 events

The assumptions for the sample size calculation are shown in Table 10-2.

Table 10-2 Assumptions behind sample size calculation

Recruitment	Annualised rate of subjects for whom MACE information is unavailable at trial closure	Annualised rate of subjects with a first MACE	Duration of trial
2,500 randomised every 4 month	1.0%	2.0%	59 months

The assumption of 2,500 subjects being randomised every four months is based on what has been achieved in trial EX1250-4080 (DEVOTE).

The annualised rate of subjects with a first MACE (primary endpoint) is based on the event rates seen in SUSTAIN 6 and EX2211-3748 (LEADER). These event rates were compared to the event rates in other non-T2D CVOTs (FOURIER, SCOUT and IRIS[18-20]) and adjusted to the inclusion and exclusion criteria of the current trial. In the SCOUT trial, which was conducted in subjects with overweight or obesity, the subgroup that only had established CV disease had ~30% fewer MACE events compared with the subgroup that had established CV disease and T2D[19]. Based on this

literature, an event rate around half of that seen in LEADER and SUSTAIN 6 is assumed when including subjects with prior MI, prior stroke or symptomatic PAD but without T2D.

Accordingly, the overall annualised event rate across the two treatment arms is assumed to be 2.0%, (i.e. 1.8% in the semaglutide arm and 2.2% in the placebo arm).

With these assumptions the number of events accrued over a period of 7 years with various sample sizes is seen on the below figure.

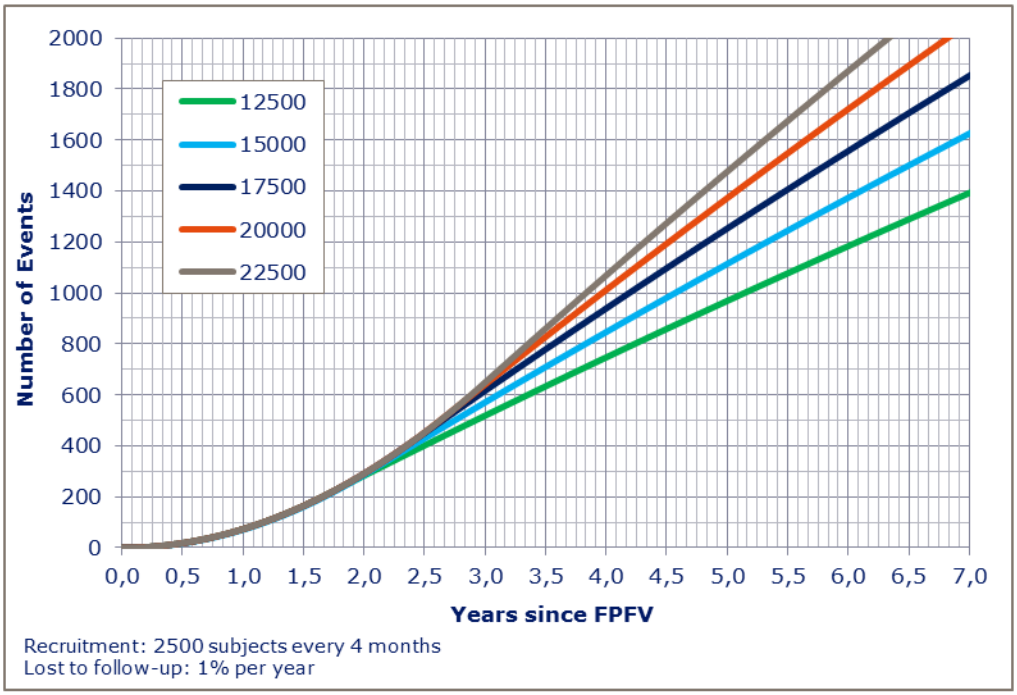

Figure 10-2 Number of events over time with various sample sizes

With a sample size of 17,500 subjects randomised 1:1 to semaglutide 2.4 mg or semaglutide placebo the 1225 events will be accrued at month 59 (~5 years).

To examine the sensitivity of the trial duration depending on the actual event rate the following figure provides an overview:

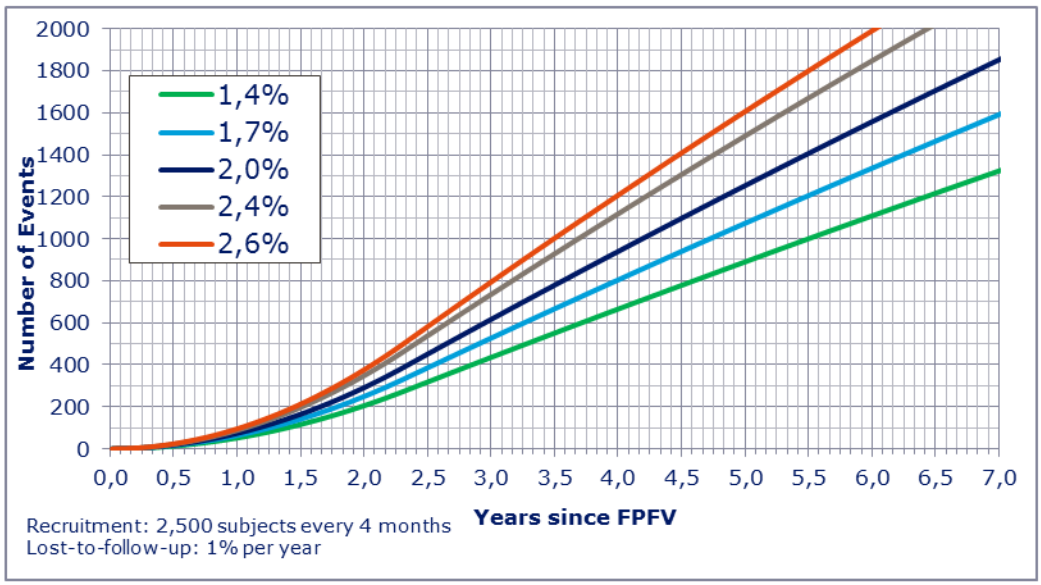

Figure 10-3 Number of events over time with different event rates

From this figure it is seen that the time to accrue 1225 first MACEs will be less than 49 months (4.1 years) if the event rate is as high as 2.6% and 79 months (6.5 years) if the event rate is 1.4%.

In summary the sample size calculations provide the following information about the trial and expected trial conduct:

Table 10-3 Key numbers and timelines

Randomisation scheme	Total number of subjects to be randomised	Number of subjects with an event	Duration of recruitment period	Duration of trial	Time from LPFV to LPLV	Mean observation time
1:1	17,500	≥1,225	28 months (2 year and 4 months)	59 months (4 years and 11 months)	31 months (2 years and 7 months)	44 months (3 years and 8 months)

10.2 Definition of analysis sets

Data selection for statistical analyses will be a two-step process, first selecting subjects based on the analysis population and subsequently events/data on those subjects based on the observation period.

Full analysis set (FAS): All randomised subjects. Subjects will be analysed according to the treatment to which they were assigned at randomisation.

In-trial observation period: This observation period is defined as the period from date of randomisation to one of the following dates, whichever comes first.

- Date of end-of-trial visit

- Date of death
- Date when subject withdrew consent
- Date of last contact with subject

10.3 Statistical analyses

A statistical analysis plan (SAP) will be prepared and finalised prior to first unblinded DMC meeting. The SAP will provide further details regarding the definition of analysis variables and analysis methodology including analyses of secondary endpoints and sensitivity analyses for the primary endpoint. Additionally, further details of the interim testing will be provided in the SAP.

Novo Nordisk will perform the statistical analyses except interim testing, see section 10.3.4.

General considerations

Unless otherwise specified, all analysis and summary of all endpoints will be based on the full FAS using the in-trial observation period, see section 10.2. In statistical analyses of confirmatory endpoints, the estimated treatment effects will be presented together with 2-sided 95% confidence intervals (CI) and one-sided p-values for tests of the associated hypotheses. For non-confirmatory endpoints, two-sided p-values corresponding to testing hypotheses of no difference will be presented instead of one-sided p-values. Occurrence of time-to-event endpoints will be summarised by cumulative incidence function plots adjusted for competing risk of death/CV death (if not a component of the specific endpoint) as well as descriptive summaries with proportion of subjects with event, incidence rates for occurrence of first event and rates of occurrence of all events. Unless otherwise stated all time-to-event endpoints will be derived using the outcome of the EAC evaluations whenever applicable. Continuous endpoints will be summarised in descriptive tables using arithmetic means, geometric means, standard deviations, ranges, and interquartile ranges as appropriate. EAC confirmed events and investigator reported events will be summarised by number of subjects with events, proportion of subjects with events, number of events and rate of events per 100 PYO.

For continuous endpoints and categorical endpoints derived from continuous sources, the baseline value is defined as the last assessment taken prior to or at the randomisation visit *and* before first use of trial product. For example, if the assessment is missing at the randomisation visit (or if the assessment was done *after* first use of trial product) and the assessment also has been made at screening, then the screening value will be used as the baseline value.

Subgroup analyses will be performed to examine the consistency of the primary analysis. The relevant subgroups will be identified at baseline based on demographics and disease status, and described in the statistical analysis plan.

10.3.1 Primary endpoint

Time from randomisation to first occurrence of a composite MACE endpoint consisting of:

- CV death,
- non-fatal myocardial infarction or
- non-fatal stroke

Statistical analysis of the primary endpoint

The primary analysis of the primary endpoint will be based on the FAS using the in-trial observation period. The hazard ratio (HR) comparing semaglutide 2.4 mg versus semaglutide placebo will be estimated from a Cox proportional hazards model with treatment group (semaglutide 2.4 mg, semaglutide placebo) as fixed factor.

Subjects without a primary endpoint event prior to the in-trial end-date will be considered censored at this date.

The following superiority hypothesis will be tested:

H_0: HR $\geq$ 1.0 against H_a: HR < 1.0

where HR is the hazard ratio for the comparison of semaglutide 2.4 mg versus semaglutide placebo. Superiority of semaglutide versus placebo will be considered confirmed if the associated H_0 is rejected based on nominal significance level derived from the pre-specified alpha spending based on the actual observed number of events available for the analysis. Final inference on termination is adjusted for the group sequential design by using the likelihood ratio ordering for the p-value, 95% CI and HR.

Sensitivity analyses

The primary analysis relies on the assumption that missing data after censoring for subjects that have withdrawn consent or are lost to follow-up are missing at random. To investigate the impact of this assumption on the results of the primary analysis, a tipping point analysis based on the approach described in Zhao et al. (2014)[21] will be made. In this analysis, subjects in the semaglutide treatment group will have their survival times imputed from their conditional survival distribution with a penalty (sensitivity parameter) in the sense that their risk of MACE is increased following censoring compared to while under observation. The placebo subjects will be imputed from their conditional survival with no penalty. Multiple imputed data sets will be analysed with separate Cox regressions and results will be combined using Rubin's rule.[22]

10.3.2 Secondary endpoints

Secondary endpoints are categorised as being confirmatory when they are analysed under multiplicity control, and as supportive if the endpoints are analysed without multiplicity control.

10.3.2.1 Confirmatory secondary endpoints

The superiority hypothesis stated in section 10.3.1 is tested for each of the confirmatory endpoints under multiplicity control via a hierarchical testing scheme. The confirmatory endpoints are prioritised according to the below ordering and the testing procedure is stopped the first time an analysis fails to confirm superiority of the endpoint in question. The statistical significance levels of the confirmatory secondary endpoint analyses are specified in the SAP.

The confirmatory secondary endpoints are defined as time from randomisation to:

- CV death

- First occurrence of a composite heart failure endpoint consisting of: heart failure hospitalisation, urgent heart failure visit or CV death
- All-cause death

The confirmatory secondary endpoint will be analysed using the same proportional hazards regression model described for the primary analysis.

10.3.2.2 Supportive secondary endpoints

Each of the supportive secondary time to event endpoints will be analysed with the same Cox proportional hazards model as the primary endpoint. The estimated hazard ratio for the effect of semaglutide versus semaglutide placebo will be presented.

The continuous supportive secondary endpoints (change from baseline to year 2) will be analysed using multiple imputation. Missing values are defined as data that are planned to be observed but are not present in the database. In case the trial is terminated before 90% of subjects have reached the visit around year 2 the visit around year 1 will be used instead of year 2. Thus if less than 10% of subjects have missing values for the year 2 visit due to termination earlier than planned the events rate exceeded expectations) the missing value in question will be imputed.

The imputation model will include baseline value as a covariate and fitted to subjects that are off treatment for the first time, but have an observed data point at the specific visit. The fitted model will be used to impute values for all subjects that do not have an observed data point at the specific visit. Each of the completed data sets will be analysed separately for year 1 and year 2 assessments by an ANCOVA adjusted for treatment as fixed factor and baseline value as covariate. Rubin's rule[22] will be used to combine the results to draw inference. Analysis of lipids and hsCRP will be on logarithmic scale. The estimated treatment difference (ratio for lipid and hsCRP endpoints) for the effect of semaglutide versus semaglutide placebo will be presented. The following endpoint is defined only for subjects with a screening $HbA_{1c} \geq 39$ mmol/mol (5.7%):

- $HbA_{1c} < 39$ mmol/mol (5.7%) at each visit where HbA_{1c} is assessed

The endpoint will be analysed separately at year 1 and year 2 using a logistic regression model with treatment (semaglutide, semaglutide placebo) as fixed factors and baseline HbA_{1c} as covariate. The ratio (semaglutide versus semaglutide placebo) between the estimated odds will be presented together with 95% CIs.

The following endpoint is defined only for subjects with a screening $HbA_{1c} < 39$ mmol/mol (5.7%):

- Time from randomisation to $HbA_{1c} \geq 39$ mmol/mol (5.7%)

The endpoint will be analysed using a Cox proportional hazards model with treatment group (semaglutide, semaglutide placebo) as fixed factor. The ratio (semaglutide versus semaglutide placebo) between the estimated hazards will be presented together with 95% CIs.

10.3.3 Exploratory endpoints

The exploratory smoking endpoint will be analysed separately at year 1 and year 2 using a binomial regression model with treatment (semaglutide, semaglutide placebo) and baseline smoking status as

fixed factors. The ratio (semaglutide versus semaglutide placebo) between the estimated odds will be presented together with 95% CIs.

Deterioration from baseline to 117w in glycaemic category (yes/no, where "yes" is determined by a change from normoglycaemia at baseline to pre-diabetes/diabetes at year 2 or from pre-diabetes at baseline to diabetes at year 2) will be analysed using binomial regression model with treatment (semaglutide, semaglutide placebo) as fixed factors and baseline HbA_{1c} as covariate. The ratio (semaglutide versus semaglutide placebo) between the estimated odds will be presented together with 95% CIs.

Change from randomisation to year 2 in WRSSM will be presented descriptively.

10.3.4 Interim testing for efficacy

Interim testing evaluating the primary endpoint for superiority will be performed based on locked snapshot of the study database at the time-point of the interim testing. Subjects without a primary endpoint event prior to the analysis cut-off date will be censored with the censoring date defined as the first of in-trial end-date and analysis cut-off date.

Trial integrity will be ensured by using an external independent statistical service provider (independent of trial conduct and external to Novo Nordisk) to perform interim testing. The DMC evaluates the unblinded interim testing using the group sequential stopping boundaries as guidance. Stopping the trial for superiority is allowed if a stopping boundary is crossed and the DMC makes the decision to recommend early trial termination.

If the trial is terminated early for superiority following an interim testing, definitive evaluation of superiority for the primary endpoint will be performed based on updated nominal significance levels. All events from the in-trial observation period including events collected after interim cut-off date will be included in this evaluation.

10.3.5 Sequential safety analysis and safety monitoring

Blinded and unblinded data analyses performed by the external independent statistical service provider during trial conduct will be evaluated by the DMC, as described in the DMC charter.

The sequential evaluations analyses performed by the DMC will be based on accumulated efficacy (see section 10.3.4) and safety data and will be performed to make recommendations regarding the ongoing conduct of the trial to ensure acceptable benefit/risk ratio for subjects in the trial.

The pre-specified stopping criteria for the entire trial (accrual of 1225 first MACEs) will be monitored by Novo Nordisk (see section 5.1, 8.4, Appendix 3, Appendix 4).

10.4 Pharmacokinetic and/or pharmacodynamic modelling

Not applicable.

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12 Appendices

Appendix 1 Abbreviations and Trademarks

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CLAE	clinical laboratory adverse event
COVID-19	Coronavirus disease 2019
CRF	case report form
CTR	clinical trial report
CV	cardiovascular
CVOT	cardiovascular outcome trial
DFU	direction for use
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DUN	dispensing unit number
EAC	event adjudication committee
EAS	event adjudication system
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1	glucagon-like-peptide-1
HbA_{1c}	glycated haemoglobin
HRT	hormone replacement therapy
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system

LAR	legally acceptable representative
LDL	low-density lipoprotein
LSLV	last subject last visit
MACE	major adverse cardiovascular event
NYHA	New York Heart Association
PAD	peripheral arterial disease
PCD	primary completion date
PG	plasma glucose
PP	per protocol
PRO	patient reported outcome
RA	Receptor agonist
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
SU	sulfonylurea
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TMM	trial materials manual
UNL	upper normal limit
VAS	Visual analoge scales
WOCBP	woman of child bearing potential

Appendix 2 Clinical laboratory tests

- The laboratory analyses will be performed by a central laboratory, unless otherwise specified. Lists of laboratory supplies and procedures for obtaining, handling, transportation and storage of samples, will be described in laboratory flow charts/manual, provided to all sites.
- Blood and preferably morning urine samples need to be obtained. The tests detailed in Table 12-1 and Table 12-2 will be performed by the central laboratory.
- 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 laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Brazil: For country specific requirements, please see Appendix 9.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- Ambient laboratory samples will be destroyed no later than at end of trial or no later than at finalisation of the clinical trial report.
- For haematology samples (differential count) where the test result is not normal, then a part of the sample may be kept for up to two years or according to local regulations.
- Human biosamples for retention will be stored as described in Appendix 7.

Table 12-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• HbA_{1c}
Lipids (non-fasting)	• Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides • Very low density (VLDL) cholesterol • Free fatty acids (FFA)
Urinalysis	• Urine albumin to creatinine ratio (UACR) A confirmatory test is needed in case of: • onset of macroalbuminuria (> 300mg/g) When a confirmatory test is needed, it should be done at the next scheduled contact, but no earlier than 4 weeks after UACR has reached the threshold, by obtaining a urine sample for the central laboratory for measurement of UACR. Confirmation of onset of macroalbuminuria is not needed if this has previously been confirmed for the patient.
Biomarkers	• High sensitivity C-reactive protein
Biobank	• The blood samples are collected for the purpose of allowing additional analyses of CV or metabolic biomarkers at a later point in time when new knowledge or improved measurement techniques may have become available. The analyses may include biomarkers currently known or discovered in the future. • These samples need to be frozen

	• The analyses are likely to be performed after the trial has come to an end, and results will therefore not be part of the clinical trial report. • The biobank samples may be stored up to 15 years after end of trial at a central laboratory.

Table 12-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	• Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Thrombocytes • Differential count (eosinophils, neutrophils, basophils, monocytes and lymphocytes)
Biochemistry[1, 4]	• Alanine Aminotransferase (ALT)[2] • Albumin • Albumin corrected calcium • Alkaline phosphatase • Aspartate Aminotransferase (AST)[2] • Bilirubin • Calcitonin • Calcium • Creatinine • Gamma glutamyltransferase (GGT) • Potassium • Sodium • Urea
Pregnancy Testing	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3]
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation A confirmatory test is needed in case of: • onset of ≥ 50% reduction in eGFR (CKD-EPI) • onset of eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 When a confirmatory test is needed, it should be done at the next scheduled contact, but no earlier than 4 weeks after eGFR has reached the threshold, by obtaining a blood sample for the central laboratory for measurement of creatinine. Confirmation of both a ≥ 50% reduction in eGFR (CKD-EPI) compared with baseline and eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 is not needed if this has previously been confirmed for the patient.

Notes:
[1]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 4 (Hy's Law) and section 8.1.
[2]If ALT or AST > 3 upper normal limit (UNL), additional blood samples should be taken from the subject to analyse international normalised ratio (INR) (except at screening visit). Repeated testing of the abnormal lab assessments should be performed for the subject until abnormalities return to normal or baseline state.
[3]Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC. UACR: urinary albumine to creatinine ratio.
[4]For country specific requirements, please see Appendix 9.

- For evaluation of glycaemic status either method (fasting plasma glucose (FPG), plasma glucose (PG) or HbA_{1c} reflecting current health status) listed in Table 12-3 can be used in addition to available subject information, including prescribed glucose-lowering medication.

Table 12-3 Classification of glycaemic status[16]

	FPG	**2h PG during oral glucose tolerance test**	**HbA_{1c}**
Normo-glycaemia	3.9-5.5 mmol/L (70-99 mg/dL)	< 7,8 mmol/L (< 140 mg/dL)	< 39 mmol/mol (< 5.6%)
Prediabetes	5.6-6.9 mmol/L (100-125 mg/dL)	7.8-11.0 mmol/L (140-199 mg/dL)	39-47 mmol/mol (5.7-6.4%)
Diabetes	≥ 7.0 mmol/L (≥ 126 mg/dL)	≥ 11.1 mmol/L (≥ 200 mg/dL)	≥ 48 mmol/mol (≥ 6.5%)

Appendix 3 Trial governance considerations

1) Regulatory and ethical considerations

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

Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[23] and applicable ICH Good Clinical Practice (GCP) Guideline[24]

Applicable laws and regulations

- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements), must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:

providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities

notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

ensuring submission of the clinical trial report (CTR) synopsis to the IRB/IEC

2) Financial disclosure

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

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

3) Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the subject and answer all questions regarding the trial. This includes the use of an impartial witness where required according to local requirements.
- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.

- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[24], Declaration of Helsinki[23] and the IRB/IEC or trial site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements.
- Subjects (or their legal authorised representative (LAR)) 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 or the subject's LAR.

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. Different initiatives for subject retention will be implemented throughout this trial. 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 healthy lifestyle management and will not exceed local fair market value.

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.

5) Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.
- The subject must be informed that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

6) Committee structure

Novo Nordisk safety committee

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

Data monitoring committee

The data monitoring committee (DMC) is an independent, external committee composed of members whose expertise covers relevant specialties including statistics. The DMC is established to review and evaluate accumulated data from the trial at predefined time points as well as ad hoc. This is done in order to protect the safety of the subjects and to evaluate the benefit-risk balance. The DMC will have access to unblinded data, and will provide recommendations on trial continuation, modification or termination.
Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

Event adjudication committee

An independent external event adjudication committee is established to perform ongoing blinded adjudication of selected AEs and deaths (see Table 9-1). The EAC will evaluate events sent for adjudication using pre-defined definitions and guidelines in accordance with the EAC Charter. The evaluation is based on review of pre-defined clinical data collected by the investigational sites.
The EAC is composed of permanent members covering all required medical specialities. EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk. The EAC will have no authorisations to impact on trial conduct, trial protocol or amendments.
The purpose of the adjudication is to confirm events in a consistent manner according to standardised criteria using independent external medical experts.

In this trial, cardiovascular events will be adjudicated in order to adequately characterize the cardiovascular effects, since cardiovascular disease is an important and serious comorbidity of obesity[25]. Nephropathy is increasingly recognised to be related to obesity and overweight[26, 27]. Events of chronic renal replacement therapy and renal death will be confirmed by adjudication and included in the Nephropathy endpoint. In addition, events of acute pancreatitis will be confirmed by adjudication as treatment with GLP-1 RA has been associated with acute pancreatitis.

Steering committee

A steering committee will provide scientific and operational leadership for the trial. The committee will consist of experts from outside Novo Nordisk, and designated Novo Nordisk employees. The committee will operate under a charter agreed with Novo Nordisk.

Supportive panels

Global expert panel

A global expert panel (GEP) will consist of selected principal investigators, identified as national leaders and scientific experts, and of designated Novo Nordisk employees. The panel will discuss

and advise on global and local operational issues related to trial conduct. The panel will operate under a charter agreed with Novo Nordisk. National investigators that are not part of the global panel may be appointed in some of the large countries.

Patient recruitment and retention panel
A patient recruitment and retention panel (PRRP) will consist of study coordinators, highly experienced in the conduct of CV outcomes trials from a few selected countries, and designated Novo Nordisk employees. The panel will discuss and advise on global recruitment, retention and adherence issues related to trial conduct. The panel will operate under a charter agreed with Novo Nordisk.

National study coordinators
For each country participating in the trial, where it is appropriate, a national study coordinator (NSC) will be selected. The national study coordinators will provide operational input to subject recruitment, retention and adherence related topics. The national study coordinators will operate under a charter agreed with Novo Nordisk.

7) Publication policy

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

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial.
The information obtained during this trial may be made available to other investigators who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

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

The co-chairs of the steering committee will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigators) on behalf of all participating investigators.

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

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. At the end of the trial, one or more scientific publications may be prepared collaboratively by the

investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

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

Authorship
The steering committee will be responsible for communication of primary trial results. This will include appointing the publication group and authorship, overseeing the preparations and final approval of manuscripts and congress communications of trial results.

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[28].

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

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

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

Investigator access to data and review of results
As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database. Individual investigators will have their own research subjects' data, and will be provided with the randomisation code after results are available.

8) Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[29], the Food and Drug Administration Amendment Act (FDAAA)[30], European Commission Requirements[1, 31] 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 last visit (LSLV). The trial will therefore be registered with an estimated PCD corresponding to the estimated LSLV, which is first subject randomised plus 59 months. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDA Amendment Act.

9) Data quality assurance

Case Report Forms (CRFs)

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

All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data, PRO questionnaires and subject surveys). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF and for ensuring that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this by choosing the appropriate option. Free-text comments are discouraged.

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

AE forms
Safety information forms
Technical complaint forms (also to be used to report complaints that are not subject related, e.g. discovered at trial site before allocation)

The following will be provided as paper CRFs:

Pregnancy forms
Other CRFs

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

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

Monitoring

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify

and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

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

- Monitors will review the subject's medical records and other source data to ensure consistency and/or identify omissions compared to the CRF.

Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

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

10) Source documents

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

11) Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by Novo Nordisk. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the trial site. If the provided electronic data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.
- Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice

12) Trial and site closure

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

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

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a trial site by Novo Nordisk or investigator may include but are not limited to:

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

Pre-planned interim testing may allow for premature termination of the trial.

13) Responsibilities

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

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

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

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of subjects to a specific qualified physician who will be readily available to subjects during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires) a new investigator will be appointed in consultation with Novo Nordisk.
The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

14) Indemnity statement

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

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

For any country specific indemnity requirements supplementing the above, please refer to Appendix 9.

Appendix 4 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results or safety assessments, including those that worsen from randomisation, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms or the clinical sequelae of a suspected overdose of trial product regardless of intent.
- A "lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.

Events NOT meeting the AE definition

- Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed up until time of randomisation.

Note: pre-existing conditions should be recorded as medical history/concomitant illness.

- Medical or surgical procedures is not an AE, the cause of the procedure is the AE. An exception is coronary artery revascularisation procedures which must be reported as a separate AE in addition to the cause of the procedure See Figure 9-1 .

Definition of an SAE

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

- **Results in death**
- **Is life-threatening**
  The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalisation or prolongation of existing hospitalisation**
- Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.
- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from randomisation is not considered an AE.
  Note:
  - Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs.
  - Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.
- **Results in persistent disability/incapacity**
- 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.

- **Is a congenital anomaly/birth defect**
- **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 trial product.
  - 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).

Description of AEs requiring additional data collection (via specific event form) or events for adjudication are found in Table 9-1.

AE and SAE recording

- All SAEs, AEs leading to discontinuation of trial product, AE with additional data collection, events for adjudication and AEs in connection with pregnancies, must be recorded by the investigator on an AE form. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.
- For all non-serious AEs the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE related forms refer to "SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

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

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

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

Assessment of causality

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

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

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

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

The investigator should use the Investigator's Brochure for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always provides causality for every AE also for the initial SAE reporting**.

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 at the first trial-related activity after the subject signed the informed consent.
- **Recovering/resolving:** The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
- **Recovered/resolved with sequelae:** The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequelae meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the subject has not improved and the symptoms are unchanged or the outcome is not known.
- **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the subject is lost to follow-up.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.
New or updated information will be recorded in the CRF.

SAE reporting via electronic CRF

- Relevant forms (AE and safety information form) must be completed in the CRF.
- For reporting and sign-off timelines, see box below.
- If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form and if the CRF is unavailable for more than 5 calendar days then the site will use the safety information form (see box below).
- The site will enter the SAE data into the CRF as soon as it becomes available, see section 9.2.1.
- After the trial is completed, 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.

SAE reporting via paper CRF

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by fax, e-mail or courier.

Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting time frames (as illustrated in Figure 9-1):

- AE form within 24 hours.
- Safety information form within 5 calendar days.
- Both forms should be signed within 7 calendar days from the investigator's knowledge of the event.

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

Reporting of trial product-related SUSARs by Novo Nordisk:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP[24]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP[24], unless locally this is an obligation of the investigator.

To avoid introducing bias and to maintain the integrity of the primary analysis, Novo Nordisk will exempt SAEs that are part of the primary objective evaluation (MACE) from unblinding during regulatory reporting, even though the cases fulfil the definition of SUSARs. The definition of MACE is: Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke. The DMC (Appendix 3) receives unblinded data and makes recommendations to the Novo Nordisk safety committee on an ongoing basis. This ensures adequate monitoring of safety while maintaining SAE reports related to the primary endpoint blinded for Novo Nordisk.

At the end of the trial, when treatment is revealed, all exempted cases which meet the criteria for expedited reporting SUSARs will be submitted to the regulatory authorities. Because multiple cases will be identified simultaneously, Novo Nordisk will not be able to fulfil the 7 days requirement for fatal or life-threatening events but will within 60 days after code break have all SUSARs submitted to the regulatory authorities.

In case a regulatory authority requires the blinded report on an expedited basis, Novo Nordisk will submit individual blinded case reports related to investigational product to the relevant regulatory authorities on an expedited basis.

Appendix 5 Contraceptive guidance and collection of pregnancy information

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarcheal
2. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of subject's medical records, medical examination or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high Follicle Stimulating Hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or Hormonal Replacement Therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrolment.

Contraception guidance

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

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

Table 12-4 Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent [a and b] Failure rate of < 1% per year when used consistently and correctly.
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • oral

• intravaginal • transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • oral • injectable
Highly effective methods that are user independent [b]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine Device (IUD) • Intrauterine hormone-releasing System (IUS) • Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence[b] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.
Notes: [a]Failure rates may differ from 1% per year, if not used consistently and correctly. [b]Contraception should be utilised during the treatment period and for at least 35 days after the last dose of trial product.

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

1. known intolerance to the highly effective methods mentioned in Table 12-4 or where the use of any of the listed highly effective contraceptive measures are contraindicated in the individual subject, and/or
2. if the risk of initiating treatment with a specific highly effective method outweighs the benefit for the female

Justification for accepting double barrier method should be at the discretion of the investigator taking into consideration his/hers knowledge about the female's obesity history, concomitant illness, concomitant medication and observed AEs. The justification must be stated in the medical records.
Algeria, Austria, Belgium, Germany, Spain, Sweden, United Kingdom: For country specific requirements, please see Appendix 9.

Pregnancy testing

Highly sensitive serum testing (sensitivity of 5-25 mIU/mL) is mandatory if required by local regulations or ethics committees, or to resolve an indeterminate test or to confirm a positive urine test.

- WOCBP should only be included after a negative highly sensitive urine pregnancy test.
- Home urine pregnancy testing may be performed between visits during the trial, if additional urine pregnancy testing is required locally.

- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- WOCBP needs the last urine pregnancy test at the end of trial visit (P-FU). If the end of trial visit is a phone contact, the subjects can take the urine test at home and inform the investigator of the result.

Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden and United Kingdom: For country specific requirements, please see Appendix 9.

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.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to Novo Nordisk. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- For abnormal pregnancy outcomes collection of information on the paternal form for male partners of female subjects require signing of specific informed consent.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to Novo Nordisk as described in Appendix 4. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

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

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

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

Examples of technical complaints:

- Problems with the physical or chemical appearance of trial products (e.g. discoloration, particles or contamination).
- Problems with packaging material including labelling.
- Problems related to medical devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen-injector and the needle).

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

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

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within 24 hours if related to an SAE. All other technical complaints within 5 calendar days. If the CRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

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

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

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

Appendix 7 Retention of human biosamples and genetics

In countries where allowed, the trial will involve collection of human biosamples to be stored in a central archive for future use as noted in section 9.7 and 9.8. The following samples will be stored:

- Whole blood (for genetic analysis)
- Serum (for analyses of circulating biomarkers)

The samples will be stored at a secure central bio-repository after end of trial and until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.

Subjects may withdraw from the biobank component of the trial at any time, independent of participation in the trial. The subject can choose to do so at any given time while in the trial or after the end of the trial. If a subject withdraws from the biobank component all stored biosamples obtained from their own body will be destroyed.

Confidentiality and personal data protection will be ensured during storage after the end of trial.

In the event that the collected biosamples will be used in the future, care will be taken to target analyses within the scope defined in section 9.8.

Appendix 8 Monitoring of calcitonin

Background

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

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

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

- renal dysfunction
- tobacco use
- autoimmune thyroiditis
- several drug classes (e.g. proton pump inhibitors, beta-blockers, H_2-blockers and glucocorticoids)

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

Calcitonin monitoring

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

In case a subject has a calcitonin value ≥ 10 ng/L, the algorithm outlined in Figure 12-1 and described below should be followed. The algorithm applies for all calcitonin values in the trial.

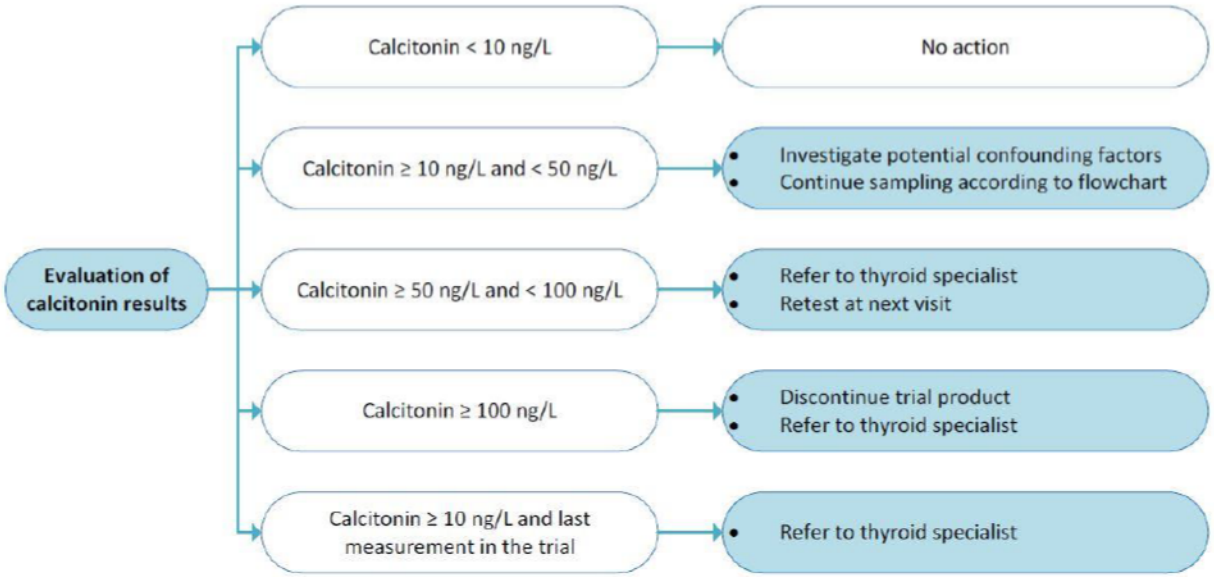

Figure 12-1 Flow of calcitonin monitoring

Calcitonin ≥ 100 ng/L
Action: The subject must immediately be referred to a thyroid specialist for further evaluation and the trial product must be discontinued (see section 8.1). The subject should remain in the trial; however, all medications suspected to relate to this condition must be discontinued until diagnosis has been established.

Background: These values were found in 9 (0.15%) of a population of 5817 subjects with thyroid nodular disease[32]. All of these subjects were diagnosed with MTC, resulting in a positive predictive value of 100%.

Diagnostic evaluation should include:

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

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

Calcitonin ≥ 50 and < 100 ng/L
Action: The subject should be referred to a thyroid specialist for further evaluation. The subject should remain in the trial and can continue on trial product. Retest of calcitonin should be done at the next visit.

Background: These values were found in 8 (0.14%) of the population of 5817 subjects with thyroid nodular disease[32]. Two of these subjects were diagnosed with MTC and two were diagnosed with C cell hyperplasia, resulting in a positive predictive value of a C-cell anomaly of 50%.

Diagnostic evaluation should include:

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

Calcitonin ≥ 10 and < 50 ng/L
Action: The subject can continue in the trial on trial product. Continue sampling of calcitonin according to the protocol.

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

Background: Calcitonin values from 20–50 ng/L were found in up to 1% of subjects of the population of 5817 subjects with thyroid nodular disease[32]. The predictive value of a C-cell anomaly for this calcitonin level was 8.3%. However, the likelihood of having a medullary carcinoma > 1 cm with calcitonin in this range is extremely low.

For calcitonin values between 10-20 ng/L Costante et al.[32] identified 216 (3.7%) subjects. One subject out of the 216 had a subsequent basal (unstimulated) calcitonin value of 33 ng/L, and had C-cell hyperplasia at surgery. Two other studies used a cut-off of calcitonin > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on subjects with basal CT > 10 and < 20 ng/L to allow conclusions[33, 34].

Appendix 9 Country-specific requirements

The below list is not an exhaustive list of country specific requirements. The list will only be updated in case of global protocol amendments.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities of trial product-related SUSARs. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden and United Kingdom:

- A monthly pregnancy test (urine) is required for all women of childbearing potential.
- Biochemistry laboratory assessment: In addition to the parameters listed in Appendix 2 amylase and lipase will be analysed.
- All AEs, irrespective of seriousness, should be collected from the day of randomisation and until the follow-up visit/end of trial visit, at the time points specified in the flowchart.

Table 12-5 Central laboratory assessments during the dose escalation period

	Screening	Randomisation	Dose escalation period			
Visit	V1	V2	V3	V4	V5	V6
Timing of Visit (Weeks)	Up to -3	0	4	8	12	16
Visit Window (Days)			±7	±7	±7	±7
Central laboratory assessments						
Haematology (Appendix 2)		X	X	X	X	X
Biochemistry (Appendix 2)		X	X	X	X	X
Lipids (Appendix 2)		X	X	X	X	X
High sensitive C-reactive protein (Appendix 2)		X	X	X	X	X
Urinalysis (Appendix 2)		X	X	X	X	X

- Exclusion criteria

General safety:

8. Presence or history of pancreatitis (acute or chronic)
9. Presence or history of pancreatic cancer or pancreatic neuroendocrine tumour (benign or malignant)
10. Personal or first degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
11. End stage renal disease or chronic or intermittent haemodialysis or peritoneal dialysis
12. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening Basal and squamous cell skin cancer and any carcinoma in-situ are allowed
13. Severe psychiatric disorder which in the investigator's opinion could compromise compliance with the protocol

14. Known or suspected hypersensitivity to trial product(s) or related products
15. Previous participation in this trial. Participation is defined as randomisation
16. Receipt of any investigational medicinal product within 30 days before screening
17. 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
18. Any disorder, unwillingness or inability, which in the investigator's opinion, might jeopardise the subject's safety or compliance with the protocol
19. Overweight or obesity induced by an endocrinologic disorder (e.g. Cushing syndrome) as per investigator's judgement

Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Italy, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden and United Kingdom:

- **Guidance on standard of care for patients with chronic kidney disease (CKD):**
  Investigators have the clinical responsibility for the trial participants. Since patients with chronic kidney disease (except those with end-stage renal disease) may be included in the trial, guidance for the standard of care for these patients is described below:
  No safety concern has been identified regarding nephropathy when treating patients with semaglutide or other GLP-1 receptor agonists. On the contrary, in the LEADER and SUSTAIN 6 trials, cardiovascular outcomes trial with patients with type 2 diabetes at high risk for cardiovascular disease, the GLP-1 receptor agonists resulted in a lower risk of a composite renal outcome than placebo.[4, 35] To study this effect, a composite nephropathy endpoint has been included in SELECT.
  Definition and evaluation of CKD[36]
  In international kidney guidelines, CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications on health. CKD is classified based on cause, presence or absence of systemic disease, GFR category, and albuminuria category (CGA) (**Figure 12-2**).
  Monitoring kidney function[36]
  It is recommended to assess glomerular filtration rate (GFR) and albuminuria at least annually in patients with CKD. Assess GFR and albuminuria more often for individuals at higher risk of progression, and/or where measurement will impact therapeutic decisions. In **Figure 12-2** a guide to the frequency of monitoring is outlined. It might be needed to monitor more frequently than stated in the protocol.

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
GFR categories (ml/min/ 1.73 m²) Description and range	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

Figure 12-2 GRF and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year)[36].

CKD and risk of acute kidney injury(AKI)[36]

Patients with CKD are at increased risk of AKI. The KDIGO AKI Guideline[37] should be followed for management of those at risk of AKI during intercurrent illness, or when undergoing investigation and procedures that are likely to increase the risk of AKI. Since gastrointestinal adverse events such as nausea, vomiting and diarrhea with risk of dehydration are associated with the use of semaglutide, it is recommended to remind all patients, especially those with CKD, that rehydration in case any of these adverse events is important.

Referral to specialist[36]

It is recommended to refer to specialist kidney care services for people with CKD in case of AKI or abrupt sustained fall in GFR, a GFR ≤30 ml/min/1.73 m2 (GFR categories G4-G5), a consistent finding of significant albuminuria (albumin-to-creatinine-ratio ≥300 mg/g [≥30 mg/mmol] or albumin-excretion-rate ≥300 mg/ or hypertension refractory to treatment with 4 or more antihypertensive agents.

Treatment of CKD:

Therapeutics[37, 38]

Ensure optimal treatment of the cause of CKD. Avoid nephrotoxic drugs. Blood pressure control should be ensured in accordance with the SELECT standard of care guidance. Angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) are first line therapy unless they are not tolerated. For patients with urine albumin excretion of 30 to 300 mg per 24 hours, aim at the lower target of <130/80 mmHg. In case of patients developing diabetes, good glycemic control is recommended according to SELECT standard of care guidance. Additional therapies may be considered in some patients at the investigator´s discretion and in accordance with local guidelines and polices.

Diet[39]

It is recommended to offer dietary advice about potassium, phosphate, calorie and salt intake appropriate to the CKD stage. Additionally, it is recommended to offer guidance on limited

consumption of salt, red meat, saturated or trans fats, sweets, and sugar-sweetened beverages and to restrict calorie intake in patients who will benefit from weight loss (500 kcal/day deficit).

For additional country specific requirements, please refer to below.

Algeria:

- For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.
- No subjects from Algeria will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

- Section 8.1: Sentence related to discontinuation/withdrawal criterion#3 'Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator's discretion without discontinuing trial treatment.' is not applicable.

Argentina:

- In reference to Protocol section Treatment after discontinuation of trial products: The sponsor commits to comply with what is stated in point 6.8 of the current local regulation, disposition 6677/10. According to it, commits to comply with the following: "For Argentina, after the conclusion of subjects participation in the study, trial doctor will discuss with subjects the best alternatives for future treatment. If trial doctor, based on his/her adequately justified medical analysis, decides that the Sponsor's study drug is the best available treatment option for the subject, trial doctor will prescribe the study drug, which must be approved by the Ethics Committee. The Sponsor (Novo Nordisk Pharma Argentina S.A.) will provide access to the Sponsor's study drug to the subject for the time the Ethics Committee decides or until access is ensured by any other means and in accordance with the applicable provisions in Argentina. Subjects must visit trial doctor to receive the Sponsor's study drug and will have to provide information about health status and any possible side effects that may have been experienced since last visit
- In reference to Protocol Exclusion criteria 17: The contraceptive methods will be reimbursed by the sponsor.

Australia:

- Comply with Medicines Australia Guidelines for Compensation for Injury Resulting from Participation in a Company Sponsored Clinical Trial, version 160104 16 January 2004.

Austria:

- A monthly pregnancy test (urine) is required for all women of childbearing potential.
- Indemnity statement: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBl. I Nr. 40/2017

Belgium:

- Novo Nordisk accepts liability in accordance with:

Indemnity statement: Law concerning experiments on the human person of 07 May 2004 - Article 29: §1. Even if without fault, the sponsor is liable for the damage which the subject and/or his rightful claimants sustain and which shows either a direct or an indirect connection with the trial.

Contraception: Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly; such as implants, injectables, combined oral contraceptives, some IUDs, true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) or vasectomised partner.

Brazil:

- Resolution (Res. CNS 466/12): At the end of the trial, all participant subjects should be assured the access to the best proved prophylactic, diagnostic and therapeutic methods identified during the study.
- Exclusion criterion #16: Participation in other trials within one year prior to screening visit (Visit 1) unless there is a direct benefit to the research subject at the investigator's discretion.
- No subjects from Brazil will take part of the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.
- All laboratory results will be communicated to the investigators.

Columbia:

- No subjects from Columbia will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

Czech Republic:

- Contraceptive measures considered adequate include highly effective contraceptive methods as listed in Table 12-4‘Highly effective contraceptive methods’ in Appendix 5. This means that the use of double barrier methods is not applicable for the Czech Republic

Finland:

- Contraceptive measures considered adequate include highly effective contraceptive methods as listed in Table 12-4‘Highly effective contraceptive methods’ in Appendix 5. This means that the use of double barrier methods is not applicable for Finland.
  No subjects from Finland will participate in the optional biobank part of the trial, and no genetictesting will be performed as noted in section 9.7 and 9.8.

France:

- Novo Nordisk accepts liability in accordance with:

Indemnity statement: “The French Public Health Code article L.1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX Journal Officiel of 11 August 2004. The sponsor 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 the sponsor's 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."

Germany:

- Contraceptive measures considered adequate include highly effective contraceptive methods as listed in Table 12-4'Highly effective contraceptive methods' in Appendix 5. This means that the use of double barrier methods is not applicable for Germany
- Section 8.1: Sentence related to discontinuation/withdrawal criterion#3 'Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator's discretion without discontinuing trial treatment.' is not applicable.

Ireland:

- Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical trials.
  This means that the following contraceptive methods are not applicable for Ireland:
  - Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
  - Male or female condom with or without spermicide 5 cap
  - Diaphragm or sponge with spermicide 5
- Contraception should be utilised during the treatment period and for at least 35 days after the last dose of trial product. Elimination half-life for semaglutide is approximately 1 week (For details please refer to the current version of the IB[12] or any updates hereof.) and a wash out of 5 half-lifes while using contraception is considered sufficient.

Israel:

- No subjects from Israel will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

Japan:

- According to Japanese GCP, storage and drug accountability of the trial products at the study site is not in charge of Investigator, but in charge of the head of study site.
- The head of study site should assign some or all of the responsibilities for accountability of the trial products at the sites to a trial product storage manager (a pharmacist in principle). The trial product storage manager should control and take accountability of the trial products in accordance with procedures specified by the sponsor. The head of the study site or the trial product storage manager (if assigned by the head of the study site) must ensure the availability of proper storage conditions of trial products, record and evaluate the temperature.
- A seal is accepted as signature.
- **AE reporting requirements for Japan**: For Japan all AEs, irrespective of seriousness, should be collected from the day of randomisation and until the follow-up visit/end of trial visit, at the time points specified in the flowchart.

Mexico:

- Should the subject his/her family members parents or legal representative decide to withdraw the consent for participation in the trial, the subject will be entitled to receive appropriate, free of charge medical care and/or trial drug during the follow up period of the protocol when it will be established with certainty that no untoward medical consequences of the subject´s participation in the research occurred.
- In the case of Mexico, the following responsibilities will be included for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility:

  a) Investigation follow-up

  b) Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the Subject;

  c) Timely compliance of the terms in which the authorization of a research for health in human beings had been issued;

  d) To present in a timely manner the information required by the Health Authority.
- Novo Nordisk accepts liability in accordance with:

Indemnity statement: Novo Nordisk carries product liability for its products assumed under the special laws, acts/and/or guidelines for conducting trials in any country, including those applicable provisions on the Mexican United States. If the subject feels that something goes wrong during the course of this trial, the subject should contact the trial staff in the first instance. If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the trial medication and/or a trial procedure that otherwise would not have been part of his/her regular care, the subject will receive from the Institution or Medical Care Establishment and free of charge, the appropriate medical treatment as required. In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by the trial sponsor in accordance with the terms provided by all applicable regulations; even if the subject discontinues his/her participation in the trial by his own will or by a decision from the investigator. By signing the informed consent, the subject will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the trial; any additional expense resulting from the subject's participation in the trial will be covered by the trial sponsor.

Norway:

- Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical trials. This means use of double barrier methods is not applicable for Norway.

Poland:

- Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical trials. This means use of double barrier methods is not applicable for Poland.

Russia:

- Novo Nordisk accepts liability in accordance with:
- Indemnity statement: Novo Nordisk accepts liability in accordance with: Federal law of 12 April 2010 No. 61-FZ 'On Medicinal Drugs' Circulation and Ministry of Healthcare of Russian Federation' order of 01 April 2016 No. 200n "Approval of rules of good clinical practice.
- Subjects developing T2D will be provided with a blood glucose meter including ancillaries and instruction for use.

South Africa:

- No subjects from South Africa will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

Spain:

- Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical trials. This means use of double barrier methods is not applicable for Spain.

Sweden:

- Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical trials. This means use of double barrier methods is not applicable for Sweden

Turkey:

- In case a subject needs to change their regular dose of a concomitant medication due to a protocol requirement, this medication will be reimbursed by Novo Nordisk.
- No subjects from Turkey will participate in the optional biobank part of the trial, and no genetic testing will be performed as noted in section 9.7 and 9.8.

United Kingdom:

Contraceptive measures considered adequate include highly effective contraceptive methods as listed in Table 12-4 'Highly effective contraceptive methods' in Appendix 5. This means that the use of double barrier methods is not applicable for UK.

Appendix 10 Protocol amendment history

The protocol amendment summary of changes table for the current updated protocol is located directly before the Table of Contents.

Protocol amendment no. 8, including amendment 6 and 7 (04-January-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].

This amendment addresses changes to allow for simultaneous participation in the SELECT trial and COVID-19 trials and expansion of the AE collection to include the reporting of non-serious COVID-19 events.

This amendment also addresses changes to the statistical considerations related to the testing strategy for the confirmatory secondary endpoints, implementation of home health care service to mitigate challenges e.g. due to the COVID-19 pandemic and the change of the wash-out period and follow-up period from 7 to 5 weeks.

The amendment also includes minor updates and administrative changes, please see table below.

Section # and name	Description of change	Rationale
Changes from protocol V3 to V6		
Throughout the protocol	Wash-out period and consequently follow-up period and period for contraception use after treatment discontinuation, has been updated to 5 weeks.	SELECT contains no antibody sampling and the follow-up period can be reduced to the standard 5 times the half-life of semaglutide (5 weeks).
Section 4.2.2.2 Supportive secondary endpoints and 4.2.2.3 Exploratory endpoints	WRSSM deleted from supportive secondary endpoints and included in exploratory endpoints.	In the psychometric evaluation of WRSSM it became clear that the measure is not sensitive to weight loss.
Section 7.5.1 Shipment of trial product to subject's home	Text revised	To simplify the requirements for the naming of the specific document describing the process for shipping trial product directly from the site to the subject's home.
Section 7.8 Concomitant medication	Text included for collection of COVID-19 concomitant medication	To specify that medication(s) in relation to a clinical trial for COVID-19 prevention or treatment as well as approved COVID-19 vaccine must be recorded.
Section 8.1 Discontinuation/Withdrawal criteria	Text added to discontinuation criterion 3 *Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal	Due to the current COVID-19 pandemic and to protect the retention of subjects in the SELECT trial, co-participation in COVID-19 trials is allowed. Patient safety is key and it has been evaluated that the individual patient safety is not

	product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator discretion without discontinuing trial product.	compromised by allowing for co-participation.
Section 9 Trial assessments and procedures	Implementation of mitigations for the investigator to engage with a health care professional from a third party home health care service provider to perform protocol procedures at the subject's home or other alternate location.	To ensure subject safety and data integrity under special circumstances where on-site visits are not feasible for the subject or for the site, e.g. due to COVID-19.
Section 9.2 Adverse events, Section 9.2.1 Time period and frequency for collecting AE and SAE information and Figure 9-1.	Text regarding COVID-19 AEs included.	To describe the inclusion of COVID-19 AEs in the targeted data collection approach of this trial (all COVID-19 AEs should be collected both prospectively and retrospectively). This will allow for sensitivity analyses related to COVID-19 infection.
Section 9.4 Safety assessments	Addition of COVID-19 in text	To include COVID-19 to the concomitant illness/medical history that should be reported. This will allow for sensitivity analyses related to COVID-19 infection.
Section 10.3.2.1 Confirmatory secondary endpoints	Updated text for the statistical testing strategy for the confirmatory secondary endpoints.	To preserve control of the type 1 error for confirmatory endpoints.
Section 10.3.2.2 Supportive secondary endpoints	Included 'and hsCRP'	hsCRP is better described by a log-normal distribution than a normal distribution
10.3.3 Exploratory endpoints	WRSSM will be presented descriptively.	Since WRSSM is not sensitive to weight loss we judge that data can be evaluated by descriptive statistics
Appendix 4	Change from 'must' to 'should' in the sentence: "Both forms should be signed within 7 calendar days from the investigators knowledge of the event".	To clarify the criticality of the timing of investigator signatures on the forms.
Appendix 9	Update of country specific requirements for: Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Italy, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden and United Kingdom in regard to standard of care for patients with chronic kidney disease.	In agreement with feedback from BfArM on 17 October 2019.

Appendix 9	Text regarding contraception revised for Ireland	To reflect the change of the follow-up period from 7 to 5 weeks and to refer to the current IB.
Additional changes from protocol V5 to V6		
Throughout the document	References to the IBs for Oral semaglutide (Rybelsus®) and Ozempic® removed.	The IB for weight management have substantial safety and efficacy data in the target population and includes relevant data from other programmes, therefore IBs for other indications are no longer necessary.
	Reference to specific SAP version removed.	To ensure that the correct version of the document is always referred to.
	Reference to specific DMC charter version removed.	To ensure that the correct version of the document is always referred to.
	Country specific requirements for VHP countries and Netherlands moved to Appendix 9 and links included in relevant sections.	To make the protocol applicable for all countries.
	Addition of country specific requirement for non-VHP countries, see Appendix 9.	To make the protocol applicable for all countries.

Protocol amendment no. 4 (07 March 2019)

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 amendment no. 4:

This amendment addresses inclusion of interim testing for superiority as well as administrative changes.

Section # and name	Description of change	Rationale
Sec 5.1 Overall design	Interim included	Recent data for semaglutide and other GLP1-RAs suggest a potential for greater effect size in SELECT than originally assumed and to accommodate such scenarios it has been decided to include interim testing for superiority.

Sec 10.1 Sample size	Update due to inclusion of interim included	Recent data for semaglutide and other GLP1-RAs suggest a potential for greater effect size in SELECT than originally assumed and to accommodate such scenarios it has been decided to include interim testing for superiority. Originally the SELECT trial was designed as a group sequential design with one interim testing after two thirds of the total 1,225 primary endpoint events. This was changed to a fixed design without interim testing, but without changing the sample size. Thus, the sample size is not changed by re-introducing the interim testing in the SELECT trial.
Sec 10.3 Statistical analysis	Interim included	Recent data for semaglutide and other GLP1-RAs suggest a potential for greater effect size in SELECT than originally assumed and to accommodate such scenarios it has been decided to include interim testing for superiority.
Sec 10. 3.1 Primary endpoint	Interim included	Recent data for semaglutide and other GLP1-RAs suggest a potential for greater effect size in SELECT than originally assumed and to accommodate such scenarios it has been decided to include interim testing for superiority.
Sec 10.3.2.1 Confirmatory secondary endpoints	Interim included	Recent data for semaglutide and other GLP1-RAs suggest a potential for greater effect size in SELECT than originally assumed and to accommodate such scenarios it has been decided to include interim testing for superiority.
Sec 10.3.4 Interim testing for efficacy	Interim included	Recent data for semaglutide and other GLP1-RAs suggest a potential for greater effect size in SELECT than originally assumed and to accommodate such scenarios it has been decided to include interim testing for superiority.

Sec 10.3.5 Sequential safety analysis and safety monitoring	Interim included	Recent data for semaglutide and other GLP1-RAs suggest a potential for greater effect size in SELECT than originally assumed and to accommodate such scenarios it has been decided to include interim testing for superiority.
Appendix 3	Interim included	Recent data for semaglutide and other GLP1-RAs suggest a potential for greater effect size in SELECT than originally assumed and to accommodate such scenarios it has been decided to include interim testing for superiority.
Sec 9.2 Adverse events	Transient ischemic attack included as an event for adjudication	Event description for stroke updated to also include reporting of transient ischemic attack (TIA) events that will be sent for adjudication. The purpose of sending potential events of TIA for adjudication is to ensure that all potential stroke events are captured
Sec 9.2 Adverse events	Adjudication outcome updated from Nephropathy to Chronic renal replacement therapy	It was not deemed to be necessary to have expert adjudicators evaluate nephropathy events that are based solely on laboratory findings and that can be derived in the statistical analyses using central laboratory data. With this change the 3 components of the 5-component nephropathy composite will no longer be confirmed by adjudication Furthermore, changes are made to clarify the requirements for confirmatory laboratory testing of these changes in renal function.
9.2.1.1 Events for Adjudication	Removal of laboratory triggered events as these will not be used for identification of potential nephropathy	It was not deemed to be necessary to have expert adjudicators evaluate nephropathy events that are based solely on laboratory findings and that can be derived in the statistical analyses using central laboratory data.

		With this change the 3 components of the 5-component nephropathy composite will no longer be confirmed by adjudication Furthermore, changes are made to clarify the requirements for confirmatory laboratory testing of these changes in renal function.
Appendix 3 Trial governance considerations Event adjudication committee	Updated only to include renal replacement therapy and renal death	It was not deemed to be necessary to have expert adjudicators evaluate nephropathy events that are based solely on laboratory findings and that can be derived in the statistical analyses using central laboratory data. With this change the 3 components of the 5-component nephropathy composite will no longer be confirmed by adjudication Furthermore, changes are made to clarify the requirements for confirmatory laboratory testing of these changes in renal function.
Appendix 2 Clinical laboratory testing	Table 12-1 Removal of ≥ 20 mg/g increase from baseline in the definition of macroalbuminuria and to clarify when confirmaiton test is needed.	To simplify the procedure for confirmatory testing the requirement for ≥ 20 mg/g increase from baseline was removed. Furthermore, the text has been revised to clarify when confirmatory testing based on central lab is needed.
Appendix 2 Clinical laboratory testing	Table 12-2 Update to clarify when confirmatory test is needed for eGFR calculation.	To clarify when confirmatory test based on central lab need to be performed
Sec 9.4 Safety assessments	Clarified that concomitant illness or medical history already reported on other medical history forms, should not be included	To avoid duplicate reporting of Medical History
General	Editorial updated	
Sec 2 Flowchart	Included handout dose reminder card at visit 2	Editorial

Sec 4.2.2.2 Supportive secondary endpoints	Definition of persistent updated for eGFR and macroalbuminuria	For clarification.
Section 5.1 Overall trial design Applicable for: protocol version 1.0 15May2018	'Efficacy' included in description of the independent Data Monitoring Committee (DMC) to clarify that the DMC will oversee both efficacy and subject safety as part of the benefit-risk evaluation of semaglutide.	To highlight that the DMC will oversee efficacy as well as safety.
Section 5.5 Justification for dose Applicable for: protocol version 1.0 15May2018	Dose justification updated	Justification for dose described in more details to clarify why the dose of 2.4 mg was chosen.
Section 6.2 Exclusion criteria Applicable for: protocol version 1.0 15May2018	Country specific inclusion criteria moved to Appendix 9 country specific requirements. Criteria 8, 9 and 19 in Appendix 9 are only applicable for VHP, France and Netherlands	Editorial
Sec 8.1 Discontinuation of trial treatment	Discontinuation of trial product prior to intention of becoming pregnancy, changes from 2 months to 7 weeks.	To align with current version of the Investigator's brochure.
Sec 8.1 Discontinuation of trial treatment Applicable for: protocol version 1.0 15May2018	Discontinuation criterion 4 rephrased to reflect that in case of suspicion of pancreatitis trial treatment must be discontinued	Clarification
Section 8.4 Termination or modification of the trial Applicable for: protocol version 1.0 15May2018	Section 8.4 included to clarify that the DMC will evaluate also the efficacy data during the trial as part of the benefit-risk evaluation of semaglutide.	To clarify stopping criteria
Sec 9.1.4.1 Non-SAE hospitalisations Sec 9.4 Safety assessments Appendix 4 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting	Clarification of 'baseline', 'trial inclusion' and 'before exposure of trial product' is the time of randomisation	For clarification
Sec 9.2 Adverse events	Corrected that event definitions for events requiring adjudication are included in the charter	Correction
9.2.1.1 Events for Adjudication	References to the Event Adjudication Manual included	For clarification

9.2.1.1 Events for Adjudication	Timeline for completion of specific adjudication form in the CRF updated	Correction
Section 10.3.5 Sequential safety analysis and safety monitoring Applicable for: protocol version 1.0 15May2018	Updated to describe sequential analyses performed by the DMC.	Clarification of DMC responsibility
Appendix 2 Clinical laboratory tests	Laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures.	For clarification
Appendix 3 Trial governance considerations Event adjudication committee	Description of event adjudication added	Purpose of event adjudication described
Appendix 4	Removal of a clinical laboratory adverse event	Clinical laboratory AEs are already part of the AE definition and does not need to be defined as an entity, if defined they will need to be described together in the CTR and abnormal lab values reported as an AE are better addressed when summarised with the organ system/disease/focus area they belong to rather than as a group of non-related preferred terms just because they result from an abnormal lab value.
Appendix 4	Bullet removed: Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.	Deleted as this bullet point is already described under Sec 9.1.4.1 Non-SAE hospitalisation.
Appendix 4	Update to specify that sites will have access the CRF until trial closure.	Due to NN practice where sites have access to EDC system until data base lock. A CRF is not decommissioned at site-level, only at trial level. The system is available for safety reporting until the trial ends.

Appendix 5 Contraceptive guidance and collection of pregnancy information	The paternal form has been described which is to be used in case of abnormal pregnancy outcome.	Editorial
Appendix 6 Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting	Removed sentence stating that only technical complaints related will be reported in the clinical trial report	Technical complaints should always be included in the CTR if collected systematically
Appendix 8 Monitoring of calcitonin Applicable for: protocol version 1.0 15May2018	Figure 12-1 updated to include retest of calcitonin and continuation of sampling according to flowchart. Text for calcitonin ≥ 50 and < 100 ng/L updated to require retest of calcitonin.	Requested during the Voluntary Harmonised Procedure in Europe
Appendix 8 Monitoring of calcitonin	Deleted that screen failures should be referred to thyroid specialist	Calcitonin is not samples at screening
Appendix 3 and Appendix 9	Restructuring of country specific indemnity statements	Editorial
Appendix 9	Update of country specific requirement for Brazil, Columbia, Finland, Japan, South Africa and Turkey	To clarify responsibility of trial product handling align the description with other clinical trials in Japan Columbia, Finland, South Africa and Turkey will not participate in the biobank set-up Brazil reporting of laboratory results clarified
Appendix 9 Applicable for: protocol version 1.0 15May2018	Information about SUSAR reporting included to clarify how SUSARs are to be reported.	Requested during the Voluntary Harmonised Procedure in Europe

Updated protocol including amendment 1: 27 November 2018, version 2

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.

Overall rationale for the amendment:

This amendment addresses the updates requested during VHP submission process.

Section # and name	Description of change	Rationale

Section 6.2 Exclusion criteria	Wording of exclusion criterion #8, #9 and #19 changed to clarify the exclusion criteria.	Update requested during VHP submission process.
Section 8.1 Discontinuation of trial treatment	Rephrasing of criterion #4 to clarify that no patients developing pancreatitis continues in the trial.	Update requested during VHP submission process.
Appendix 9 Country specific requirements	Information about SUSAR reporting included to clarify how SUSARs are to be reported. Country specific paragraph added for VHP countries with addition of monthly pregnancy test, amylase and lipase in biochemistry panel, full AE collection irrespective of seriousness. Flowchart updated during dose escalation period to include additional laboratory samples.	Update requested during VHP submission process.
Appendix 5 Contraceptive guidance and collection of pregnancy information.	Additional countries having specific requirements related to pregnancy testing included.	Update requested during VHP submission process.
Appendix 8 Monitoring of calcitonin	Figure 12-1 updated to include retest of calcitonin and continuation of sampling according to flowchart. Text for Calcitonin $\geq$ 50 and < 100 ng/L updated to require retest of calcitonin.	Update requested during VHP submission process.
Section 9.2 Adverse events	Additional countries having specific AE reporting requirements included to ensure full AE collection irrespective of seriousness.	Update requested during VHP submission process.
Section 2: Flowchart	Footnotes f updated due to country specific pregnancy requirements and g added due to information about additional laboratory sampling in appendix 9.	Update requested during VHP submission process.
Section 5.1 Overall trial design	'Efficacy' included in description of the independent Data Monitoring Committee (DMC) to clarify that the DMC will oversee both efficacy and subject safety as part of the benefit-risk evaluation of semaglutide.	Update requested during VHP submission process.
Section 5.5 Justification for dose	Justification for dose described in more details to clarify why the dose of 2.4 mg was chosen.	Update requested during VHP submission process.

Section 8.4 Termination or modification of the trial	Section 8.4 included to clarify that the DMC will evaluate also the efficacy data during the trial as part of the benefit-risk evaluation of semaglutide.	Update requested during VHP submission process.
Section 10.3.5 Sequential safety analysis and safety monitoring	Updated to describe sequential analyses performed by the DMC.	Update requested during VHP submission process.

16.1.01 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

If applicable, Protocol Attachment II is also located in the Trial Master File.

Content: Global key staff and Country key staff.