Cover Page for Protocol

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Protocol

Updated protocol including:

Protocol version 1.0, dated 17-Jan-2019

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Protocol version 3.0, including protocol amendment no. 2, dated 17-Nov-2020

Protocol version 4.0, including protocol amendment no. 3, China, dated 26-Jan-2021

Protocol title: Semaglutide cardiovascular outcomes trial in patients with type 2 diabetes (SOUL)

Substance: Oral semaglutide

Universal Trial Number: U1111-1218-5368

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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

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Document	Date	Version
Updated protocol including amendment 3 (China)	26 January 2021	4.0
Updated protocol including amendment 2	17 November 2020	3.0
Updated protocol including amendment 1 (Argentina, Canada, Colombia, Mexico, Spain, United Kingdom and United States)	12 June 2019	2.0
Original protocol	17 January 2019	1.0

Protocol amendment no. 3 (protocol version 4.0 dated 26 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].

For China, 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
Appendix 8 Country-specific requirements for China, amendment 3	Section 6.2, exclusion criteria #4: *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 if the last dose of the investigational medicinal product has been received more than 30 days before screening is not applicable for China.	Co-participation in COVID-19 trials is not allowed in China due to local requirements
Appendix 8 Country-specific requirements for China, amendment 3	Section 8.1, discontinuation/withdrawal criteria: *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 discretion without discontinuing trial product is not applicable for China.	Co-participation in COVID-19 trials is not allowed in China due to local requirements

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1 Synopsis

Rationale

To evaluate the hypothesis that oral semaglutide lowers the risk of cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular disease.

Objectives and endpoints

The primary objective

To demonstrate that oral semaglutide lowers the risk of major adverse cardiovascular events compared to placebo, both added to standard of care in patients with type 2 diabetes and at high risk of cardiovascular events.

The key secondary objectives

To compare the effects of oral semaglutide versus placebo, both added to standard of care in patients with type 2 diabetes and at high risk of cardiovascular events with regards to:

- Chronic kidney disease
- Cardiovascular events
- Peripheral artery disease
- Glycaemic control and body weight
- Safety

The primary endpoint

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

Key confirmatory secondary endpoints

Time from randomisation to first occurrence of:

- A composite chronic kidney disease endpoint consisting of: cardiovascular death, renal death, onset of persistent ≥ 50% reduction in estimated glomerular filtration rate (CKD-EPI) compared with baseline, onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 or initiation of chronic renal replacement therapy (dialysis or kidney transplantation)
- cardiovascular death
- Major adverse limb events, a composite endpoint consisting of: acute limb ischemia hospitalisation or chronic limb ischemia hospitalisation

Estimand

The 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.

Overall design

This is a randomised, double-blind, parallel-group, placebo-controlled trial comparing oral semaglutide versus placebo both administered once daily and added to standard of care in patients with type 2 diabetes at high risk of cardiovascular events. Patients will be randomised 1:1 to receive either oral semaglutide or placebo.

All inclusion criteria are based on the patients' medical records, except for inclusion criterion for HbA_{1c} (local laboratory or point-of-care device). The key inclusion criteria are:

- Male or female, age ≥50 years at the time of signing informed consent
- Diagnosed with type 2 diabetes mellitus
- HbA_{1c} 6.5% - 10.0% (47 - 86 mmol/mol) (both inclusive)[a]
- At least one of the below conditions (a-d):
  a) Coronary heart disease defined as at least one of the following:
     i. Prior myocardial infarction
     ii. Prior coronary revascularisation procedure
     iii. ≥50% stenosis in coronary artery documented by cardiac catheterisation, computerized tomography coronary angiography
     iv. Coronary heart disease with ischaemia documented by stress test with any imaging modality
  b) Cerebrovascular disease defined as at least one of the following:
     i. Prior stroke
     ii. Prior carotid artery revascularisation procedure
     iii. ≥50% stenosis in carotid artery documented by X-ray angiography, magnetic resonance angiography, computerized tomography angiography or Doppler ultrasound
  c) Symptomatic peripheral artery disease (PAD) defined as at least one of the following:
     i. Intermittent claudication with an Ankle-brachial index (ABI) < 0.85 at rest
     ii. Intermittent claudication with a ≥50% stenosis in peripheral artery (excluding carotid) documented by X-ray angiography, magnetic resonance angiography, computerized tomography angiography or Doppler ultrasound
     iii. Prior peripheral artery (excluding carotid) revascularization procedure
     iv. Lower extremity amputation at or above ankle due to atherosclerotic disease (excluding e.g. trauma or osteomyelitis)
  d) Chronic kidney disease defined as:
     i. eGFR < 60 mL/min/1.73 m^2 [b]

[a] Latest available and no more than 30 days old local laboratory assessment based on medical records or point of care measurement.

[b] Based on medical records using latest available and no more than 6 months old assessment.

The key exclusion criteria are:

- 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
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening
- Heart failure presently classified as being in New York Heart Association Class IV
- Treatment with any glucagon-like peptide-1 receptor agonist within 30 days before screening

Number of patients

In this trial, 9,642 patients are planned to be randomly assigned to trial product.

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 61 months or more following randomisation of the first patient. Trial duration for each subject is expected to be approximately 3.5 to 5 years.

Trial products

Oral semaglutide 3 mg, 7 mg and 14 mg tablets
Placebo tablets

2 Flowchart

Trial Periods	Protocol Section	Screening	Randomisation	First year						Remaining period		End of treatment	Follow-up
Site visit (V)/Phone contact (P)		V1	V2	V3	V4	V5	V6	V7[a]	V8	V9/V10/V11/ V13/V14/V15 V17/V18/V19 V21/V22/V23	V12 V16 V20 V24	V-EOT[b]	P-FU
Timing of visit (weeks)		Up to -3 weeks	0	4	8	13	26	39	52	Every 13 weeks	Yearly	EOT	V-EOT +5 weeks
Visit window (days)				±3	±3	±3	±7	±7	±7	±7	±7	±7	+7
PATIENT-RELATED INFO/ASSESSMENTS													
Informed consent	Appendix 3	X											
Hand out ID card		X											
Inclusion/exclusion criteria	6.1; 6.2	X											
Tobacco use[c]			X								X		
Demography[d]		X											
Medical history/concomitant illness	9.4		X										
Concomitant medication	7.7		X	X	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	
Trial product dose	7.2			X	X	X	X	X	X	X	X	X	
Training in trial product and dosing instructions	7.1		X	(X)[e]	(X)[e]	(X)[e]	(X)[e]	(X)[e]	(X)[e]	(X)[e]	(X)[e]		
Hand out and instruct in BG meter[i]	7.1		(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	(X)[i]	
CLINICAL ASSESSMENTS													
Height	9.4.1		X										
Body weight			X			X			X		X	X[f]	
Waist circumference			X										
Physical examination			X									X	
Eye examination	9.4.4	X[g]							X[h]		X[h]	X[f]	
Vital signs	9.4.2		X			X			X		X	X[f]	

Trial Periods	Protocol Section	Screening	Randomisation	First year						Remaining period		End of treatment	Follow-up
Site visit (V)/Phone contact (P)		V1	V2	V3	V4	V5	V6	V7[a]	V8	V9/V10/V11/ V13/V14/V15 V17/V18/V19 V21/V22/V23	V12 V16 V20 V24	V-EOT[b]	P-FU
Timing of visit (weeks)		Up to -3 weeks	0	4	8	13	26	39	52	Every 13 weeks	Yearly	EOT	V-EOT +5 weeks
Visit window (days)				±3	±3	±3	±7	±7	±7	±7	±7	±7	+7
HbA_{1c} point of care	6.1;9.1.1	X		X	X	X	X	X	X	X	X	X	
Montreal cognitive assessment	9.1.4		X								X		
PROTECT cognitive tests[o]	9.1.4		X[o]						X[o]		X[o]		
Patient surveys[j]	9.1.4		X[j]				X[j]		X[j]	X[j]	X[j]	X[j]	X[j]
Adverse events	9.2		X	X	X	X	X	X	X	X	X	X	X
Severe hypoglycaemic episodes	9.2		X	X	X	X	X	X	X	X	X	X	X
Technical complaints	9.2.6		X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[k]	9.2.5	X										X	X[l]
CENTRAL LABORATORY ASSESSMENTS													
HbA_{1c}	Appendix 2		X			X			X		X	X[f]	
Creatinine			X			X			X		X	X[f]	
High sensitivity C-Reactive Protein			X			X					X[n]		
Liver parameters			X										
Lipids			X			X			X		X	X[f]	
Biosamples for future analysis (biobank, genetics)[m]			X										
Biosamples for future analysis (biobank, biomarkers)[m]			X			X					X[n]		
TRIAL MATERIAL													
IWRS session		X	X	X	X	X	X	X	X	X	X	X	
Dispensing visit			X	X	X	X	X	X	X	X	X		
Drug accountability	7.5		X	X	X	X	X	X	X	X	X	X	
End of trial	5.3												X

[a] After V6, all odd numbered visits (V7, V9, V11 etc.) can be conducted as a phone contact, however the investigator needs to ensure that the subject has enough trial product within the expiry date.
[b] Will be scheduled according to trial completion.
[c] Tobacco use/smoking is defined as smoking at least one cigarette or equivalent daily.
[d] Demography: date of birth, sex, ethnicity and race (according to local regulation).
[e] As needed.
[f] If done within the past 5 weeks, assessment can be skipped.
[g] Must be performed within 90 days before screening or in the period between screening and randomisation, and results available at randomisation.
[h] Must be performed between 8 weeks before the visit and the day of visit (both included).
[i] Lancets, test strips and control solutions will be provided with the BG meter (if supplied) and during the trial as needed. Training will also be provided as needed.
[j] Patient engagement assessment will be performed every half year, i.e. V2, V6, V8, V10, V12, V14, V16, V18, V20, V22, V24 and V-EOT at all US sites. Patient expectations and experience survey will be performed at Visit 2, Visit 12 and at end-of-treatment at only a sub-set of US sites.
Visits to emergency room/urgent care unit will be recorded at every visit from V3 at all US sites.
[k] Only applicable for women of childbearing potential; urine HCG.
[l] Can be done at home.
[m] Only applicable for patients that have provided informed consent for biosamples for biomarkers and genetic analyses.
[n] Only applicable for the year two visit (V12).
[o] Only for English and/or Spanish speaking patients in Argentina, Canada, Colombia, Mexico, Spain, United Kingdom and United States. Online cognitive testing will be performed every year, i.e. V2, V8, V12, V16, V20 and V24.

3 Introduction

In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

3.1 Trial rationale

The cardiovascular (CV) effect of oral semaglutide 14 mg once daily (OD) and s.c. semaglutide 0.5 and 1 mg once weekly were assessed in 2 CV outcomes trials (NN9924-4221, PIONEER 6 and NN9535-3744, SUSTAIN 6), each designed to rule out an 80% increased CV risk in patients with type 2 diabetes (T2D) at high risk for CV disease (CVD) in accordance with FDA guidance. PIONEER 6 demonstrated CV safety with a favourable point estimate. SUSTAIN 6 however demonstrated a statistically significant 26% risk reduction with s.c. semaglutide compared with placebo for the primary endpoint (time from randomisation to first occurrence of a major adverse cardiovascular event (MACE) consisting of: CV death, non-fatal myocardial infarction (MI) or non-fatal stroke).[2] Clinical pharmacology and clinical efficacy data indicate that the action of semaglutide is the same whether administrated via a subcutaneous injection or orally in a tablet. Hence, once semaglutide has entered systemic circulation, the properties and actions of the molecule are similar and independent of the route of administration. Accordingly it is hypothesised that oral semaglutide in the dose of 14 mg OD can reduce CV risk.

The current trial serves the purpose of confirming that oral semaglutide reduces the risk of MACE in patients with T2D and established CVD and/or chronic kidney disease (CKD).

3.2 Background

To prevent the complications associated with T2D, the goal of the therapy is to mitigate the multiple heterogeneous metabolic defects associated with the disease, including hyperglycaemia.[3] However, many patients with T2D do not achieve glycaemic control, so an unmet need for simple and convenient as well as safe and efficacious treatment options exists.[4,5] In addition, CV disease is the predominant cause of death in patients with T2D, and diabetes increased the risk for coronary heart disease, stroke and CV death[6] with an about a two-fold excess, underscoring the need for therapies lowering the risk of CV events in patients with T2D.

Semaglutide is a next-generation glucagon-like peptide-1 (GLP-1) analogue with a high degree of homology to human GLP-1.[7] For oral administration, semaglutide has been co-formulated with an absorption enhancer (SNAC, 300 mg) in a tablet formulation. Non-clinical and clinical studies have established that oral semaglutide is safe and well tolerated and that it provides dose-dependent reductions in HbA_{1c} and body weight when used in compliance with the specified simple dosing conditions.[8] Detailed information for oral semaglutide is available in the current edition and any updates of the Investigator's Brochure (IB).

The trial will include patients with T2D and high CV risk defined as having established CVD and/or CKD. A population at high risk for CV events is an appropriate target population for a risk reduction intervention and will ensure that the primary objective of the trial can be met within a reasonable timeframe and sample size.

3.3 Benefit-risk assessment

3.3.1 Risks

The sections below describe identified and potential risks associated with oral semaglutide treatment. For classification and further details of the risks, please refer to the current edition and any updates of the IB. The identified/potential risks are based on findings in non-clinical studies and clinical trials with semaglutide (s.c. as well as oral) as well as other glucagon-like peptide-1 receptor agonists (GLP-1 RAs). For each of these risks, mitigating actions have been implemented to minimise the risks for patients enrolled in this trial.

Gastrointestinal adverse events

Consistent with the other GLP-1 RAs, the most frequent adverse events (AEs) with oral semaglutide are gastrointestinal AEs (nausea, vomiting, diarrhoea, dyspepsia and constipation). A low starting dose and gradual dose escalation with 4 weeks dose escalation increments have been implemented in the recent clinical trials with the intent to lower the risk of gastrointestinal AEs.

Impaired kidney function

In patients treated with GLP-1 RAs including oral semaglutide, gastrointestinal AEs such as nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating patients with impaired renal function with GLP-1 RAs as it may cause a deterioration of renal function. Impaired renal function may increase the risk of metformin associated lactic acidosis.

Patients and providers should be advised to monitor hydration levels in order to avoid dehydration in connection with gastrointestinal AEs.

Hypoglycaemia

The risk of hypoglycaemic episodes associated with the use of GLP-1 RAs, including oral semaglutide, is low when used as monotherapy. Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia compared to patients treated with semaglutide as monotherapy or in combination with other anti-hyperglycaemic medications. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with oral semaglutide. It is also recommended that the investigator ensures that patients taking or initiating sulphonylurea or insulin perform adequately frequent blood glucose monitoring to ensure patient safety.

Allergic reactions

As expected for a protein-based drug, patients treated with oral semaglutide may develop localised or generalised immune and allergic reactions including urticaria, rash or pruritus. Severe allergic reactions such as anaphylactic reactions could potentially also pose a risk to patients treated with oral semaglutide. Data from the both the s.c. and the oral semaglutide development programmes indicate that the potential risk of allergic reactions is low.

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 RA drug class. As a precaution, trial product should be discontinued in case of suspicion of acute pancreatitis in accordance with Section 8.1.

Acute gallstone disease (cholelithiasis)

Patients with T2D are often overweight or obese and have an inherent risk of developing gallstones (cholelithiasis). Events of cholelithiasis have been associated with the use of GLP-1 RAs including semaglutide. In the clinical development programme, events were mainly mild and non-serious and did not lead to an increased risk of complications such as cholecystitis or pancreatitis.

Diabetic retinopathy complications

The cardiovascular outcome trial in the s.c. semaglutide development programme (SUSTAIN 6) showed an increased risk of events related to diabetic retinopathy complications in patients treated with semaglutide compared to placebo, albeit the proportion of patients with an event of diabetic retinopathy complications was low. The imbalance was driven by patients with a history of diabetic retinopathy at baseline and patients who were treated with insulin. As a precaution, patients with a history of uncontrolled and potentially unstable diabetic retinopathy or maculopathy will be excluded from the trial, and eye examination will be performed according to flowchart (see Section 2).

Pancreatic cancer

There is currently no support from non-clinical studies, clinical trials or post-marketing data that GLP-1 RA-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies based on the unknown long-term effects on β-cell stimulation and α-cell suppression.

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

Thyroid C-cell tumours were seen in the mice and rat carcinogenicity studies, after daily exposure to semaglutide for 2 years. No C-cell tumours were observed in monkeys after 52 weeks exposure of up to 40-fold higher doses than the clinical plasma exposure at 14 mg/day. The GLP-1 receptor is not expressed in the normal human thyroid[9]; and therefore, these findings are not likely to be

clinically relevant. To mitigate this risk, patients with a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2) are excluded from clinical trials with semaglutide.

Pregnancy and fertility

Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. Therefore, oral semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, treatment with oral semaglutide should be discontinued immediately. Exclusion and discontinuation criteria related to pregnancy have been implemented in the trial.

3.3.2 Benefits

In clinical trials oral semaglutide has provided superior long-term glycaemic control in T2D and clinically relevant reductions in body weight as compared to commonly used marketed products and placebo. A statistical significant reduction in CV events has been demonstrated for semaglutide s.c. (SUSTAIN 6[2]) and this finding was supported by the results from the PIONEER 6 trial with oral semaglutide.

During this trial it is expected that all patients, including those randomised to placebo will benefit from participation through frequent contact with the trial site, where diabetes and CV diseases are monitored and treated following careful medical examinations. To ensure all patients, including those receiving placebo have an adequate glycaemic control and CV risk factor management, investigators are encouraged to optimise treatment with anti-diabetic medications as well as medications affecting CV risk factors throughout the trial. All patients in this trial will receive trial product and auxiliary supplies free of charge.

3.3.3 Risk and benefit conclusion

Data from the clinical development programme for semaglutide has not revealed any safety issues that would outweigh the benefits. The trial population will consist of T2D patients with high risk of CV events. Assessment of diabetes and CV risk factors and appropriate attention to the standard of care treatment will be ensured throughout the trial. It is therefore concluded that the potential benefits from the trial will outweigh the potential risks for the oral semaglutide as well as the placebo treated patients.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of oral semaglutide may be found in the Investigator's Brochure and any updates thereof.

4 Objectives and endpoints

4.1 Primary, secondary and exploratory objective(s)

The primary objective

To demonstrate that oral semaglutide lowers the risk of major adverse cardiovascular events (MACE) compared to placebo, both added to standard of care in patients with T2D and at high risk of CV events.

The secondary objectives

To compare the effects of oral semaglutide versus placebo, both added to standard of care in patients with T2D and at high risk of CV events with regards to:

- CKD
- CV events
- Peripheral artery disease (PAD)
- Glycaemic control and body weight
- Safety

The exploratory objectives

To compare the effects of oral semaglutide versus placebo, both added to standard of care in patients with T2D and at high risk of CV events with regards to:

- Cognitive function
- Smoking

Estimand

The 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, secondary and exploratory endpoint(s)

4.2.1 Primary endpoint

Endpoint title	Time Frame	Unit
Time to first occurrence of MACE, a composite endpoint consisting of: • CV death • non-fatal myocardial infarction • non-fatal stroke	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)

[a] Trial is event driven.

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

Endpoint title	Time Frame	Unit
Time to first occurrence of a composite endpoint consisting of: • CV death • renal death • onset of persistent ≥ 50% reduction in eGFR (CKD-EPI)[b] • onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 • initiation of chronic renal replacement therapy (dialysis or kidney transplantation)	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to occurrence of CV death	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of major adverse limb events (MALE), a composite endpoint consisting of: • acute limb ischemia hospitalisation • chronic limb ischemia hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)

[a] Trial is event driven.

[b] Compared with baseline.

Abbreviations: eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease – epidemiology collaboration

Definitions

Estimated glomerular filtration rate (eGFR) will be calculated using the – CKD-EPI formula.[10] A persistent change in eGFR is defined as having 2 consecutive samples meeting the criteria. The 2 samples must be at least 4 weeks apart.

4.2.2.2 Supportive secondary endpoints

Endpoint title	Time Frame	Unit
Time to first occurrence of an expanded MACE composite endpoint consisting of: • CV death • non-fatal myocardial infarction • non-fatal stroke • coronary revascularisation • unstable angina requiring hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of a composite heart failure endpoint consisting of: • CV death • heart failure requiring hospitalisation • urgent heart failure visit	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of a composite CKD endpoint consisting of: • renal death • onset of persistent ≥ 50% reduction in estimated glomerular filtration rate (eGFR) (CKD-EPI)[b] • onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 • initiation of chronic renal replacement therapy (dialysis or kidney transplantation)	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to occurrence of all-cause death	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of non-fatal myocardial infarction (MI)	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of non-fatal stroke	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time from randomisation to heart failure requiring hospitalisation or urgent heart failure visit	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of coronary revascularisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of unstable angina requiring hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to occurrence of renal death	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of onset of persistent ≥ 50% reduction in eGFR (CKD-EPI)[b]	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)

Endpoint title	Time Frame	Unit
Time to first occurrence of initiation of chronic renal replacement therapy (dialysis or kidney transplantation)	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of a composite endpoint consisting of: • all-cause death • non-fatal myocardial infarction • non-fatal stroke	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of acute limb ischemia hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Time to first occurrence of chronic limb ischemia hospitalisation	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)
Annual rate of change in eGFR (CKD-EPI) (total eGFR slope)	From randomisation (week 0) to end of treatment (up to 60 months or more[a])	ml/min/1.73 m^2 per year
Change in glycosylated haemoglobin (HbA_{1c})	From randomisation (week 0) to 2 years (visit 12)	%-points
Change in body weight	From randomisation (week 0) to 2 years (visit 12)	Kilogram
Number of severe hypoglycaemic episodes[11]	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Number of events
Time to first occurrence of a severe hypoglycaemic episode [11]	From randomisation (week 0) to end-of-trial (up to 61 months or more[a])	Month(s)

[a] Trial is event driven.

[b] Compared with baseline.

4.2.2.3 Exploratory endpoints

Endpoint title	Time Frame	Unit
Change in Montreal Cognitive Assessment (MoCA) score	From randomisation (week 0) to 2 years (visit 12)	Score (0-30)
Change in Montreal Cognitive Assessment (MoCA) score	From randomisation (week 0) to 3 years (visit 16)	Score (0-30)
Current smoking	At year 2	Yes/no

English and/or Spanish speaking patients in Argentina, Canada, Colombia, Mexico, Spain, United Kingdom and United States:

Endpoint title	Time Frame	Unit
Change in Working Memory Index	From randomisation (week 0) to 2 years (visit 12)	Score
Change in Verbal Reasoning	From randomisation (week 0) to 2 years (visit 12)	Score

Change in Attentional Intensity Index	From randomisation (week 0) to 2 years (visit 12)	msec
Change in Cognitive Reaction Time	From randomisation (week 0) to 2 years (visit 12)	msec
Change in Sustained Attention Index	From randomisation (week 0) to 2 years (visit 12)	%-points

5 Trial design

5.1 Overall design

This is a randomised, double-blind, parallel-group, placebo-controlled trial comparing oral semaglutide versus placebo OD added to standard of care in patients with T2D at high risk of CV events. Patients will be randomised 1:1 to receive either oral semaglutide or placebo.

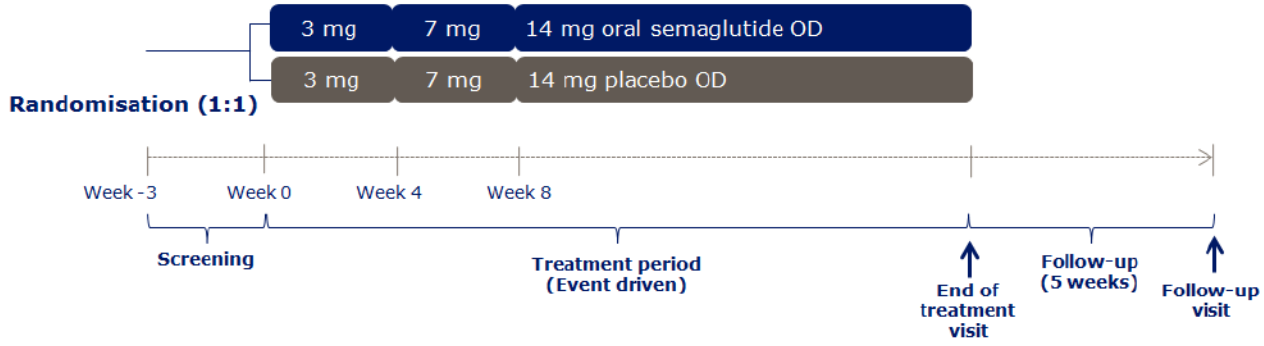
The trial is event driven with trial closure being performed when the targeted number of primary endpoint events (1225) has been reached. The trial will employ a group sequential design and interim testing for efficacy will be performed by an independent external Data Monitoring Committee (DMC). With the assumed event rate and a recruitment period of approximately 18 months, expected trial duration for an individual patient is approximately 3.5 to 5 years including the follow-up period. The follow-up period is 5 weeks after end of treatment.

Patients will be followed for the complete duration of the trial and extensive efforts will be made to collect outcome data for all randomised patients. A schematic overview of the trial design is shown in Figure 5-1 below.

The trial is designed to evaluate CV outcomes and will apply a targeted approach to collection of safety data focusing on serious AEs (SAEs), AEs leading to discontinuation of trial product and other selected AEs. An adequate characterisation of the less serious and more common AEs are evaluated in the phase 3a trials conducted with oral semaglutide comprising more than 5,500 patients with T2D.

An external event adjudication committee (EAC) will perform ongoing adjudication of predefined CV events and other selected AEs in an independent and blinded manner.

Figure 5-1 Trial design



5.2 Patient and trial completion

In this trial 9,642 patients are planned to be randomly assigned to trial product. The recruitment period is expected to be approximately 18 months.

Trial period completion for a patient is defined as when the randomised patient has:

- attended the final scheduled visit (follow-up visit (P-FU) according to the flowchart)

or

- died during trial.

The trial is event driven; therefore, end of treatment visit (V-EOT) and follow-up contact (P-FU) will be scheduled according to projected trial closure. When trial closure is initiated the investigators will be notified and instructed by Novo Nordisk regarding the visit schedules for their patients.

When the trial comes to an end, the investigator must make every effort to ascertain efficacy endpoint data and AEs with a focus on those related to the primary objective for all patients. This should be done by direct contact with the patient whenever possible. If a patient 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 medical records, the patients' primary physician or other health care professionals and, as a last resort, vital status (dead or alive) should be obtained. Publicly available data sources should also be searched. A search agency may be used to facilitate identifying updated contact details for a missing patient or provide vital status (dead or last alive date). The above suggestions should be followed unless prohibited by local regulation and may be modified according to practical aspects.

In a case where several attempts are required to establish direct contact to a patient, it may be necessary to exceed the visit window of a follow-up visit. 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 will be made and documented in the source documents:

- To patients: 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 to public registries of deceased persons, if available and allowed by local regulation

5.3 End of trial definition

The end of the trial is defined as the date of the last visit (P-FU) of the last patient in the trial.

5.4 Scientific rationale for trial design

To minimise bias the trial is randomised, double-blinded and placebo-controlled. Blinded treatment with oral semaglutide or placebo offers a robust method for assessment of the effects of oral semaglutide. A broad spectrum of concomitant anti-hyperglycaemic medication, as well as treatments for co-morbidities and CV risk factors can be introduced or adjusted throughout the trial based on individual requirements and at investigator's discretion. This is in accordance with a pragmatic approach to compare two treatment regimens: one where oral semaglutide is available and another where it is not.

To support the patient 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, e.g. regarding glycaemic control, the patient 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 patients and to reflect the anticipated patient population. The 5-week follow up is chosen due to the half-life of oral semaglutide and is considered appropriate for end of systemic exposure.

The trial will include a population of patients with T2D and established CV disease and/or CKD which is an appropriate high risk target population for a CV risk reduction intervention and will ensure that the primary objective of the trial can be evaluated within a reasonable timeframe and sample size.

6 Trial population

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

6.1 Inclusion criteria

All inclusion criteria are based on the patients' medical records, except for inclusion criterion for HbA_{1c} (local laboratory or point-of-care device). Patients 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 ≥50 years at the time of signing informed consent.
3. Diagnosed with type 2 diabetes mellitus.
4. HbA_{1c} 6.5% - 10.0% (47 - 86 mmol/mol) (both inclusive).[a]
5. At least one of the below conditions (a-d):
   a) Coronary heart disease defined as at least one of the following:
      i. Prior myocardial infarction
      ii. Prior coronary revascularisation procedure
      iii. ≥50% stenosis in coronary artery documented by cardiac catheterisation or CT coronary angiography
      iv. Coronary heart disease with ischaemia documented by stress test with any imaging modality
   b) Cerebrovascular disease defined as at least one of the following:
      i. Prior stroke
      ii. Prior carotid artery revascularisation procedure
      iii. ≥50% stenosis in carotid artery documented by X-ray angiography, MR angiography, CT angiography or Doppler ultrasound
   c) Symptomatic peripheral artery disease (PAD) defined as at least one of the following:
      i. Intermittent claudication with an Ankle-brachial index (ABI) < 0.85 at rest
      ii. Intermittent claudication with a ≥50% stenosis in peripheral artery (excluding carotid) documented by X-ray angiography, MR angiography, CT angiography or Doppler ultrasound
      iii. Prior peripheral artery (excluding carotid) revascularization procedure
      iv. Lower extremity amputation at or above ankle due to atherosclerotic disease (excluding e.g. trauma or osteomyelitis)
   d) Chronic kidney disease defined as:
      i. eGFR < 60 mL/min/1.73 m^2 [b]

[a] Latest available and no more than 30 days old local laboratory assessment based on medical records or point of care measurement.

[b] Based on medical records using latest available and no more than 6 months old assessment.

6.2 Exclusion criteria

All exclusion criteria are based on the patients' medical records, except for exclusion criterion 3, urine pregnancy test. Patients are excluded from the trial if any of the following criteria apply:

1. Known or suspected hypersensitivity to trial product or related products.
2. Previous participation in this trial. Participation is defined as randomisation.
3. 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.
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening.*
5. Any disorder, which in the investigator's opinion might jeopardise patient's safety or compliance with the protocol.
6. Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack (TIA) within the past 60 days prior to the day of screening
7. Planned coronary, carotid or peripheral artery revascularisation.
8. Heart failure presently classified as being in New York Heart Association (NYHA) Class IV.
9. Treatment with any GLP-1 receptor agonist (RA) within 30 days before screening.
10. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.
11. Presence or history of malignant neoplasm within 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ is allowed.
12. Personal or first degree relative(s) history of MEN2 or MTC.
13. End stage renal disease or chronic or intermittent haemodialysis or peritoneal dialysis.
14. History of major surgical procedures involving the stomach or small intestine potentially affecting absorption of drugs and/or nutrients, as judged 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 if the last dose of the investigational medicinal product has been received more than 30 days before screening.

Argentina, Austria, Belgium, Brazil, China, Denmark, Thailand and United Kingdom: For country specific requirements, please see Appendix 8.

6.3 Justification for dose

Three doses of oral semaglutide have been investigated in the phase 3a development programme: 3 mg, 7 mg and 14 mg. The selected doses are based on the data derived from the NN9924-3790 dose-finding trial. For further details regarding the results obtained in the phase 2 dose-finding trial (NN9924-3790), please refer to the current edition of the IB for oral administration of semaglutide (NN9924), or any updates thereto.

Similar to other cardiovascular outcomes trials, the maximum treatment dose (14 mg oral semaglutide) will be investigated and compared to placebo in the present trial.

6.4 Lifestyle restrictions

Not applicable.

6.5 Screen failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not eligible for participation according to in/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients 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).

If patients withdraw their consent prior to randomisation or do not return for randomisation a screen failure session must be made in the interactive web response system (IWRS). The reason for failure will in all cases be captured in the electronic case report forms (eCRF).

Due to the long recruitment period re-screening is allowed. A new patient number must be assigned in the IWRS.

6.6 Assessment of eligibility

It is the responsibility of the investigator to have sufficient evidence to ensure eligibility. If a patient is not from the investigators practice; reasonable efforts must be made to obtain a copy of the patient's 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 patient is eligible. The values used to assess eligibility must reflect the patient's current health status.

7 Treatments

7.1 Treatments administered

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

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

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Semaglutide 3 mg tablet (IMP, test product)	3 mg	Tablet	Oral	Dose-pack[a]
Semaglutide 7 mg tablet (IMP, test product)	7 mg			
Semaglutide 14 mg tablet (IMP, test product)	14 mg			
Placebo tablet (IMP, reference therapy)	NA			

[a] A dose-pack contains one blister card with 7 tablets

The active trial product and the corresponding placebo are packed blinded and are identical with regard to visual appearance. Furthermore, all tablets are visually identical to each other, irrespective of dose levels. Strength will be written on the dose-pack e.g. Semaglutide 3 mg or placebo.

All baseline assessments must be done prior to administration of the first dose of trial product. The patients must be trained in dosing instructions (see Section 7.2.1). The investigator must document that patients are trained in the dosing instructions according to Section 2.

Auxiliary supplies are provided by Novo Nordisk:

- blood glucose meters including lancets, test strips, control solutions and instructions for use

At (or after) the randomisation visit patients may be provided with a blood glucose meter. The patients will be instructed in how to use the device and the instructions will be repeated during the trial as needed. The investigator or the individual patient may choose to continue using their own glucose meter or decide that self-measurement of glucose is not needed. If circumstances change, then the glucose meter can be provided.

7.2 Dose modification

Randomised patients will initiate treatment with 3 mg oral semaglutide/placebo OD and follow a fixed 4-week dose escalation regimen until reaching the treatment dose of 14 mg oral semaglutide/ placebo OD as illustrated in Table 7-2.

The 4-week dose escalation interval is applied in order to mitigate the risk of gastrointestinal AEs.

Patients should remain on the 14 mg dose level until the end of treatment visit; however, dose reductions, extensions of dose escalation intervals and treatment pauses are allowed e.g. if treatment with the trial product is associated with unacceptable AEs or due to other circumstances.

Table 7-2 Treatment and trial periods

Trial periods	Screening	Dose escalation	Dose escalation	Maintenance	Follow-up
Visits in each period	Visit 1 to Visit 2	Visit 2 to Visit 3	Visit 3 to Visit 4	Visit 4 to end of treatment Visit	End of treatment Visit to Follow-up Visit
Duration	Up to 3 weeks	4 weeks	4 weeks	Up to ~58 months	5 weeks
Daily dose	-	3 mg	7 mg	14 mg	-

Any change to trial product dose including date of change or discontinuation should be recorded in the eCRF throughout the trial.

If trial product is discontinued, patients should continue to follow the trial schedule without being withdrawn from the trial. Treatment with trial product should be resumed if deemed safe at the discretion of the investigator.

7.2.1 Dosing instructions

Absorption of oral semaglutide is significantly affected by food and fluid in the stomach, therefore dosing should be in the morning in a fasting state and at least 30 minutes before the first meal of the day. Oral semaglutide can be taken with up to half a glass of water (approximately 120 mL/ 4 fluid oz.). The tablet should be taken immediately after removal from the blister and swallowed whole and must not be broken or chewed. Other oral medication should not be taken together with trial product but can be taken 30 minutes after trial product.

7.2.2 Missed doses

The trial product should be administered once daily; however, if one or more doses of trial product are missed due to circumstances not related to the safe use of the trial product (as judged by the investigator) and treatment with trial product is resumed, the below recommendations for dose adjustment apply:

- If ≤ 21 consecutive doses of 14 mg oral semaglutide/placebo are missed, the once daily regimen can be resumed as prescribed without dose reduction.
- If 22-35 consecutive doses of 14 mg oral semaglutide/placebo are missed, it is recommended to resume treatment at 7 mg oral semaglutide/placebo and subsequently, escalate to the higher dose after 4 weeks of treatment.
- If ≥ 36 consecutive doses of 14 mg oral semaglutide/placebo are missed, it is recommended to resume treatment at 3 mg oral semaglutide/placebo and subsequently, escalate to the higher doses with 4-week dose escalation steps.

Please refer to section 8.1.1 for instructions on how to use the IWRS in relation to patients discontinuing and resuming trial product treatment.

In case of questions related to resuming trial treatment, the investigator can consult Novo Nordisk.

7.3 Method of treatment assignment

All patients 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 patient will be assigned a unique 6-digit patient number which will remain the same throughout the trial. Each site is assigned a 3-digit number and all patient numbers will start with the site number.

7.4 Blinding

The trial products containing the active drug and the placebo 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 patient. 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.

7.5 Preparation/Handling/Storage/Accountability

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

Product storage, in-use conditions and in-use time will be available on the label and in the Trial Materials Manual (TMM).

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to screening and randomisation. The first shipment to each site will be triggered by the first patient 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 patient before it has been evaluated and approved for further use by Novo Nordisk.

Patients must ensure that all used, partly used and unused trial products including empty packaging material is returned 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 is performed by using the IWRS and must be done on tablet level.

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.

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 patient'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 patient's home by courier service.

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

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

Japan: For country specific requirements, please see Appendix 8.

7.6 Treatment compliance

Throughout the trial, the investigator will remind the patient to follow the trial procedures and requirements to ensure patient compliance.

Treatment compliance will be assessed by monitoring of drug accountability and by discussing treatment compliance and dosing conditions with the patient. Treatment compliance is defined as taking between 80%-120% of the dose as prescribed between visits. The investigator must assess the amount of trial products returned compared to what was dispensed at the previous visit and, in case of discrepancies, question the patient.

If a patient is found to be non-compliant, the investigator will remind the patient of the importance of following the instructions given including taking the trial products as prescribed and should document this discussion in the patient's medical record.

If the patient has been off treatment, continuation of trial product should be encouraged if considered safe as per the investigator's discretion. Previous dose and gastrointestinal adverse reactions as well as number of missed doses should be taken into consideration when evaluating whether to repeat dose escalation (see section 7.2.2).

7.7 Concomitant medication

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

- To treat diabetes
- To treat or prevent CV diseases (for example anti-hypertensives, lipid-lowering agents, anticoagulants, aspirin and other antiplatelet agents)
- In relation to an SAE, if relevant
- 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, and related AE number when applicable.

For antidiabetic medication, the total daily dose needs to be included in the eCRF. Stable dose changes (2 weeks or more) should be captured as new concomitant medication with the new dose and relevant start and stop date.

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

Initiating treatment with any other GLP-1 receptor agonists are not permitted during the entire trial. Other changes to background medications can take place during the trial. Risk of hypoglycaemic episodes is described in section 3.3.1.

Importantly, investigators should ensure that patients are treated according to recommended standard of care for both glycaemic management as well as CV risk management. Recommendations for this will be provided in guidance documents from the steering committee and global expert panel during trial conduct. Surveillance of adherence to standard of care will be performed centrally by Novo Nordisk. For patients where standard of care is not achieved, investigators may be asked for an optimisation plan which will be recorded in the eCRF or approached to discuss treatment options. If allowed according to local regulation, Novo Nordisk may compensate parts of the cost of some concomitant medication used to ensure glycaemic control and CV risk management.

Brazil and Turkey: For country specific requirements, please see Appendix 8.

7.8 Treatment after the end of the trial

When discontinuing trial product at the end of the treatment period, the patient should be transferred to a suitable marketed product at the discretion of the investigator. GLP-1 RAs are not allowed to be prescribed during the 5 week follow-up period. Oral semaglutide will not be available for prescription until marketing authorisation is issued.

Argentina and Brazil: For country specific requirements, please see Appendix 8.

8 Discontinuation/Withdrawal criteria

8.1 Discontinuation of trial treatment

The patient must be discontinued from trial product at any time during the trial, 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 acute pancreatitis is suspected, trial product should be discontinued; if confirmed, trial product should not be restarted
5. Other safety concerns, at the discretion of 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 discretion without discontinuing trial product.

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

Ad 3: Patients should be advised not to participate in other clinical trials, while participating in this trial. If done, treatment with trial product should be discontinued. If participation in the other trial is stopped, treatment can be resumed if there are no safety concerns at the discretion of the investigator after discussing with a Novo Nordisk medical expert.

The patient may be discontinued from trial product at any time during the trial at the discretion of the investigator for safety, compliance or administrative reasons. Treatment with trial product can be resumed if later deemed safe.

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

When initiating new anti-diabetic treatment after the discontinuation of trial product, the half-life of semaglutide of approximately one week should be kept in mind.

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, patients 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 7.2.2). Date and last trial product dose should be recorded in the eCRF. A treatment status session in the IWRS should be performed when a patient is on treatment pause or resumes treatment.

8.2 Withdrawal from the trial

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

If considering withdrawing from the trial, the patient 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 patient that this must include information on their AEs, especially those related to the primary objective that occurred since last contact to the patient. Only if the patient declines all alternatives, should the patient be recorded as withdrawn.

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

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

Although a patient 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 patient's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the end of trial form in the eCRF.

For patients who are withdrawn, when the trial comes to an end, the investigator must scrutinise publicly available registries to determine vital status, unless prohibited by local regulations or specifically prohibited by the patient upon withdrawal of consent. Please also refer to section 5.2 for further details.

Mexico: For country specific requirements, please see Appendix 8.

8.2.1 Replacement of patients

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

8.3 Lost to follow-up

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

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

The attempts to contact the patient must be documented in medical records at the site.

9 Trial assessments and procedures

- Trial procedures and their timing are summarised in the flowchart, 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 patients meet all eligibility criteria.
- The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, patients 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 patients' primary physician about the patients' participation in the trial if the patient has a primary physician and if the patient agrees to the primary physician being informed.
- Each patient 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 patient during the trial. The sites are encouraged to maintain these details as current as possible throughout the course of the trial.
- The randomisation visit can be performed on the same day as the screening visit if the patient is assessed as eligible (Section 6) and if sufficient trial product is available.
- It is the responsibility of the investigator to schedule the visits and contacts as per protocol (flowchart, Section 2) and to ensure they take place.
- After V6, all odd numbered site visits (V7, V9, V11 etc.) can be conducted as a phone contact, however 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 patient throughout the entire trial, and at all times have updated contact information. Even if a visit (or phone contact) is missed and it is not possible to re-schedule, the investigator must take every effort to have all patients followed for endpoint related outcomes including MACE.
- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the trial.
- Review of completed laboratory reports etc. must be documented either on the documents or in the patient's source documents.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 for further details on laboratory samples.
- The investigator may provide the patients with a mobile phone to mediate easier contact if allowed according to local regulation and approved by institutional review board (IRB)/independent ethics committee (IEC). The investigator should consider sending text messages to the patients to remind them of site visits, dosing of trial product, and other trial requirements.
- If warranted by special circumstances, 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.

9.1 Efficacy assessments

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

9.1.1 HbA_{1c} point of care

HbA_{1c} can be measured while patient is at site for assessing eligibility at Visit 1 and at site visits during the trial as a supportive measurement for investigator's treatment decisions. Sites will either use their own equipment or a device provided by Novo Nordisk. Local laboratory can be used if the HbA_{1c} point of care device for any reason cannot be used. Point of care device measurements performed at scheduled visits should be recorded in the eCRF starting at Visit 3.

9.1.2 Self-measured plasma glucose

If deemed helpful by the investigator, patients may be provided with a BG meter including auxiliaries as well as instructions for use. The patients will be instructed in how to use the device and the instruction will be repeated as needed. The investigator will advise the individual patient of when the self-measured plasma glucose values should be measured and how to note the values and

dates. The measurements are supportive for investigator's treatment decisions when optimising glycaemic control, and should be filed at site.

9.1.3 Clinical efficacy laboratory assessments

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

9.1.4 Cognitive testing, patient surveys and visits to emergency room/urgent care unit

The Montreal Cognitive Assessment (MoCA) is the cognitive testing used in this trial. If clarification of the test is needed, care must be taken not to bias the patient.

Argentina, Canada, Colombia, Mexico, Spain, United Kingdom and United States:
Online cognitive testing will be performed using the PROTECT Cognitive Test Battery in English and/or Spanish speaking patients. The test battery includes the following tests:

- Verbal Reasoning
- Paired Associate Learning
- Self-Ordered Search
- Digit Vigilance
- Simple Reaction Time
- Choice Reaction Time

Performing the tests comprise doing a pre-test for practice as well as an actual test. The tests should be performed at visits specified in the flowchart (see Section 2).

Patient surveys will be performed in a subset of patients in selected countries:

- A patient expectations and experience survey. This data will not be transferred to the trial database.
- A patient engagement assessment. This data will not be transferred to the trial database.

Visits to emergency room/urgent care unit will be recorded in the eCRF for the US.

9.2 Adverse events

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

Japan: For AE reporting requirements please see Appendix 8.

This trial employs a selective approach for collection of safety data. The investigator is responsible for detecting, documenting, recording and following up on:

- SAEs
- AEs requiring event adjudication or additional data collection on specific event forms, irrespective of seriousness, see Table 9-1
- 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.
- Pregnancies
- Technical complaints

Table 9-1 AEs requiring event adjudication or additional data collection

Event type (serious and non-serious) including description	Adjudication outcome	Additional form(s) required
Death All cause death	• Cardiovascular death • Renal death • Non-cardiovascular, non-renal death	• Adjudication form
Acute coronary syndrome (ACS) All types of acute myocardial infarction Unstable angina pectoris requiring hospitalisation	• Acute myocardial infarction • Hospitalisation for unstable angina pectoris	• Adjudication form and • Specific event form in case of revascularisation
Events leading to coronary artery revascularisation (non-ACS) Non-ACS events (e.g. stable angina pectoris) leading to a catheter-based (percutaneous coronary intervention (PCI)) or a surgical procedure (Coronary artery bypass surgery) designed to improve myocardial blood flow Note: The underlying condition should be reported as the AE diagnosis	• Not applicable	• Specific event form
Stroke or 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 • Modified Rankin scale form*
Heart failure requiring hospitalisation or urgent heart failure visits New episode or worsening of existing heart failure leading to an urgent, unscheduled hospital admission or clinic/office/emergency department visit	• Heart failure hospitalisation • Urgent heart failure visit	• Adjudication form
Acute or chronic limb ischemia requiring hospitalisation Acute limb ischemia is defined as a sudden decrease in limb perfusion threatening viability of the limb and leading to an urgent, unscheduled hospitalisation Chronic limb ischemia is defined as a chronic condition with rest pain, non-healing ulcers or gangrene and leading to an urgent, unscheduled hospitalisation with need for intervention such as a revascularization procedure, amputation or pharmacological therapy	• Acute limb ischemia hospitalisation • Chronic limb ischemia hospitalisation	• Adjudication form
Acute pancreatitis Events of acute pancreatitis	• Acute pancreatitis	• Adjudication form

Event type (serious and non-serious) including description	Adjudication outcome	Additional form(s) required
Events leading to renal replacement therapy Dialysis treatment (haemodialysis or peritoneal dialysis) Kidney transplantation Note: The underlying condition should be reported as the AE diagnosis	• Chronic renal replacement therapy	• Adjudication form
Malignant neoplasm Malignant neoplasm by histopathology or other substantial clinical evidence	• Not applicable	• Specific event form
Diabetic retinopathy New onset or worsening of diabetic retinopathy	• Not applicable	• Specific event form
Acute gallbladder disease Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis)	• Not applicable	• Specific event form
Medication errors related to trial product Medication error (accidental errors related to trial product): Wrong drug administered instead of trial product. Wrong route of administration or accidental administration of a lower or higher dose than intended where clinical consequences for the patient were likely to happen, although they did not necessarily occur	• Not applicable	• Specific event form
Severe hypoglycaemic episode An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose values may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration (American Diabetes Association[11])	• Not applicable	• Specific event form • If the episode fulfils the criteria of an SAE, an AE form and a safety information form must also be completed Japan: For country specific require-ments, see Appendix 8.

* Disability after a stroke or TIA event, see section 9.4.5

Description of events is to guide investigators with regards to reporting of AEs. Event definitions 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) and AEs leading to discontinuation of trial product, pregnancies 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 follow-up visit, at the time points specified in the flowchart.

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.

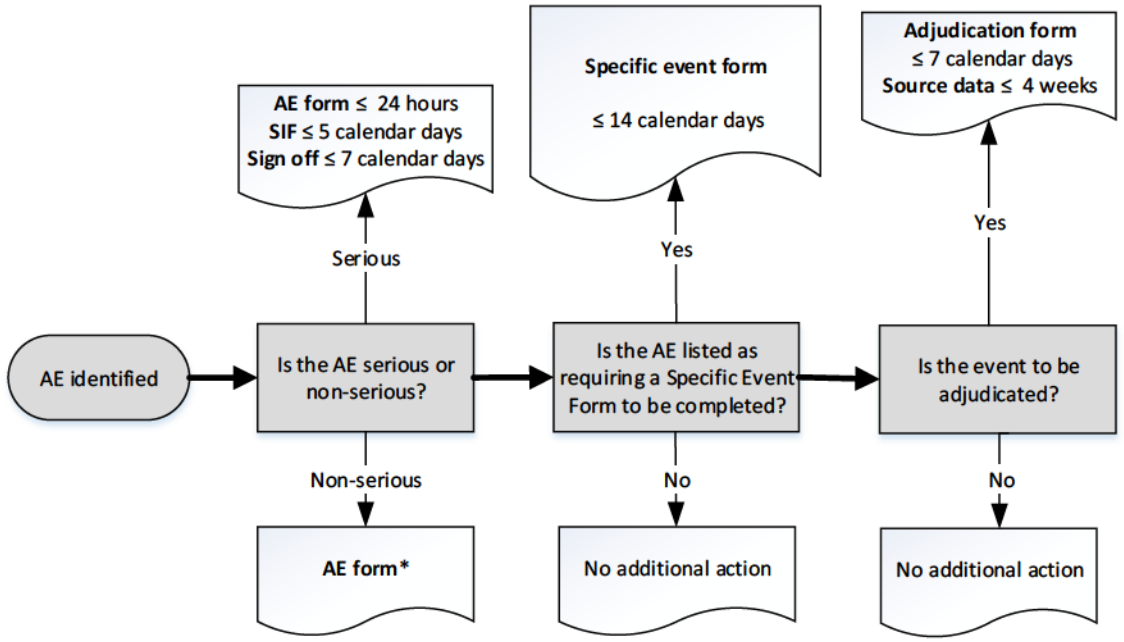
Investigators are not obligated to actively seek for AEs or SAEs in former trial patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related 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, including events for adjudication, Section 9.2.1.1, are listed in Figure 9-1.

Some AEs require additional data collection via a specific event form. The relevant AEs are listed in Table 9-1 and the reporting timelines in Figure 9-1.

Figure 9-1 Safety reporting timelines



Timelines are from the awareness of an AE.
Queries and follow-up requests to be resolved ≤ 7 calendar days.
* Only for non-serious adverse events required to be reported according to section 9.2
AE: Adverse Events, SAE: Serious Adverse Events, SIF: Safety Information Form

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 patients. 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 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 patients' 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 adjudication form will be generated in the eCRF. This form must be completed, and all source documents (as specified in the Event Adjudication Site Manual) 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 adjudication form for the event in question should be completed in the eCRF within 7 calendar days from the AE is reported in the eCRF.

Copies of source documents should be labelled with trial ID, patient 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 which source documents are relevant and how these should be provided 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 patient 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 events 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 patients 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.

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 and regulatory reporting during trial conduct, even though the cases fulfil the definition of suspected unexpected serious adverse reactions (SUSARs). The definition of MACE is: Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke. The independent 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.

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

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

9.2.5 Pregnancies and associated adverse events

Details of pregnancies in female patients will be collected after randomisation and until pregnancy outcome.

If a pregnancy is reported in female patients, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

Pregnancy outcome should be documented in the patient's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.

The investigator should report information on the patient and the pregnancy outcome until the new-born infant is one month of age in accordance with European Medicines Agency (EMA).[12] Information about the pregnancy and pregnancy outcome/health of the new-born infant has to be reported on paper pregnancy forms and be forwarded to Novo Nordisk either by fax, encrypted e-mail or courier.

9.2.6 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. Limited data are available with regard to overdose in patients treated with oral semaglutide. Based on data from treatment with s.c. semaglutide, the most commonly reported adverse reaction was nausea and all patients recovered without complications. In the event of an overdose, appropriate supportive treatment should be initiated according to the patients' clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the half-life of semaglutide of approximately one week.

In the event of an overdose, the investigator should closely monitor the patient for overdose-related AE/SAEs. Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the patient. Accidental overdose must be reported as a medication error. Refer to Section 9.2.1 for further details. For more information on overdose, also consult the current version of the oral semaglutide IB.

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 before exposure to trial product.
Medical history is a medical event that the patient has experienced in the past, i.e. prior to randomisation.

The following concomitant illness/medical history should be recorded in the eCRF:

- Type 2 diabetes - date of diagnosis
- Diabetes complications
- History of cardiovascular and chronic kidney diseases. This also includes each medical condition(s) that qualified the patient for participation in the trial according to inclusion criterion #5 a-d
- History of eye diseases
- History of gallbladder diseases
- History of pancreatitis
- Other relevant concomitant illness/medical history including malignant neoplasms and COVID-19

In case of an abnormal and clinically significant finding, the investigator must record the finding on relevant disease specific history form or the Medical History/Concomitant Illness form if it is present before randomisation. Any new finding fulfilling the AE definition (see Appendix 4) during the trial and any clinically significant worsening from baseline (visit 2) must be reported as an AE, if applicable, (see Section 9.2).

9.4.1 Physical examinations

Physical examinations should be performed according to local procedures, when indicated in Section 2.

A physical examination will include assessments of the:

- General appearance
- Thyroid gland
- Respiratory system
- Cardiovascular system
- Gastrointestinal system incl. mouth
- Extremities
- 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 forms in the eCRF in accordance with Section 9.4. Findings not present at randomisation should be reported as AEs according to Section 9.2.

Body measurements (e.g. height, weight and waist circumference) will be measured and recorded as specified in the flowchart Section 2.

Height should be measured without shoes in centimetres (cm) or inches (in) and recorded in the eCRF.

Body weight should be measured in kilogram (kg) or pound (lb), with an empty bladder, without shoes and only wearing light clothing. The actual value of the weight should be recorded in the eCRF without rounding and the same equipment should be used throughout the trial.

Waist circumference is the abdominal circumference measured midway between the lower rib margin and the iliac crest. It should be measured when the patient is in a standing position with a non-stretchable measuring tape and to the nearest cm or inch.

Waist circumference and liver parameters are measured at baseline for calculation of fatty liver index.

9.4.2 Vital signs

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

9.4.3 Clinical 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.

9.4.4 Eye examination

Patients with uncontrolled and potentially unstable diabetic retinopathy or maculopathy are not eligible as this indicates retinopathy that has recently progressed to a level that requires intervention or is approaching intervention, but has yet to be brought under control.

Results of an eye examination performed by an ophthalmologist or another suitably qualified health care provider (e.g. optometrist) must be available and evaluated by the investigator before randomisation to assess eligibility. The eye examination should be performed as a fundus photography (e.g. 2-field 60 degree or better, colour or red-free) or by slit-lamp biomicroscopy examination (e.g. using a pre-corneal or corneal contact lens examination). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

If the patient had such an eye examination performed within 90 days prior to screening, the investigator may base his/her evaluation upon the results of that examination. The examination must be repeated before randomisation if the patient has experienced worsening of visual function since

the last examination. If the applicable eye examination was performed before the patient signed the informed consent form, it must be documented that the reason for performing the examination was not related to this trial.

After randomisation an eye examination performed according to above must be performed as per the flowchart in Section 2. The investigator should indicate the outcome of each eye examination. Relevant findings prior to randomisation must be recorded as concomitant illness/medical history. While relevant findings occurring after randomisation should be reported as an AE according to section 9.2.

9.4.5 Disability after a stroke or TIA event

The modified Rankin Scale is used to measure the degree of disability in daily activities after a stroke. A modified Rankin Scale form should be completed for all events sent to adjudication for stroke including evens of TIA to ensure that all events of an EAC confirmed stroke will have a disability outcome recorded. The degree of disability according to the scale should be assessed after a minimum of 90 days post-event (most often this will be at the patient's second site visit after the stroke or TIA). The event should be recorded in the eCRF.

9.5 Pharmacokinetics

Not applicable.

9.6 Pharmacodynamics

Not applicable.

9.7 Genetics

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

Brazil, China, Columbia, Israel, South Korea and Turkey: For country specific requirements, please see Appendix 8.

9.8 Biomarkers

Collection of samples for biomarker research is a component of this trial. Participation in the biobank component is optional. Patients 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 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 at monthly intervals 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).

Brazil, China, Columbia, Israel, South Korea and Turkey: For country specific requirements, please see Appendix 8.

10 Statistical considerations

10.1 Sample size determination

The trial is designed with 90% power to confirm superiority for the primary endpoint, i.e. reject the null-hypothesis of hazard ratio (HR) ≥ 1.0 against the one-sided alternative of HR < 1.0, where HR is the hazard ratio of oral semaglutide versus placebo. An alpha spending function will be used that approximates O'Brien Fleming stopping boundaries for the overall Type I error probability of 2.5% (one-sided). Based on a randomisation ratio of 1:1 and assuming a true HR of 0.83 a total of 1,225 primary endpoint events are required for 90% power. For calculation the number of randomised patients the following is assumed:

- annual primary endpoint rate in the placebo group of 3.5%
- uniform recruitment occurs in 18 months
- annual lost to follow-up rate in both treatment groups of 1%
- trial duration is five years and five weeks

Under these assumptions, a total of 9,642 patients are needed for randomisation.

Confirmatory secondary endpoints

If superiority is confirmed for the primary endpoint the below confirmatory secondary endpoints will be controlled for multiplicity through a hierarchical testing strategy. The marginal powers below are calculated under the assumptions that the trial continues to the final analysis and a significance level of 2.5% (one-sided).

The marginal power for superiority in favour of oral semaglutide for the CKD endpoint with 9,642 randomised patients is 94%. This is based on an assumed hazard ratio of 0.80 and an annual event rate of 2.8% in the placebo group.

The marginal power for superiority in favour of oral semaglutide for CV death with 9,642 randomised patients is 56%. This is based on an assumed hazard ratio of 0.83 and an annual event rate of 1.4% in the placebo group.

The marginal power for superiority in favour of oral semaglutide for the MALE endpoint with 9,642 randomised patients is 44%. This is based on an assumed hazard ratio of 0.75 and an annual event rate of 0.44% in the placebo group.

The assumptions for annual event rate of primary endpoint and confirmatory secondary endpoints, lost to follow-up rates and the true hazard ratios are based on the LEADER[13] and SUSTAIN 6[2] CV outcomes trials.

10.2 Definition of analysis sets

The full analysis set (FAS) is defined as all randomised patients and grouped in analyses according to the treatment assigned at randomisation.

Patients continue in the trial and are part of FAS regardless of discontinuation of randomised treatment and any other intercurrent event. A patient is considered lost to follow-up (LTFU) if the patient does not complete the trial and does not withdraw consent. Trial completers are defined as patients that either attend the end-of-trial follow-up visit or who die during the in-trial period.

The in-trial observation period for a patient is defined as the period from date of randomisation to the first of (both inclusive):

- date of follow-up visit
- date when patient withdrew consent
- date of last contact with patient (for patient lost to follow-up)
- date of death

10.3 Statistical analyses

A comprehensive statistical analysis plan (SAP) will be available before first patient first visit (FPFV), including further details of interim testing.

Novo Nordisk will perform the statistical analyses except interim testing, see Section 10.3.4. A statistician independent of trial conduct, DMC analyses, interim testing, and external to Novo Nordisk will repeat the statistical analyses of the primary endpoint and secondary confirmatory endpoints.

General considerations

For confirmatory endpoints controlled for multiplicity, estimated treatment effects will be presented together with two-sided 95% confidence intervals (CIs) and one-sided p-values for test of the hypothesis of superiority. For reporting of results, the estimated treatment effect and the 95% confidence interval will be accompanied by the two-sided p-value.

For non-confirmatory endpoints, the estimated treatment effects will be reported together with two-sided 95% CIs and two-sided p-values.

Baseline value is defined as the latest available measurement from the randomisation visit or the screening visit. Thus, if a randomisation assessment is missing then the assessment from screening is used as the baseline assessment, if available.

Missing data are defined as data that are planned and can be observed but are not present in the database. This implies that data that are structurally missing due to death or administrative censoring are not considered missing.

If adjudicated, time-to-event endpoints are defined based on outcomes of the EAC evaluations. If a patient experiences the event of interest during the in-trial observation period, the endpoint is the time from randomisation to the date of event. While vital status is ascertained systematically throughout the trial, non-fatal events (e.g. non-fatal MI or non-fatal stroke) cannot be systematically collected after withdrawal of consent, lost-to-follow-up, or after end-of-trial visit. For this reason, any event occurring after the in-trial observation period is not included in analyses, unless otherwise stated.

Time-to-event endpoints are censored at the end of the in-trial period if the event of interest did not happen during this period and the patient is alive at the end of the period. Censoring due to LTFU and withdrawal of consent assume independent censoring. Additional anticipated intercurrent events and handling of these in context of the estimand for the primary and confirmatory secondary time-to-event endpoints are described in Table 10-1.

10.3.1 Primary endpoint

The HR for comparing oral semaglutide versus placebo will be estimated from a Cox proportional hazards model with treatment group (semaglutide, placebo) as fixed factor together with the 2-sided 95% CI and one-sided fixed design p-value for hypothesis testing. The score test from the Cox model will be used for testing. The following superiority hypothesis will be tested:

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

Superiority of oral 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.

Competing risk from non-CV deaths will be handled as censorings in the primary Cox analysis. Please, refer to Table 10-1 for handling of other intercurrent events.

Sensitivity analysis

If superiority is established for the primary endpoint, the following sensitivity analysis is performed. The primary analysis assumes independent censoring for patients who are LTFU or who withdrawn consent. To investigate the impact of this assumption on the superiority results of the primary analysis, a tipping point analysis will be made. In this analysis, patients in the oral semaglutide treatment group will have their event times imputed with an increasing penalty in the sense that their risk of MACE is increased (the penalty) following censoring compared to while under observation. The placebo patients will be imputed with no penalty, i.e. assuming same event before and after censoring. Multiple imputed data sets will be analysed for each penalty using the above Cox model and results will be combined using Rubin's rule. The tipping point is then defined as the penalty needed to turn around the superiority conclusion.

10.3.2 Secondary endpoints

Secondary endpoints are categorised as being confirmatory when they are analysed under multiplicity control.

10.3.2.1 Confirmatory secondary endpoints

If superiority is established for the primary endpoint, the superiority hypothesis stated in section 10.3.1 is tested for the confirmatory secondary endpoints under multiplicity control via a hierarchical testing scheme using the following order:

- composite CKD endpoint
- CV death
- MALE endpoint

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 will be analysed and tested separately with a Cox proportional hazards model as described for the primary endpoint.

The following Table 10-1 describes how anticipated intercurrent events during the trial are handled for confirmatory endpoints.

Table 10-1 Statistical handling of intercurrent events for the confirmatory endpoints

Endpoint	Intercurrent event	Handling
Time to first occurrence of MACE	• Treatment discontinuations • Medication modifying cardio-renal risk • Initiation of chronic renal replacement therapy	Patients will be followed and events collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• Non-CV death (competing risk)	Censoring at time of non-CV death in the Cox model
Time to first occurrence of composite CKD	• Treatment discontinuations • Medication modifying cardio-renal risk	Events and follow-up time will be collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• Non-renal and Non-CV death (competing risk)	Censoring at time of non-renal or non-CV death in the Cox model
Time to occurrence of CV death	• Treatment discontinuations • Medication modifying cardio-renal risk • Initiation of chronic renal replacement therapy	Events and follow-up time will be collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• Non-CV death (competing risk)	Censoring at time of non-CV death in the Cox model
Time to first occurrence of MALE	• Treatment discontinuations • Medication modifying cardio-renal risk • Initiation of chronic renal replacement therapy	Patients will be followed and events collected after intercurrent events and used in the analysis
	• Trial discontinuation (withdrawal of consent or lost-to follow-up)	Censoring at time of trial discontinuation
	• All cause death (competing risk)	Censoring at time of death in the Cox model

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 continuous supportive secondary endpoints (change from baseline to 2 years) are analysed using multiple imputation for missing values. An imputation model (linear regression) is estimated separately for each treatment group. It will include baseline value as a covariate estimated based on patients having an observed data point, irrespective of adherence to randomised treatment, at 2 years. The fitted model is used to impute values for all patients that do not have an observed data point at 2 years to create 500 complete data sets. The completed data sets are analysed by an ANCOVA adjusted for treatment as fixed factor and baseline value as covariate. Rubin's rule is used to combine the results.

Number of severe hypoglycaemic episodes will be analysed using a marginal recurrent event regression model taking into account the competing risk of all-cause death.

10.3.3 Exploratory endpoints

The statistical analyses of the exploratory endpoints based on the PROTECT cognitive tests and the MoCA score will be detailed in the SAP.

Current smoking at year two (yes/no) will be analysed using a binary regression model adjusted for baseline smoking status (yes/no).

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 an interim testing. Patients 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.

Interim testing will be performed by a statistician independent of trial conduct and external to Novo Nordisk. 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 confirmatory evaluation.

10.3.5 Sequential safety analysis and safety monitoring

Blinded and unblinded data analyses during trial conduct will be performed by the DMC, as described in the DMC charter. Trial integrity will be ensured by using a statistician independent of trial conduct and external to Novo Nordisk to prepare data for the DMC. The sequential 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 patients in the trial.

10.4 Pharmacokinetic and/or pharmacodynamic modelling

Not applicable.

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12 Appendices

Appendix 1 Abbreviations and Trademarks

ABI	ankle-brachial index
ACS	acute coronary syndrome
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease – epidemiology collaboration
COVID-19	Coronavirus disease 2019
CRF	case report form
CT	computerized tomography
CTR	clinical trial report
CV	cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcome trial
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DUN	dispensing unit number
EAC	event adjudication committee
EAS	event adjudication system
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
eGFR	estimated glomerular filtration rate
FAS	full analysis set

FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPFV	first patient first visit
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA_{1c}	glycosylated haemoglobin
HDL	high-density lipoprotein
hCG	human chorionic gonadotropin
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LAR	legally acceptable representative
LDL	low-density lipoprotein
LPLV	last patient last visit
LTFU	lost to follow-up
MACE	major adverse cardiovascular events
MALE	major adverse limb events
MEN2	multiple endocrine neoplasia type 2
MI	myocardial infarction
MCI	Mild cognitive impairment
MoCA	Montreal Cognitive Assessment
MR	magnetic resonance
MTC	medullary thyroid cancer

NYHA	New York Heart Association
OD	once daily
PAD	peripheral artery disease
PCD	primary completion date
PCI	percutaneous coronary intervention
PG	plasma glucose
PP	per protocol
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous(-ly)
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
TIA	transient ischemic attack
TMM	trial materials manual
T2D	type 2 diabetes
ULN	upper limit of normal
WOCBP	woman of child bearing potential

Appendix 2 Clinical laboratory tests

- The laboratory analyses will be performed by a central laboratory, unless otherwise specified. A list of laboratory supplies and procedures for obtaining, handling, transportation and storage of samples, will be described in laboratory flow charts/manual and provided to all sites.
- Blood samples need to be obtained. The tests detailed in Table 12-1 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. Such data will not be transferred to the trial database. Brazil: For country specific requirements, please see Appendix 8.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- Ambient laboratory samples will be destroyed shortly after the analyses have taken place.
- Human biosamples for retention will be stored as described in Appendix 7.

Table 12-1 Protocol-required central laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• HbA_{1c}

Renal function	• Creatinine
	• eGFR, calculated per CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)
	• A confirmatory test is needed when
	  • 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 blood samples for the central laboratory for measurement of creatinine
	• Confirmation of a ≥ 50% reduction in eGFR (CKD-EPI) compared with baseline is needed unless a persistent 50% reduction in eGFR compared with baseline, has previously been confirmed for this patient
	• Confirmation of a eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 is needed unless persistent eGFR below < 15 mL/min/1.73 m^2 has previously been confirmed for this patient
	• For the central laboratory calculation of the eGFR information on race (black/white/other) and year of birth will be collected on the laboratory requisition form. 01-Jan of the year of birth will be used for the calculation

Liver parameters	• Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Gamma glutamyltransferase (GGT) • Total bilirubin
Lipids (non-fasting)	• Total cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides
Biobank	• These samples need to be frozen and should be sent at monthly intervals in batches to the central laboratory
Inflammation	• High sensitivity C-Reactive Protein (hsCRP)
Pregnancy testing	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[1]
Notes: [1] Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.	

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[14] and applicable ICH Good Clinical Practice (GCP) Guideline[15]
  - 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 patients.
- Before a trial site is allowed to start screening patients, 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.

Japan, Mexico and Russia: For country specific requirements please see Appendix 8.

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 patient 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 patient ample time to come to a decision whether or not to participate in the trial.
- Patients must be informed that their participation is voluntary.
- Patients will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[15], Declaration of Helsinki[14] 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.
- Patients and/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 patient or the patient's LAR

Brazil: For country specific requirements, please see Appendix 8

4) Information to patients during trial

The site will be offered a communication package for the patient 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 patients. The written information will be translated and adjusted to local requirements and distributed to the patient at the discretion of the investigator. The patient may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further the patient may receive other written information during the trial.

All written information to patients 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

- Patients will be assigned a 6-digit unique identifier, a patient number. Any patient records or datasets that are transferred to Novo Nordisk will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

- The patient and any biological material obtained from the patient will be identified by patient number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of patients as required by local, regional and national requirements.
- The patient 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 patient.
- The patient 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 patients 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 authority to impact trial conduct, trial protocol or amendments.

The purpose of the adjudication is to confirm events in a consistent manner according to standardized criteria using independent external medical experts.

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 diabetes and CV outcomes trials, 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 patient 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.

A chair of the steering committee will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) 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. This includes the right not to release the results of interim testing, because the release of such information may influence the results of the entire trial.

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

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

Authorship

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.[16]

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 patients, 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 patients' 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)[17], the Food and Drug Administration Amendments Act (FDAAA)[18, 19, 20], European Commission Requirements[19, 20] and other relevant recommendations or regulations. If a patient 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 patient. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The trial is event-driven. The Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this trial the last patient last visit (LPLV). The trial will therefore be registered with an estimated PCD corresponding to the estimated LPLV, which is first patient randomised plus 61 months. The PCD determines the deadline for results disclosure at Clinicaltrials.gov according to FDA Amendments Act.

China: For country specific requirements, please see Appendix 8.

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 patient data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data, cognitive testing and patient surveys). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF 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 all sites to be used when access to the electronic CRF is revoked or is unavailable:

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

The following will be provided as paper CRFs, if needed:

- Pregnancy forms
- Other CRFs

In case of the use of paper forms, they need to be forwarded to Novo Nordisk either by fax, encrypted e-mail or courier.

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 patients 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 patient'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 without any delay and the implications of the deviation must be reviewed and discussed.

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

10) Source documents

- All data entered in the CRF must be verifiable in source documentation other than the CRF.
- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the trial site.
- Data reported on the paper CRF or entered in the electronic 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 patient's medical history in source documents such as patient'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 patient 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 patient 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.
- Patient'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 patients 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 patients 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 patients.

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 patient 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 patients to a specific qualified physician who will be readily available to patients 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 said site or investigator are responsible.

Austria, Belgium, France and Mexico: For country specific indemnity statements, please see Appendix 8.

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 patient 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. • Abuse: Persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm) • Misuse: Situations where the medicinal product is intentionally or inappropriately used not in accordance with the protocol • 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.
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 before exposure to trial product. Note: pre-existing conditions should be recorded as medical history/concomitant illness. • Pre-planned procedures, unless the condition for which the procedure was planned has worsened from randomisation.

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

- 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 patient 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) and events for adjudication can be found in Table 9-1

Medication error:

A medication error is an unintended failure in the trial drug treatment process that leads to, or has the potential to lead to, harm to the patient, such as:

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

Treatment pauses are allowed in the trial, this should not to be reported as a medication error.

AE and SAE recording

- All SAEs, AEs leading to discontinuation of trial product, AEs described in Table 9-1 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.
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
- For all non-serious AEs the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE related forms refer to "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 patient, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: Severe is a category used for rating the intensity of an event; and both an AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the outcomes described in the definition of an SAE and not when it is rated as severe

Assessment of causality

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

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

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

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

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

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

The investigator may change his/her opinion of causality in light of follow-up information and 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 patient 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 patient signed the informed consent.
- **Recovering/resolving:** The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial or has died from another AE.
- **Recovered/resolved with sequelae:** The patient 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 patient has not improved and the symptoms are unchanged or the outcome is not known.
- **Fatal:** This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient 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 patient 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 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 patient 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, encrypted e-mail or courier.

- Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting time frames (as illustrated in Figure 9-1):
  - AE form within 24 hours.
  - Safety information form within 5 calendar days.
  - Both forms must be signed within 7 calendar days from the investigators knowledge of the event.
- Contact details for SAE reporting can be found in the investigator trial master file.

Appendix 5 Contraceptive guidance and collection of pregnancy information

It must be recorded in the CRF whether female patients 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. 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 patient's medical records, medical examination or medical history interview.
2. 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 patients
No contraception measures are required for male patients as the risk of teratogenicity/fetotoxicity caused by transfer of semaglutide in seminal fluid is unlikely.

Female patients
Female patients of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly as described in Table 12-2.

Table 12-2 Highly effective contraceptive methods

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 [a and 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 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 patient.
Notes: [a] Failure rates may differ when used consistently and correctly. [b] Contraception should be utilised during the treatment period and for at least 5 weeks 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 known intolerance to the highly effective methods mentioned above or where the use of any listed highly effective contraceptive measures are contraindicated in the individual patient, and/ or
- if the risk of initiating treatment with a specific highly effective method outweigh the predicted benefits of trial participation for the female patient.

Justification for accepting double barrier method should be at the discretion of the investigator. The justification must be stated in the medical records.

Argentina, Belgium, Brazil, Denmark, Thailand and United Kingdom: For country specific requirements, please see Appendix 8.

Pregnancy testing

- Highly sensitive serum testing (sensitivity of 5-25 mIU/mL) is only 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.
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Additional urine pregnancy testing should be performed during the treatment period, if required locally (Appendix 8.).
- Home urine pregnancy testing may be performed between visits during the trial, if additional urine pregnancy testing is required locally.
- WOCBP needs the last pregnancy test at least 5 weeks after the last dose. As the FU visit is a phone contact, the patients can take a urine test at home and inform the investigator of the result.

Austria: For country specific requirements, please see Appendix 8.

Collection of pregnancy information

Female patients who become pregnant

- Investigator will collect pregnancy information on any female patient, 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 patient's pregnancy.
- Patient will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on patient 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.
- 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 patients, he or she may learn of an SAE through spontaneous reporting.
- For abnormal pregnancy outcomes collection of information on the paternal form for male partners of female patients require signing of specific informed consent. Any female patient 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).
- Problems with packaging material including labelling.

Time period for detecting technical complaints
All technical complaints, which occur from the time of receipt of the product at 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 days. If the CRF is unavailable or when reporting a technical complaint that is not patient 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.

Appendix 7 Retention of human biosamples for biomarkers and genetic analyses

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 analyses)
- 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.

Patients may withdraw from the biobank component of the trial at any time, independent of participation in the trial. The patient can chose to do so at any given time while in the trial or after the end of the trial. If a patient 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..

Brazil, China, Columbia, Israel, South Korea and Turkey: For country specific requirements, please see Appendix 8.

Appendix 8 Country-specific requirements

Argentina:

- Section 6.2, exclusion criterion #3 and Appendix 5 as described in Table 12-2: The contraceptive methods and pregnancy tests will be reimbursed by the sponsor. Monthly testing with highly sensitive urine pregnancy tests are required for WOCBP. Use of double contraceptive method is required for WOCBP.
- Section 7.8: 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

Austria:

- Appendix 3: Indemnity statement: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBl. I Nr. 59/2018
- Section 6.2, exclusion criterion #3 and Appendix 5: A monthly pregnancy test (urine) is required for all women of childbearing potential.

Belgium:

- Appendix 3: 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.
- Section 6.2, exclusion criterion #3 and Appendix 5: Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) or vasectomised partner.

Brazil:

- Section 6.2, exclusion criterion #3 and Appendix 5: 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.
- Section 6.2, exclusion criterion #4: Participation in other trials within one year prior to the screening visit (Visit 1) unless there is a direct benefit to the research subject at the investigator's discretion.
- Section 7.7: Novo Nordisk will reimburse costs of standard-of-care treatment for T2D.
- Section 7.8: 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 (according to resolution CNS 466/12).
- Section 9.7, 9.8 and Appendix 7: 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.
- Appendix 2: All laboratory results will be communicated to the investigators.
- Appendix 3, section 3: Two original informed consent forms will be signed and dated and one original will be given to the subject (according to resolution CNS 466/12).

China:

- Section 6.2, exclusion criteria #4: '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 if the last dose of the investigational medicinal product has been received more than 30 days before screening.' is not applicable for China.
- Section 8.1, discontinuation/withdrawal criteria: '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 discretion without discontinuing trial product.' is not applicable for China.
- Section 9.7, 9.8 and Appendix 7: No subjects from China 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.
- Appendix 2: Laboratory samples for Chinese subjects will be destroyed according to local regulatory requirements, both for samples tested inside and outside China. No sample will be stored after the latest date of local regulatory approval.
- Appendix 3: Information of the trial will be disclosed at clinicaltrials.gov, china, drugtrials.org.cn and novonordisk-trials.com as China HA has requested to disclose trial information (phase 1-3) at chinadrugtrials.org.cn since 2013.

Columbia:

- Section 9.7, 9.8 and Appendix 7: 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.

Denmark:

- Section 6.2, exclusion criterion #3 and Appendix 5: Contraceptive measures considered adequate includes intrauterine devices or hormonal contraception (oral contraceptive pills, implants, transdermal patches, vaginal rings or long-acting injections).

France:

- Appendix 3, section 14: Indemnity statement: 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 (according to 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).

Germany:

- Subject's full Date of Birth is not allowed to be collected and must be shortened to year of birth.

Israel:

- Section 9.7, 9.8 and Appendix 7: 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:

- Section 7.5: The head of the study site or the trial product storage manager assigned by the head of the study site (a pharmacist in principle) is responsible for control and accountability of the trial products.
- Section 9.2: Table 9-1: For Japan all AEs, irrespective of seriousness, should be collected from the day of randomisation and until the follow-up visit, at the time points specified in the flowchart. A non-severe non-serious hypoglycaemic episode should be reported as an AE. A severe non-serious hypoglycaemic episode should be reported as an AE and in addition a specific event form (severe hypoglycaemic episode) should be filled out.
- Appendix 3, section 1: A name and seal is accepted as a signature.

Mexico:

- Section 8.2: 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.

- Appendix 3, section 1: 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:
    - Investigation follow-up
    - Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the Subject;
    - Timely compliance of the terms in which the authorization of a research for health in human beings had been issued;
    - To present in a timely manner the information required by the Health Authority.
- Appendix 3, section 14:
    - 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.

Russia:

- Appendix 3, section 1: The trial should be conducted in compliance with the protocol, Ministry of Healthcare of Russian Federation' order #200н from April, 01, 2016 "Approval of rules of good clinical practice" and legal requirements of the Russian Federation regulating circulation of medicines.

South Korea:

- Section 9.7, 9.8 and Appendix 7: No subjects from South Korea 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.

Thailand:

- Section 6.2, exclusion criterion #3 and Appendix 5: Adequate contraceptive measures are: diaphragm, condom (by the partner), intrauterine device in place for last three months before trial starts, sponge, cap with spermicide, contraceptive patch, approved hormonal implant (i.e. Norplant), oral contraceptives taken without difficulty for the last three months before trial starts, post-menopausal state or sterilisation.

Turkey:

- Section 7.7: 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.
- Section 9.7, 9.8 and Appendix 7: 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:

- Section 6.2, exclusion criterion #3 and Appendix 5: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group) guideline: Recommendations related to contraception and pregnancy testing in clinical trials, as listed in Table 12-2: This means use of double barrier methods is not applicable.

Appendix 9 Protocol amendment history

Protocol amendment no. 1 (version 1.0 dated 12 June 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. 1:

People with diabetes have a higher risk for decline in cognitive function and a twofold increased risk for developing dementia compared to people without diabetes. Animal studies and limited clinical data indicate that GLP-1 RA may have an effect on the rate of cognitive decline. A battery of online cognitive testing is introduced to further explore cognitive function and semaglutide's effects on mild cognitive impairment (MCI).

Section # and name	Description of change	Rationale
Section 2 Flowchart	Online cognitive testing included	See overall rationale
Section 4.2.2.3 Exploratory endpoints	Online cognitive testing included	See overall rationale
Section 9.1.4 Cognitive testing, patient surveys and visits to emergency room/urgent care unit	Online cognitive testing included	See overall rationale
Appendix 2	Abbreviation included	See overall rationale

Protocol amendment no. 2 (protocol version 3.0 dated 17 November 2020)

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. 2:

Due to the COVID-19 pandemic the exclusion and discontinuation criteria have been amended to allow for simultaneous participation in trials with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions. In addition, the AE collection has been expanded to include the reporting of non-serious COVID-19 events.

This amendment also addresses statistical considerations, as well as administrative changes.

Section # and name	Description of change	Rationale
Throughout the protocol	All information related to Algeria has been removed	Algeria was not included in the trial
Throughout the protocol	Reference to specific IB edition removed	To ensure that the most current version of the IB is always referred to
Section 2 Flowchart and Section 9 Trial assessments and procedures	Changes to footnote a) Sentence revised	To specify that the investigator needs to ensure that the subject has enough trial product within the expiry date
Section 2 Flowchart	Changes to footnote j) removed X at V3, V4, V5 and V7	To clarify when the patient expectations & experience survey and the patient engagement assessments will take place.
Section 2 Flowchart	Ensure updated contact persons list: added X at V-EOT	To ensure that the contact persons list is updated
Section 4.2.2.2 Supportive secondary endpoints	The two HF endpoints combined into one endpoint: Time from randomisation to heart failure requiring hospitalisation or urgent heart failure visit.	To reflect that it differs across countries when worsening of HF symptoms can be handled during an urgent HF visit or during hospitalisation.
Section 4.2.2.2 Supportive secondary endpoints	Description of endpoints updated to 'Time to first occurrence of acute limb ischemia hospitalisation' and 'Time to first occurrence of chronic limb ischemia hospitalisation'	To reflect the description of the combined MALE endpoint and match the data that we collect for adjudication.
Section 4.2.2.3 Exploratory endpoints	Exploratory endpoints related to the online PROTECT Cognitive Test Battery for mild cognitive impairment updated.	The PROTECT Cognitive Test Battery consists of 6 tests and produces 12 individual data points, which individually do not provide room for a clinically meaningful interpretation. Thus, the exploratory endpoints have been updated to consist of change from randomisation (week 0) to 2 years (visit 12) in 5 distinct and clinically meaningful aspects of cognitive function which can be calculated as composites based on the 12 individual data points.

Section 6.2 Exclusion criteria	Addition to exclusion criterion 4 *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 if the last dose of the investigational medicinal product has been received more than 30 days before screening	To allow for co-participation in COVID-19 trials
Section 7.5 Preparation/Handling/Storage/Accountability	The sentence "..and reconciled by the monitor" removed	To specify the procedure of trial product destruction
Section 7.5 Preparation/Handling/Storage/Accountability	'Patients must return all used, partly used and unused trial products including empty packaging material as instructed by the investigator' changed to 'Patients must ensure that all used, partly used and unused trial products including empty packaging material is returned as instructed by the investigator.'	To allow flexibility in case the patient can't come to the site.
Section 7.7 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 product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator discretion without discontinuing trial product.	To allow for co-participation in a COVID-19 trial

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 and in case of restrictions due to epidemics/pandemics (e.g. COVID-19)
Section 9.2 Adverse events and Figure 9-1	Text regarding COVID-19 AEs included	To describe the inclusion of COVID-19 AEs in the selective data collection approach of this trial
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 in the eCRF
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 10.3.2.1 Confirmatory secondary endpoints	Deleted: 'including tipping point analyses'	To align with the SAP
Section 10.3.2.1 Confirmatory secondary endpoints	Sentence deleted: For the composite CKD endpoint, the analysis will exclude patients who already have met relevant renal components at baseline.	Patients can be followed for other components of the endpoint. To be detailed in SAP.
Section 10.3.2.1 Confirmatory secondary endpoints	Sentence deleted: Furthermore for this endpoint, missing data for eGFR, due to missing blood samples while patients are still being followed, will be imputed using multiple imputation.	To align with the SAP
Section 10.3.3 Exploratory endpoints	Text updated	To reflect the updates of the PROTECT endpoints in the statistical analyses.