Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03819153
Sponsor trial ID:	NN9535-4321
Official title of study:	FLOW – Effect of Semaglutide versus Placebo on the Progression of Renal Impairment in Subjects with Type 2 Diabetes and Chronic Kidney Disease
Document date:	25 January 2021

*Document date refers to the date on which the document was most recently updated.

Protocol

Including:

amendment 1 (Argentina), 2 (Germany) and 3 (India), dated 11 November 2020, protocol version 4.0

amendment 4 (all countries), dated 03 November 2020, protocol version 3.0

amendment 5 (China), dated 25 January 2021, protocol version 5.0

Protocol title: FLOW - Effect of semaglutide versus placebo on the progression of renal impairment in subjects with type 2 diabetes and chronic kidney disease

Substance name: Semaglutide

Universal Trial Number: U1111-1217-6259

EUdraCT Number: 2018-002878-50

Trial phase: 3b

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

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document	Date	Version
Updated protocol including amendment 5 (China)	25 January 2021	5.0
Updated protocol including amendment 1 (Argentina), 2 (Germany), 3 (India)	11 November 2020	4.0 (includes all amendments from 1-4)
Updated protocol including amendment 4 (all countries)	03 November 2020	3.0
Original protocol	07 December 2018	2.0 (version 1.0 was never part of a CTA submission)

Protocol amendment no. 5 (dated 25 January 2021, included in version 5.0)

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]

Co-participation in COVID-19 trials is not allowed in China 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 5	The following change is not applicable for 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	Co-participation in COVID-19 trials is not allowed in China due to local requirements
Appendix 8 Country-specific requirements for China, amendment 5	The following change 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	Co-participation in COVID-19 trials is not allowed in China due to local requirements
Appendix 10 Protocol amendment history, amendment 5	Previous protocol amendments relocate in Appendix 10	To align with internal SOP

Table of Contents

1 Synopsis

Rationale

Chronic kidney disease (CKD) and diabetes often co-exist and for the majority of cases, the kidney damage and/or reduced kidney function is caused directly by longstanding and poorly controlled diabetes. Improved glycaemic control has been suggested to reduce the progression of CKD in type 2 diabetes (T2D) and both glycaemic and blood pressure control are key recommendations in international treatment guidelines for CKD in T2D. Yet there remains a major unmet medical need to improve the treatment of CKD in patients with T2D. The purpose of this trial is to demonstrate that semaglutide subcutaneously (s.c.) delays the progression of renal impairment and lowers the risk of renal and cardiovascular (CV) mortality in subjects with T2D and CKD.

Objectives and endpoints

The primary objective is to demonstrate that semaglutide delays the progression of renal impairment and lowers the risk of renal and cardiovascular mortality compared to placebo, both added to standard-of-care, in subjects with type 2 diabetes and chronic kidney disease.

The key secondary objectives are to compare the effect of treatment with semaglutide versus placebo, both added to standard-of-care in subjects with type 2 diabetes and chronic kidney disease with regards to cardiovascular morbidity, peripheral artery disease, glycaemic control, body weight, blood pressure and safety.

The primary endpoint is time to first occurrence of a composite endpoint consisting of: Onset of persistent ≥ 50% reduction in estimated glomerular filtration rate (eGFR) (CKD-EPI) compared with baseline, onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2, initiation of chronic renal replacement therapy (dialysis or kidney transplantation), renal death, or cardiovascular death.

The key secondary endpoints are annual rate of change in eGFR (CKD-EPI) (total eGFR slope), time to first occurrence of a composite major adverse cardiovascular event (MACE) endpoint (consisting of: non-fatal myocardial infarction, non-fatal stroke, CV death) and all-cause death.

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

Overall design

This is a multi-centre, international, randomised, double-blind, parallel-group, placebo-controlled trial comparing semaglutide 1.0 mg versus placebo both administered s.c. once weekly and added to standard-of-care in subjects with T2D and pre-existing CKD. Subjects will be randomised 1:1 to receive either semaglutide or placebo. Randomisation will be stratified by use of sodium glucose cotransporter-2 (SGLT-2) inhibitors (yes versus no) at baseline. The number of subjects with inclusion eGFR ≥ 60 mL/min/1.73 m^2 will be capped at 20%.

Key inclusion criteria

- Male or female, age ≥ 18 years at the time of signing informed consent. Japan: For country specific requirements, please see Appendix 8.
- Diagnosed with type 2 diabetes mellitus

- $HbA_{1c} \leq 10\%$ (≤ 86 mmol/mol)
- Renal impairment defined either by:
  a) serum creatinine-based eGFR ≥ 50 and ≤ 75 mL/min/1.73 m^2 (CKD-EPI) and UACR > 300 and < 5000 mg/g

or

  b) serum creatinine-based eGFR ≥ 25 and < 50 mL/min/1.73 m^2 (CKD-EPI) and UACR > 100 and < 5000 mg/g
- Treatment with maximum labelled or tolerated dose of a renin-angiotensin-aldosterone system (RAAS) blocking agent including an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), unless such treatment is contraindicated or not tolerated. Treatment dose must be stable for at least 4 weeks prior to the date of the laboratory assessments used for determination of the inclusion criteria for renal impairment and kept stable until screening.

Key exclusion criteria

- Congenital or hereditary kidney diseases including polycystic kidney disease, autoimmune kidney diseases including glomerulonephritis or congenital urinary tract malformations
- Use of any glucagon-like peptide-1 (GLP-1) receptor agonist within 30 days prior to screening
- Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 60 days prior to the day of screening
- Presently classified as being in New York Heart Association (NYHA) Class IV heart failure
- Planned coronary, carotid or peripheral artery revascularisation
- Current (or within 90 days) chronic or intermittent haemodialysis or peritoneal dialysis
- 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

Number of subjects

Approximately 5,400 subjects will be screened to achieve 3,508 subjects randomly assigned to trial product.

Treatment groups and duration

The trial is event driven and includes a pre-defined minimum number of renal endpoint events; therefore, end of trial will be scheduled according to projected trial closure. Trial duration from the first subject visit is expected to be 61 months or more following randomisation of the first subject. Trial duration for each subject is expected to be approximately 3 to 5 years.

The trial products are:

- Active trial product: Semaglutide 1.34 mg/mL, solution for injection.
- Semaglutide placebo, solution for injection.

2 Flowchart

Trial Periods	Protocol Section	Optional pre-screening	Screening	Randomisation	Treatment period First year								Treatment period Remaining years		End of treatment	Follow-up
Physical Visit (V)/ Phone (P)		V	V	V	P	P	V	V	V	V	P	V	V/P	V	V	V
Visit number		0	1	2	3	4	5	6	7	8	9	10	P11/V12/P13/ P15/V16/P17/ P19/V20/P21/ P23/V24/P25	V14 V18 V22 V26	V-EOT	V-FU
Timing of visit (weeks)		Before V1	-3 weeks to -3 days	0	1	2	4	8	12	26	39	52	Every 13 weeks[k]	Yearly	EOT	EOT +5 weeks
Visit window (days)					±3	±3	±3	±3	±7	±7	±7	±7	±10	±7	±7	+7
SUBJECT RELATED INFO/ ASSESSMENTS																
Informed consent	Appendix 3	X[a]	X													
In/exclusion criteria	6.1; 6.2		X	X												
Randomisation	7.3			X												
Medical history	9.5			X												
Concomitant medication	7.7		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Creatinine values from medical records	9.2.2				X	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	X	X	X	
Hand out directions for use and training in trial product, injection technique and pen handling[b]	7.1			X			X			X				X		
Hand out and instruct in BG Meter	9.2.1			X												
Demography[c]			X													
Tobacco use[d]			X											X	X	

Trial Periods	Protocol Section	Optional pre-screening	Screening	Randomisation	Treatment period First year								Treatment period Remaining years		End of treatment	Follow-up
Physical Visit (V)/ Phone (P)		V	V	V	P	P	V	V	V	V	P	V	V/P	V	V	V
Visit number		0	1	2	3	4	5	6	7	8	9	10	P11/V12/P13/ P15/V16/P17/ P19/V20/P21/ P23/V24/P25	V14 V18 V22 V26	V-EOT	V-FU
Timing of visit (weeks)		Before V1	-3 weeks to -3 days	0	1	2	4	8	12	26	39	52	Every 13 weeks[k]	Yearly	EOT	EOT +5 weeks
Visit window (days)					±3	±3	±3	±3	±7	±7	±7	±7	±10	±7	±7	+7
CLINICAL ASSESSMENTS																
Height	9.5.1			X												
Body weight	9.5.1			X					X			X		X	X	X
Blood pressure and pulse	9.5.2		X	X					X			X		X	X	X
Eye examination	9.5.3		X									X		X	X	
EQ-5D-5L questionnaire	9.2.3			X								X		X	X	
Physical examination	9.5.1			X											X	
Adverse events (AEs)	9.3				X	X	X	X	X	X	X	X	X	X	X	X
Severe hypoglycaemic episodes	Table 9-1				X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS																
HbA_{1c}	Appendix 2	X[e]	X	X					X	X		X	X[f]	X	X	X
Creatinine (eGFR)	9.2.2; Appendix 2	X[e]	X	X			X		X	X		X	X[f]	X	X	X
Urinary albumin-to-creatinine ratio (UACR)[g]	Appendix 2	X[e]	X	X			X		X	X		X	X[f]	X	X	X
Biochemistry	Appendix 2		X						X			X		X	X	
Cystatin C	Appendix 2			X					X			X		X[h]		
hsCRP	Appendix 2			X					X			X		X[i]		

Trial Periods	Protocol Section	Optional pre-screening	Screening	Randomisation	Treatment period First year								Treatment period Remaining years		End of treatment	Follow-up
Physical Visit (V)/ Phone (P)		V	V	V	P	P	V	V	V	V	P	V	V/P	V	V	V
Visit number		0	1	2	3	4	5	6	7	8	9	10	P11/V12/P13/ P15/V16/P17/ P19/V20/P21/ P23/V24/P25	V14 V18 V22 V26	V-EOT	V-FU
Timing of visit (weeks)		Before V1	-3 weeks to -3 days	0	1	2	4	8	12	26	39	52	Every 13 weeks[k]	Yearly	EOT	EOT +5 weeks
Visit window (days)					±3	±3	±3	±3	±7	±7	±7	±7	±10	±7	±7	+7
Biosamples for future analysis (biobank, biomarkers)	9.9 Appendix 7			X					X			X		X[i]		
Urine pregnancy test[j]	Appendix 2 Appendix 5		X	X											X	X
TRIAL MATERIAL																
IWRS session			X	X			X	X	X	X		X	X[f]	X	X	
Dispensing visit				X			X	X	X	X		X	X[f]	X		
Drug accountability	7.5			X			X	X	X	X		X	X[f]	X	X	
Subject contact information check	9				X	X	X	X	X	X	X	X	X	X	X	

[a] A separate informed consent is needed for pre-screening (V0), see protocol Section 9.1.

[b] Directions for use must be handed out and subjects must be trained in trial product, injection technique and pen handling at randomisation (V2) and thereafter as indicated in the flowchart and as needed during the trial.

[c] Demography consists of date of birth, sex and race (according to local regulation).

[d] Smoking is defined as smoking at least one cigarette or equivalent daily.

[e] Urine and blood samples obtained during pre-screening (V0) must be analysed locally, see Section 9.1.

[f] Only at site visits.

[g] For all applicable visits, except for the screening visit (V1), subjects will be asked to collect first morning urine sample on the day prior to the visit as well as on the day of the visit and bring the samples to the site

[h] Only at year 2 and 3 (week 104 and 156)

[i] Only at year 3 (week 156)

[j] Only applicable for women of childbearing potential; urine HCG.

[k] The yearly visits should take place approximately 13 weeks after the previous visit

2.1 Flowchart explanatory descriptions

As individual follow up time will differ depending on enrolment date, visits in the treatment maintenance period will be added or removed depending on time of randomisation and trial closure timing.

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

Chronic kidney disease (CKD) and diabetes often co-exist and for the majority of cases the kidney damage and/or reduced kidney function is caused directly by longstanding and poorly controlled diabetes. Up to 40% of patients with type 2 diabetes (T2D) have some degree of CKD, and diabetes is the single leading cause of end-stage renal disease (ESRD) requiring chronic dialysis treatment or kidney transplantation.[2] Improved glycaemic control has been suggested to reduce the development and progression of CKD in T2D[3, 4] and both glycaemic and blood pressure control are key recommendations in international treatment guidelines for CKD in T2D.[5] Blocking the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting-enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARBs) for the treatment of CKD in patients with T2D and increased levels of albuminuria is recommended as first-line therapy and some of the RAAS blocking agents (irbesartan[6], losartan[7] and captopril[8]) have a labelled indication for the treatment of CKD in diabetes.[5] However, up to 70% of the patients with T2D and CKD experience continued deterioration of the kidney function despite RAAS blocker treatment.[9-11] Hence, there is a major unmet medical need to improve the treatment of CKD in patients with T2D, thereby reducing the risk of developing ESRD. The aim of the current trial is to demonstrate that treatment with once weekly semaglutide subcutaneously (s.c.) delays the progression of renal impairment and lowers the risk of renal and cardiovascular mortality in subjects with T2D and CKD.

3.2 Background

Recently conducted clinical trials with the glucagon-like peptide-1 (GLP-1) receptor agonists semaglutide, liraglutide, dulaglutide, and exenatide have suggested a possible renoprotective effect in patients with T2D, CKD and high cardiovascular (CV) risk.[12-16] A similar beneficial effect on new or worsening nephropathy in patients with T2D and established or high risk for CV disease has also been suggested[17-19] in another class of glucose lowering drugs; the sodium glucose cotransporter-2 (SGLT-2) inhibitors, and dedicated renal outcomes trials are currently running or have been announced for empagliflozin[20] and dapagliflozin (ClinicalTrials.gov Identifier: NCT03036150). In addition, the CREDENCE renal outcomes trial with canagliflozin (ClinicalTrials.gov Identifier: NCT02065791) was stopped early based on the achievement of pre-specified efficacy criteria at a pre-planned interim analysis.

The current trial will include subjects with T2D and established CKD defined by increased urinary albumin-to-creatinine ratio (UACR) and reduced estimated glomerular filtration rate (eGFR). These enrichment criteria are selected as reduced eGFR and increased UACR have been shown to be independent risk factors for progression of renal impairment and development of ESRD.[21] Thus, a population of subjects with T2D and primarily moderate CKD and increased UACR is considered 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. The number of subjects with inclusion eGFR values in the high end of the eGFR range, i.e. eGFR $\geq$ 60 mL/min/1.73 m^2, will be capped at 20% to ensure a sufficient event rate for the primary endpoint, as the event rate is expected to be lower in these subjects.

The inclusion and exclusion criteria in this study have been selected to capture a study population with an increased risk for progression of renal impairment and therefore most patients should have severely increased albuminuria at enrolment. Communications to sites may be used over the course of the recruitment period to focus recruitment efforts on patients with high risk for CKD progression without restricting the enrolment of any eligible subgroups.

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

3.3 Benefit-risk assessment

3.3.1 Benefits related to semaglutide

In clinical trials semaglutide has provided superior long-term glycaemic control in T2D patients and clinically relevant reductions in body weight as compared to commonly used marketed glucose lowering products and to placebo. The CV outcome trial SUSTAIN 6 established the CV safety of semaglutide and reported a clinically relevant CV risk reduction with semaglutide compared to placebo when added to standard-of-care.[13]

During the current trial, all subjects will be treated within a regimen anticipated to be better than or equal to the treatment they receive at the time of entry into the trial. It is expected that all subjects will benefit from participation through frequent, close contact with investigators and other site staff who will ensure that subjects are treated according to recommended standard-of-care for T2D, CKD and CV risk management, and disease development and progression will be closely monitored and treated. To ensure all subjects, including those receiving placebo, have adequate glycaemic control, investigators are encouraged to optimise treatment with anti-hyperglycaemic medications (GLP-1 receptor agonists excluded) throughout the trial in accordance with local clinical practice. All subjects in this trial will receive trial product and auxiliary supplies free of charge.

3.3.2 Risks related to semaglutide

Identified risks
Based on the clinical development programme a causal relationship with semaglutide was suggested for the following risks:

Gastrointestinal disorders: For semaglutide as for other GLP-1 receptor agonists, the most frequently reported adverse reactions in clinical trials were gastrointestinal (GI) disorders, including nausea, diarrhoea and vomiting. In general, these reactions were mild or moderate in severity and of short duration. A dose dependency has been observed for most of the GI disorders. Clinical trials have shown that a low starting dose and gradual dose escalation mitigates the risk of GI adverse events (AEs).

In patients treated with GLP-1 receptor agonists, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating patients with impaired renal function as it may lead to further deterioration of renal function. Subjects with GI AEs are recommended to drink plenty of fluids, unless medically contraindicated, to avoid volume depletion.

Hypoglycaemia: 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 semaglutide.

Diabetic retinopathy complications: Adjudicated events of diabetic retinopathy complications occurred in more patients treated with semaglutide (3.0%) when compared to placebo (1.8%) in a 2-year clinical trial involving 3,297 subjects with T2D and high CV risk, long duration of diabetes and poor glycaemic control. Diabetic retinopathy complications were a composite of: need for retinal photocoagulation, need for treatment with intravitreal agents, vitreous haemorrhage and onset of diabetes-related blindness. The absolute risk increase for diabetic retinopathy complications was greatest among patients with a history of diabetic retinopathy at baseline. In patients who did not have a documented history of diabetic retinopathy, the number of events was similar for semaglutide and placebo.

In other clinical trials of up to 1 year duration involving 4,807 subjects with T2D, AEs related to diabetic retinopathy were distributed similarly between subjects treated with semaglutide (1.7%) and comparators (2.0%).

Rapid improvement in glycaemic control, for example with insulin, has been associated with a temporary worsening of diabetic retinopathy. Long-term sufficient glycaemic control decreases the risk of diabetic retinopathy. Subjects with a history of diabetic retinopathy should be monitored for worsening and treated according to clinical guidelines.

Other risks: Patients treated with semaglutide may also experience cholelithiasis, decreased appetite, dizziness, dysgeusia, fatigue, increased heart rate, increased lipase and amylase, injection site reactions and weight decrease.

Potential risks
A possible association with semaglutide has been suspected for the following risks, although the relationship has not yet been confirmed:

Allergic reactions: As in the case with all protein-based pharmaceuticals, treatment with semaglutide may evoke allergic reactions, including serious allergic reactions such as anaphylactic reactions.

Acute pancreatitis: Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis and if pancreatitis is suspected, semaglutide should be discontinued. If confirmed, semaglutide should not be restarted.

Malignant neoplasms: Based on available data, there is no indication of a causal relationship between semaglutide and malignant neoplasms. However, it is not possible to draw any firm conclusions due to very low numbers.

Pancreatic cancer: Patients with T2D have an increased risk of certain types of cancer such as pancreatic cancer. In the development programme, rates of pancreatic cancer were low and do not support a causal association with semaglutide. Furthermore, no safety concerns related to

the pancreas were identified in the nonclinical programme with semaglutide. Pancreatic cancer has however, been classified as a potential class risk for all marketed GLP-1 receptor agonists by regulatory agencies.

Medullary thyroid cancer: Thyroid C-cell tumours were seen in mice and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. No C-cell tumours were observed in monkeys after 52 weeks of exposure up to 27-fold above the clinical plasma exposure at 1.0 mg/week. The GLP-1 receptor is not expressed in the normal human thyroid and the risk of GLP-1 receptor-mediated C-cell changes in humans is considered to be low.

Other safety considerations

Drug interactions: Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. The potential effect of semaglutide on the absorption of co-administered oral medications was studied in trials at semaglutide 1 mg/week steady state exposure. No clinically relevant drug-drug interactions with semaglutide were observed based on the evaluated medications.

Semaglutide did not change the overall pharmacodynamics of warfarin as measured by the international normalised ratio (INR). However, upon initiation of semaglutide treatment in patients on warfarin and/or coumarin derivatives, frequent monitoring of INR is recommended.

Pregnancy, lactation and fertility: Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a subject wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued, see Appendix 5 for details. In lactating rats, semaglutide was excreted in milk. As a risk to a breast-fed child cannot be excluded, semaglutide should not be used during breast-feeding.

The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats. In female rats, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss.

3.3.3 Risk-benefit conclusion

Data from the development programme for semaglutide has not revealed any safety issues that would outweigh the benefits of participation in this trial. The trial population will consist of T2D subjects with CKD. Assessment of diabetes and CKD and appropriate attention to the standard-of-care treatment will be provided throughout the trial. It is therefore concluded that the potential benefits from trial participation will outweigh the potential risks for the semaglutide as well as the placebo treated subjects.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of semaglutide may be found in the Investigator's Brochure.

4 Objectives and endpoints

4.1 Primary, secondary and exploratory objectives

Primary objective
To demonstrate that semaglutide delays the progression of renal impairment and lowers the risk of renal and cardiovascular mortality compared to placebo, both added to standard-of-care, in subjects with type 2 diabetes and chronic kidney disease.

Secondary objectives
To compare the effect of treatment with semaglutide versus placebo, both added to standard-of-care in subjects with type 2 diabetes and chronic kidney disease with regards to: Cardiovascular morbidity, peripheral artery disease, glycaemic control, body weight, blood pressure and safety.

Exploratory objective
To compare the effect of treatment with semaglutide versus placebo, both added to standard-of-care in subjects with type 2 diabetes and chronic kidney disease with regards to: Patient reported outcomes (PROs).

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

4.2 Primary, secondary and exploratory endpoints

Primary, secondary and exploratory endpoints are listed in Figure 4-1. All event-based endpoints are assessed from randomisation until end-of-trial.

Figure 4-1 Primary, secondary and exploratory endpoints

Endpoint title	Time frame	Unit
4.2.1 Primary endpoint		
Time to first occurrence of a composite endpoint consisting of: • Onset of persistent ≥ 50% reduction in eGFR (CKD-EPI) compared with baseline • Onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 • Initiation of chronic renal replacement therapy (dialysis or kidney transplantation) • Renal death • CV death	From randomisation (week 0) to end-of-trial (up to 61 months or more)[a]	Month(s)
4.2.2 Secondary endpoints		
4.2.2.1 Confirmatory secondary endpoints		

Annual rate of change in eGFR (CKD-EPI) (total eGFR slope)	From randomisation (week 0) to end-of-trial (up to 61 months or more)[a]	(mL/min/1.73 m^2)/year
Time to first occurrence of a composite cardiovascular MACE endpoint consisting of: • Non-fatal myocardial infarction • Non-fatal stroke • CV death	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)
4.2.2.2 Supportive secondary endpoints		
Time to occurrence of each of the individual components of the primary composite endpoint and of the confirmatory secondary MACE endpoint	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)
Annual rate of change in eGFR (CKD-EPI) (chronic eGFR slope)	From week 12 to end-of-trial (up to 61 months or more)[a]	(mL/min/1.73 m^2)/year
Change in eGFR (CKD-EPI)	From randomisation (week 0) to week 12	mL/min/1.73 m^2
Change in eGFR (cystatin C CKD-EPI)	From randomisation (week 0) to year 3	mL/min/1.73 m^2
Relative change in UACR	From randomisation (week 0) to year 3	Percentage
Change in body weight	From randomisation (week 0) to year 3	Kilogram
Change in glycosylated haemoglobin (HbA_{1c})	From randomisation (week 0) to year 3	Percentage point
Change in systolic blood pressure	From randomisation (week 0) to year 3	mmHg
Change in diastolic blood pressure	From randomisation (week 0) to year 3	mmHg
Number of severe hypoglycaemic episodes[22, 23]	From randomisation (week 0) to end-of-trial (up to 61 months or more)[a]	Number of events
4.2.3 Exploratory endpoints		
Change in EQ-5D-5L index score	From randomisation (week 0) to year 3	Index score (0-1)
Change in EQ-5D-5L visual analogue scale score	From randomisation (week 0) to year 3	Visual analogue scale (0-100)

[a] End-of-trial: a period expected to be up to 61 months or more for the individual subject. Abbreviations: CKD-EPI, chronic kidney disease - epidemiology collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EQ-5D-5L, five-level version of the EuroQol five-dimensional questionnaire; MACE, major adverse cardiovascular event; UACR, urinary albumin-to-creatinine ratio.

Definition of terms

When classifying chronic renal replacement therapy or kidney transplantation, the date of event should be the date of initiation of the therapy or surgery, respectively. The baseline for eGFR is defined as the mean of the two assessments from the screening visit (V1) and the randomisation visit (V2).

eGFR will be calculated using the chronic kidney disease – epidemiology collaboration (CKD-EPI) formula.[24] Sustained kidney failure is defined as persistent eGFR < 15 mL/min/1.73 m^2 or initiation of chronic renal replacement therapy. For the eGFR components of the primary endpoint, a persistent outcome in eGFR is defined as having two consecutive central laboratory assessments at least 4 weeks apart meeting the criteria. When classifying the events based on consecutive laboratory assessments, the date of the event should be the date of the first sample meeting the definition.

5 Trial design

5.1 Overall design

This is a multi-centre, international, randomised, double-blind, parallel-group, placebo-controlled trial comparing semaglutide 1.0 mg versus placebo both administered s.c. once weekly (subsequently referred to as semaglutide and placebo) and added to standard-of-care in subjects with T2D and pre-existing CKD. Subjects will be randomised 1:1 to receive either semaglutide or placebo. Randomisation will be stratified by SGLT-2 inhibitor use at baseline (yes versus no). The number of subjects with inclusion eGFR ≥ 60 mL/min/1.73 m^2 will be capped at 20%.

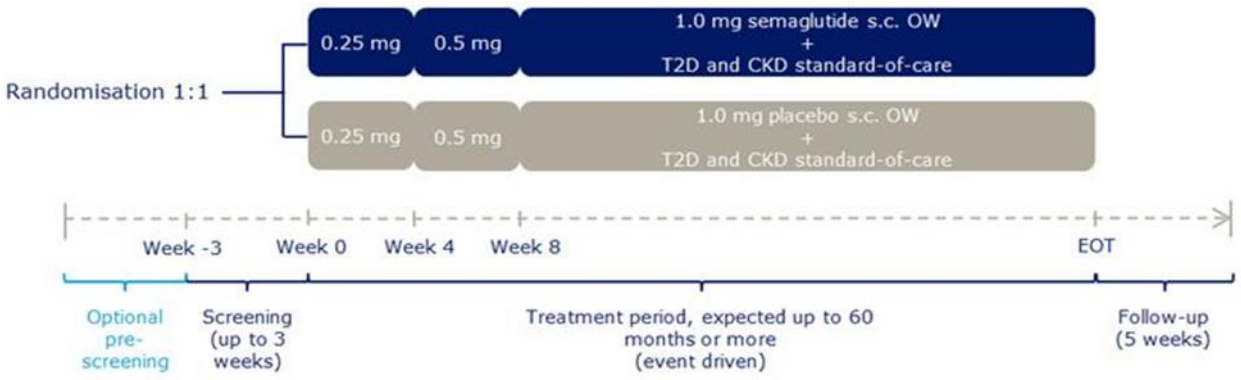
The trial is event driven with a pre-defined minimum number of renal endpoint events (all components of the primary composite endpoint except CV death) for the primary endpoint. The trial will employ a group sequential design and interim testing for efficacy will be performed by an independent external Data Monitoring Committee (DMC). The DMC will provide recommendation on trial continuation, modification or termination. The observed number and type of confirmed primary endpoint events will be monitored throughout the trial. If the trial is not stopped for efficacy at a planned interim testing the trial will be terminated when both of the following criteria are fulfilled:

- A minimum of 854 primary endpoint events
- A minimum of 515 primary renal endpoint events

The follow-up period after end of treatment is 5 weeks for all subjects.

A schematic overview of the trial design is shown in Figure 5-1.

Figure 5-1 Trial design diagram



5.2 Subject and trial completion

Approximately 5,400 subjects will be screened to achieve 3,508 subjects randomly assigned to trial product. For a description of screen failures see Section 6.4. The recruitment period is expected to be 21 months. Subjects will be followed for the complete duration of the trial and extensive efforts will be made to collect data for all randomised subjects.

Trial period completion for a subject

Trial period completion is defined as:

- when the randomised subject has completed the final scheduled visit (follow-up visit according to the flowchart).

or

- when the randomised subject has died during trial.

Treatment period completion for a subject

Treatment period completion is defined as when the randomised subject has received the required treatment and attended the end of treatment visit, according to the flowchart.

The trial is event driven; therefore, end of treatment and follow-up visit will be scheduled according to projected trial closure. When the trial is approaching the end investigators will be notified and instructed by Novo Nordisk regarding the visit schedules for their subjects.

When the trial comes to an end, the investigator must make every effort to ascertain efficacy and safety endpoint data for all subjects. This should be done by direct contact with the subject whenever possible. If a subject proves difficult to reach for the follow-up visit, all attempts to re-establish direct contact must be made (see section 8.3). In case several attempts are required to establish direct contact to a subject, exceeding the visit window of the follow-up visit may be needed. In order for the data set to be as complete as possible, end of trial follow-up information can be collected until the randomisation codes are broken. If allowed by local regulations, publically available data sources may also be searched for withdrawn subjects in order to determine their vital status.

5.3 End of trial definition

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

5.4 Scientific rationale for trial design

To ensure robust evaluation the trial is randomised, double-blinded and placebo-controlled. Blinded treatment with semaglutide or placebo offers a robust method for assessment of the effects of semaglutide. A broad spectrum of concomitant anti-hyperglycaemic medication, as well as treatments for comorbidities, CKD 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 treatments: one where semaglutide is available and another where it is not.

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

5.5 Justification for dose

In order to lower the risk of gastrointestinal AEs, a dose-escalation regimen is included. The dose of 1.0 mg per week has been tested for glycaemic control in patients with T2D in a comprehensive phase 3a programme and shown to have a positive benefit risk profile. Further, the benefit risk profile for the 1.0 mg dose was evaluated to be favourable over the 0.5 mg dose with lower proportions of subjects having a renal event in SUSTAIN 6. For information regarding dose modifications, see Section 7.2.

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

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial, except for protocol described pre-screening activities which require a separate informed consent.
2. Male or female, age above or equal to 18 years at the time of signing informed consent. Japan: For country specific requirements, please see Appendix 8.
3. Diagnosed with type 2 diabetes mellitus.
4. $HbA_{1c} \leq 10\%$ (≤ 86 mmol/mol)*.
5. Renal impairment defined either by:
    a. serum creatinine-based eGFR ≥ 50 and ≤ 75 mL/min/1.73 m^2 (CKD-EPI)*, ** *and* UACR > 300 and < 5000 mg/g.*

    or

    b. serum creatinine-based eGFR ≥ 25 and < 50 mL/min/1.73 m^2(CKD-EPI)* a*nd* UACR > 100 and < 5000 mg/g.*
6. Treatment with maximum labelled or tolerated dose of a renin-angiotensin-aldosterone system (RAAS) blocking agent including an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), unless such treatment is contraindicated or not tolerated. Treatment dose must be stable for at least 4 weeks prior to the date of the laboratory assessments used for determination of inclusion criterion 5 and kept stable until screening.

* Laboratory results for inclusion can be based on:

- measurements no more than 90 days old at screening, documented in medical records *or*
- measurements from the optional pre-screening visit (see Section 9.1), documented in medical records *or*
- central laboratory measurement obtained at the screening visit

The subject must have been/be in usual health condition at the time of sample collection used for inclusion as evaluated by the investigator and treated with a RAAS blocking agent, according to inclusion criterion 6. See Appendix 2 for all requirements regarding clinical laboratory tests.

** The number of subjects with inclusion eGFR ≥ 60 mL/min/1.73 m^2 will be capped at 20% of randomised subjects.

6.2 Exclusion criteria

Subjects are excluded from the trial if any of the following criteria apply:

1. Known or suspected hypersensitivity to trial product(s) 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 (see Appendix 5).
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening*. Brazil: For country specific requirements, please see Appendix 8.
5. Any disorder, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
6. Congenital or hereditary kidney diseases including polycystic kidney disease, autoimmune kidney diseases including glomerulonephritis or congenital urinary tract malformations.
7. Use of any GLP-1 receptor agonist within 30 days prior to screening.
8. Personal or first degree relative(s) history of multiple endocrine neoplasia type 2 (MEN2) or medullary thyroid carcinoma (MTC).
9. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 60 days prior to the day of screening.
10. Presently classified as being in New York Heart Association (NYHA) Class IV heart failure.
11. Planned coronary, carotid or peripheral artery revascularisation.
12. Current (or within 90 days) chronic or intermittent haemodialysis or peritoneal dialysis.
13. 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.
14. 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* are allowed.
15. A prior solid organ transplant or awaiting solid organ transplant.
16. Combination use of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin II receptor blocker (ARB).

*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.

6.3 Lifestyle restrictions

Not applicable for this trial.

6.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial, but are not eligible for participation according to in/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria. A screen failure session must be made in the IWRS for subjects who are not randomised.

Re-screening of previous screen failures is allowed twice in case the investigator assesses that potential changeable or fluctuating in- or exclusion criteria may have changed (e.g. biochemical parameters (eGFR, UACR and HbA_{1c}) or change in concomitant medication). Previously

randomised subjects cannot be re-screened. In case of re-screening a new subject number must be assigned in the IWRS.

6.5 Randomisation criteria

Not applicable for this trial.

7 Treatments

7.1 Treatments administered

All trial products listed in Table 7-1 are considered investigational medicinal products (IMPs). The trial products are visually identical and must only be used, if it appears clear and colourless.

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

Trial product name	Semaglutide 1.34 mg/ml	Semaglutide placebo
Dosage form	solution for injection	solution for injection
Route of administration	Subcutaneous	Subcutaneous
Recommended dosing	Refer to Section 7.2	Refer to Section 7.2
Dosing instructions	Once weekly	Once weekly
Packaging	1.5 ml pre-filled PDS290 pen-injector	1.5 mL pre-filled PDS290 pen-injector

All baseline assessments must be done prior to administration of the first dose of trial product. Subjects will be instructed to inject the trial product s.c. once weekly in the abdomen, thigh, or upper arm. The injection site can be changed without dose adjustment. The subjects must be trained in handling the pen-injector when dispensed the first time and thereafter as indicated in the flowchart and as needed during the trial. The investigator may choose to observe the subject when administering the first dose. The investigator must document that directions for use are given to the subject orally and in writing at the first dispensing visit and thereafter as needed during the trial. The subject must be advised to discard the injection needle after each injection and store the pen-injector without an injection needle attached. Needles to be used with the trial product must be provided throughout the trial as needed. Only needles provided by Novo Nordisk must be used for administration of trial product.

The injection can be administered at any time of the day irrespective of meals, but on the same day of the week. The day of weekly administration can be changed if necessary as long as the time between two doses is at least 2 days (>48 hours) or in accordance with the local label. After selecting a new dosing day, once weekly dosing should be continued.

Auxiliary supplies are provided by Novo Nordisk:

- needles for the PDS290 pen-injector (4-5 mm needles, 32 G)
- directions for use (DFU) for the prefilled PDS290 pen-injector
- blood glucose (BG) meters including lancets, test strips, control solutions and instructions for use

7.1.1 Medical devices

Detailed information about the pre-filled PDS290 pen-injector is available in the current edition and any updates of the Investigator's Brochure. Information about the use of the PDS290 pen-injector for semaglutide and placebo can be found in the DFU.

7.2 Dose modification

Subjects will initiate treatment with 0.25 mg semaglutide/placebo at randomisation. Following 4 weeks of treatment, the dose will be escalated to 0.5 mg and maintained for another 4 weeks until

escalating to the target dose of 1 mg semaglutide/placebo as shown in Table 7-2. The 4 week dose-escalation intervals are applied in order to lower the risk of GI AEs. Subjects should remain on the 1 mg dose level throughout the maintenance period. If treatment with the trial product is associated with unacceptable AEs, extensions of dose-escalation intervals, dose reductions, and treatment pauses are allowed at the discretion of the investigator.

Table 7-2 Trial periods and treatment groups

Trial periods		Screening	Dose 1	Dose 2	Maintenance	Follow-up
Duration of each period		Up to 3 weeks	4 weeks (V2 toV5)	4 weeks (V5 up to V6)	According to trial length (V6 to V-EOT)	5 weeks (V-EOT to V-FU)
Treatment	N					
Semaglutide s.c. OW	1,580	-	0.25 mg	0.50 mg	1.0 mg	Follow-up
Placebo s.c. OW	1,580	-	0.25 mg	0.50 mg	1.0 mg	Follow-up

N: number of subjects, OW: once weekly, s.c.: subcutaneous.

If trial product is discontinued, subjects 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 Missed doses

If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day. In each case, subject can then resume their regular once weekly dosing schedule. If multiple (two or more) consecutive doses are missed, continuation of trial product should be encouraged if considered safe as per the investigator's discretion. Previous dose and GI adverse reactions as well as number of missed doses should be taken into consideration when evaluating whether to repeat the dose escalation.

7.3 Method of treatment assignment

All subjects will be centrally randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed at the trial visits summarised in the flowchart, Section 1. Randomisation will be stratified by SGLT-2 inhibitor use at baseline (yes versus no).

At screening (V1), each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. Each site is assigned a 3-digit number and all subject numbers will start with the site number.

7.4 Blinding

The active drug and placebo drug are visually identical.

The IWRS is used for blind-breaking instructions. The blind may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Novo Nordisk will be

notified immediately after breaking the blind. The date when and reason why the blind was broken must be recorded in the source documentation. Whenever the blind is broken, the person breaking the blind must print the "code break confirmation" notification generated by the IWRS, record the reason and sign and date the document. Treatment with trial product can be resumed if there are no safety concerns at the discretion of the investigator.

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 subjects enrolled in the trial may receive trial product and only authorised site staff may supply or administer trial product. 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 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. For the storage and in-use conditions see the trial materials manual (TMM) and the labels of trial product. The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the TMM. Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk.

Subjects must return all used, partly used and unused trial products 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 must be performed in the IWRS by registering pen-injectors as returned either as used/partly used, unused or as lost.

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

In case local restrictions due to epidemic/pandemic lead to lockdown of a site, alternative ways of dispensing may be used if permitted by local regulations (see Appendix 9 for further details).

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

7.6 Treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant the investigator will remind the subject of the importance of following the instructions including taking the trial products as prescribed. Additionally, reporting of changes in the dose taken and monitoring of drug accountability will support documentation of treatment compliance.

7.7 Concomitant medication

Semaglutide/placebo will be added on top of standard-of-care treatment. Changes to standard-of-care medications will be allowed during trial conduct to optimise recommended standard-of-care. Initiating GLP-1 receptor agonists is not allowed during the entire trial. Additional CV and anti-hyperglycaemic medications, excluding GLP-1 receptor agonists, may be added or changed during the trial in both treatment groups at the discretion of the investigator and in accordance with local treatment guidelines. Investigators will be encouraged to optimise standard-of-care treatment for T2D, CKD, and CV risk management according to local treatment practice. Recommendations for this will be provided in guidance documents during trial conduct.
At screening subjects are required to be treated with a stable maximum labelled or tolerated dose of a RAAS blocking agent (an ACE inhibitor or an ARB) as standard-of-care treatment for CKD in T2D. The maximum labelled dose will be assessed by the investigator in accordance with local label and guidelines. If the subject is not treated with a RAAS blocking agent, previous treatment attempt must be documented in medical records and that this has led to intolerance or unacceptable side effects. If intolerance for an ACE-inhibitor is documented, due to cough, a treatment attempt with an ARB must have been made. If a subject is treated with the maximum tolerated dose but not the maximum labelled dose of the RAAS blocking agent a previous dose escalation attempt is not a requirement, but the reason why the subject is not expected to tolerate a higher dose must be documented in the medical records.
Anti-hyperglycaemic and CKD standard-of-care treatment is considered background treatment and will not be provided by Novo Nordisk A/S.
For randomised subjects the following medication(s) other than the trial product that the subject is receiving at the time of screening (V1) or receives during the trial must be recorded in the electronic case report form (eCRF):

- medication to treat T2D
- medication to treat CKD
- medication to treat or prevent CV disease
- medication administered in relation to AEs listed in Section 9.3
- medication administered in relation to a clinical trial for COVID-19 prevention or treatment
- an approved COVID-19 vaccine

The medication must be recorded in the eCRF along with start date and stop date or continuation and related AE number when applicable. For anti-hyperglycaemic medication and for RAAS blocking agents (ACE inhibitors and ARBs), the total daily dose needs to be included in the eCRF. Stable dose changes (2 weeks or more) should be captured as a new concomitant medication with the new dose and relevant start and stop date.

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE or serious adverse event (SAE), then this must be reported according to Section 9.3.

7.8 Treatment after the end of the trial

When discontinuing trial product at the end of treatment visit, the subject should be transferred to a suitable marketed product at the discretion of the investigator. Considering the long half-life of semaglutide and to avoid over-exposure to GLP-1 receptor agonists and interference with safety data collection, initiating GLP-1 receptor agonists should be avoided between the end of treatment visit and the follow-up visit. All other medications are allowed.
Brazil: For country specific requirements, please see Appendix 8.

8 Discontinuation/Withdrawal criteria

8.1 Discontinuation of trial treatment

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

The subject must be discontinued from trial product, if 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 must be discontinued; and if confirmed, trial product must not be restarted
5. Treatment with another GLP-1 receptor agonist
6. Other safety concerns

*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 3: With the exception of an approved or non-approved investigational product for prevention or treatment of COVID-19, subjects must not receive an investigational product from another clinical trial. If done, treatment with trial product must be discontinued. If the use of investigational medical product in the other trial is discontinued, treatment with trial product can be resumed if there are no safety concerns at the discretion of the investigator.

For subjects who are discontinued for any reason, a Novo Nordisk medical expert should be consulted to determine in collaboration with the investigator, whether the discontinuation will be permanent or temporary (see Section 8.1.1). For some events, when the circumstances have changed and/or there are no longer safety concerns, treatment with trial product may be continued or resumed at the discretion of the investigator and in agreement with the Novo Nordisk medical expert. If a subject becomes pregnant during the trial, the trial product must be discontinued immediately and must not be re-initiated until breast feeding, if performed, has stopped. If a subject intends to become pregnant, the trial product must be discontinued at least 5 weeks prior to the planned intention (Appendix 5).

If a trial product is discontinued, the subject should continue to follow the trial schedule without being withdrawn from the trial and encouraged to attend the site for at least the end of treatment and follow-up visits in order to collect the required data for the analysis of the primary (and confirmatory secondary) endpoints. Subjects must be educated about the continued scientific importance of their data, even if they discontinue trial product. The primary reason for discontinuation of trial product must be specified in the eCRF, and final drug accountability must be performed.

The long half-life of semaglutide (approximately one week) should be considered when initiating new anti-hyperglycaemic treatment after discontinuation of the trial product.

8.1.1 Temporary discontinuation of trial treatment

Temporary treatment discontinuation and dose adjustment is allowed at the discretion of the investigator. Treatment with trial product should be resumed if the circumstances later allow. Start and stop dates and dose should be recorded in the eCRF. A treatment status session must be made in the IWRS when a subject is on treatment pause and when resuming treatment.

8.2 Withdrawal from the trial

A subject may withdraw consent at any time at his/her own request. Only subjects who withdraw consent will be considered as withdrawn from the trial.

If a randomised subject is considering withdrawing from the trial, the investigator may offer the subject 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. It must be explained to the subject that this must include information on their AEs, especially those related to the primary objective that occurred since last contact to the subject. This is important to ensure that the information gained is complete and accurate, and that the correct conclusions are drawn. Only if the subject declines all alternatives, should the subject be recorded as withdrawn.

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

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

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the medical record. If the subject withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

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

8.2.1 Replacement of subjects

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

8.3 Lost to follow-up

A subject will be considered potentially lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site. The following actions must be taken if a subject fails to return to the trial site for a required visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.

- Before a subject is deemed lost to follow-up, the investigator must make every effort to contact the subject, see Section 5.2. The following contact attempts will be made and documented in the subject's source documents where as a minimum, renal impairment status related to primary objective, the AE status and/or vital status (dead or alive) should be determined:
    - To subjects: three phone calls and one written contact (e.g. certified letter)
    - To the primary physician and/or other health care professionals: phone calls until contact is established
    - If direct contact to the subject is not possible, relatives or other person(s) will be contacted: three phone calls and one written contact
    - Search/contact to public registries of deceased persons, if available and allowed by local regulation

Should the subject continue to be unreachable at the end of the trial, he/she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up. A subject cannot be declared lost to follow-up before the trial has come to an end.

9 Trial assessments and procedures

- Trial procedures and their timing are summarised in the flowchart (Section 1).
- Informed consent must be obtained before any trial related activity, see Appendix 3.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- The investigator should inform the subjects' primary physician, if applicable, about the subjects' participation in the trial if the subject agrees to the primary physician being informed.
- Each subject should be asked to provide contact information for persons (preferably at least 3), e.g. relatives, primary care provider or other, to whom the investigator can contact in case of issues when trying to contact the subject during the trial.
- The investigator must ensure to keep regular contact with each subject throughout the entire trial, and at all times have updated contact information for the subject. 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 subjects followed for primary endpoint events (see Section 4.2.1).
- All of the assessments and procedures at a given trial visit do not need to be performed on the same day, provided that they are completed within the visit window.
- Review of completed PROs, laboratory reports, etc. must be documented either on the documents or in the subject's source documents. The review must be performed by an investigator.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons or to confirm the primary endpoint (see Section 9.2.2). Please refer to Appendix 2 for further details on laboratory samples.
- There are no fasting visits.
- In case local restrictions due to epidemic/pandemic lead to lockdown of a site, site visits can be performed as home nursing (see Appendix 9)

9.1 Optional pre-screening

The investigator may, after obtaining separate informed consent, perform pre-screening of potential trial candidates. It is not necessary to obtain full informed consent for the remaining trial period before pre-screening. Pre-screening assessments include obtaining blood and urine samples for eGFR and/or UACR and/or HbA_{1c}. The subject must have been/be in usual health condition at the time of sample collection used for inclusion as evaluated by the investigator and treated with a RAAS blocking agent, according to inclusion criterion 6 (see Section 6.1). The pre-screening samples must be analysed locally with standardised assays as described in Appendix 2. The parameters that fulfil inclusion criteria can be used to determine eligibility for the trial, if measurements were taken no more than 90 days prior to screening and are documented in the medical records. Those subjects determined eligible for the trial based on these results will follow

the flowchart schedule for all screening assessments including eGFR, UACR and HbA_{1c} (see Section 1) to determine the baseline values (see Section 10.3).

Results of pre-screening assessments will not be collected in the trial database and will not be monitored unless used to fulfil inclusion criteria (see Section 6.1). Concerns related to any pre-screening assessment must not be reported as an AE.

Pre-screening assessments performed after signature of the separate informed consent can be reimbursed by Novo Nordisk A/S.

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

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

9.2 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart (Section 1).

9.2.1 Self-measured plasma glucose

Subjects have the option to be provided with a BG meter including auxiliaries as well as instructions for use, or to continue to use their own BG meter. Those subjects who choose to use the BG meter provided by Novo Nordisk will be instructed in how to use the device and this will be repeated as needed. The investigator will advise the individual subject of when the self-measured plasma glucose values should be measured and how to note the values and dates. The measurements are supportive for the investigator's treatment decisions when optimising glycaemic control.

The BG meters provided by Novo Nordisk, use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display.

9.2.2 Clinical efficacy laboratory assessments

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

Collection of creatinine values from medical records
Throughout the trial period the investigator should report (in the eCRF) any creatinine values measured at a local laboratory and documented in medical records if they are considered to reflect the usual kidney function. Values that are considered to be due to reversible cause (e.g. acute hospitalisation, volume depletion or nephrotoxic medication) should not be reported.

If a subject initiates chronic dialysis or receives a renal transplant, further collection of creatinine values from medical records is not needed.

Central laboratory confirmatory eGFR samples
When an eGFR result from the central laboratory indicates that one of the thresholds has been reached (see Section 4.2.1),

- $\geq$ 50% reduction in eGFR from baseline *or*
- eGFR < 15 mL/min/1.73 m^2

a confirmatory sample of this endpoint must be obtained and sent to the central laboratory as soon as possible, but at least 4 weeks after the date of the first eGFR assessment meeting the threshold was obtained. The subject should be called for an unscheduled visit in order to obtain the confirmatory test, unless a scheduled visit is planned.

If medical records indicates that one of the thresholds has been reached the subject should be called in for a central laboratory eGFR assessment as described above as soon as possible. If this central laboratory value has reached one of the thresholds, a confirmatory sample from the central laboratory must be obtained at least 4 weeks after the date of the first central laboratory measurement.

Confirmatory tests should not be collected after the end of treatment visit.

9.2.3 Patient reported outcomes

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

9.3 Adverse events

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

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

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

- All SAEs
- AEs leading to discontinuation of trial product
- AEs related to 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 positive COVID-19 test. In the absence of clinical symptoms, a positive COVID-19 test (antigen or antibody) should be reported, if available.
- Selected types of AEs (SAEs and non-SAEs) requiring additional data collection (on specific event forms) and events for adjudication (see Table 9-1).

9.3.1 Time period and frequency for collecting AE and SAE information

All events meeting the definition of an SAE (see Appendix 4) and events listed in Section 9.3 and Table 9-1 must be collected and reported. This includes events from the day of randomisation until the follow-up visit/end of trial visit, at the time points specified in the flowchart (Section 1). All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours, 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 AE or SAE in former trial subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been

discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related to the investigational trial product or trial participation, the investigator must promptly notify Novo Nordisk.

The method of recording, evaluating and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4. Timelines for reporting of AEs, including events for adjudication, Section 9.3.1.1, are listed in Figure 9-1.

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

Figure 9-1 Decision tree for determining the event type and the respective forms to complete with associated timelines

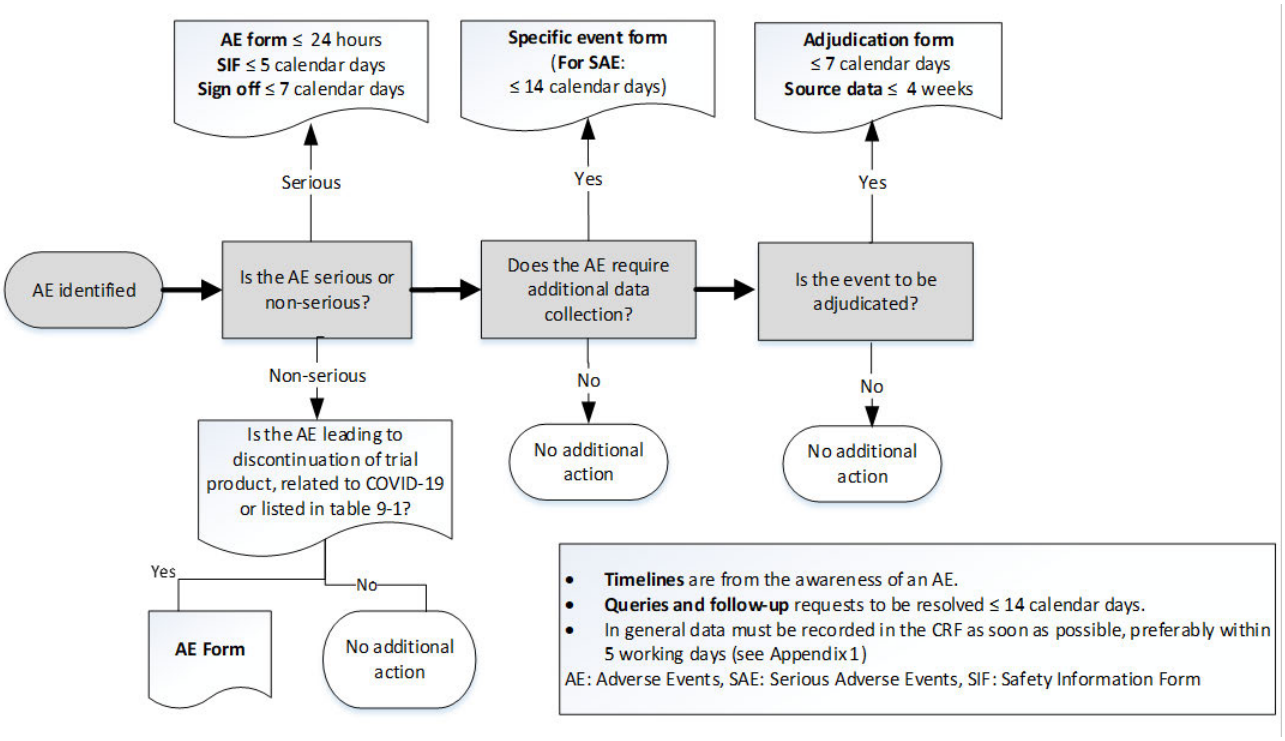


Table 9-1 AEs requiring additional data collection (via specific event forms) and events for adjudication

Event type (serious and non-serious) including description	Adjudication Outcome	Additional forms(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
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
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
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
Heart failure New onset or worsening of heart failure leading to an unscheduled hospital admission or an urgent clinic/office/emergency department visit.	Not applicable	Specific event form
Acute renal failure Abrupt decrease in renal function, e.g. one of the following: 1. $\geq$ 0.3 mg/dL ($\geq$ 26.5 µmol/l) increase in serum creatinine within 48 hours 2. $\geq$ 1.5 times increase in serum creatinine within 7 days 3. urine volume < 0.5 mL/kg/h for 6 hours	Not applicable	Specific event form
Acute gallbladder disease Event of symptomatic acute gallbladder disease (including gallstones and cholecystitis)	Not applicable	Specific event form
Acute pancreatitis Diagnosis requires at least two of the following criteria:	Not applicable	Specific event form

1. abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) 2. serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal 3. characteristic findings of acute pancreatitis on imaging		
Diabetic retinopathy New onset or worsening of diabetic retinopathy	Not applicable	Specific event form
Malignant neoplasm Malignant neoplasm confirmed by histopathology or other substantial clinical evidence.	Not applicable	Specific event form
Medication error Medication errors related to trial product. For details regarding medication errors, see Appendix 4, Table 12-4.	Not applicable	Specific event form
Severe hypoglycaemic episode Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery.[22, 23]	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 requirements, refer to Appendix 8.

9.3.1.1 Events for adjudication

The list of events for adjudication can be found in Table 9-1and the reporting timelines in Figure 9-1.

Event adjudication will be performed for events in randomised subjects. These events are reviewed by an independent external event adjudication committee (EAC) in a blinded manner; refer to Appendix 3 for further details.

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

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

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

3. AE search (standardised screening): All AEs not directly reported by the investigator as requiring adjudication, will undergo screening to identify potential events for adjudication. If the AE is deemed relevant for adjudication, an event specific adjudication form will be

generated in the eCRF. This form must be completed, and all predefined source documents must, if obtainable, be collected and uploaded to the EAS.

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

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

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

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

An Event Adjudication site manual will be provided to each site detailing 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 (CTR).

9.3.2 Method of detecting AEs and SAEs

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

9.3.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All events will be followed until resolution, stabilization, or if the event is otherwise explained (e.g. chronic condition) or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.3.4 Regulatory reporting requirements for SAEs

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

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk

will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board/independent ethics committee (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 from unblinding and reporting during trial conduct, even if the cases fulfil the definition of suspected unexpected serious adverse reactions (SUSARs). The DMC (Appendix 3) receives unblinded data and makes recommendations to the Novo Nordisk safety committee on an ongoing basis. This ensures adequate monitoring of safety while maintaining SAE reports related to the primary endpoint blinded for Novo Nordisk.

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

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

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

9.3.5 Cardiovascular and death events

Specified in Table 9-1

9.3.6 Disease-related events and/or disease-related outcomes not qualifying as an AE or SAE

Not applicable for this trial.

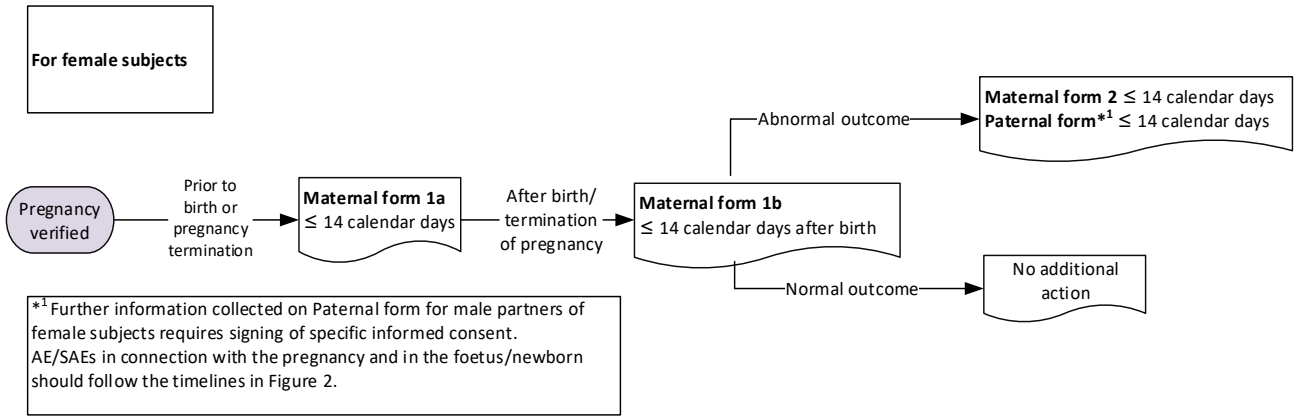
9.3.7 Pregnancies and associated adverse events

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

If a pregnancy is reported in female subjects, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Figure 9-2 and Appendix 5.

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

Figure 9-2 Decision tree for determining the forms to complete with associated timelines for pregnancy



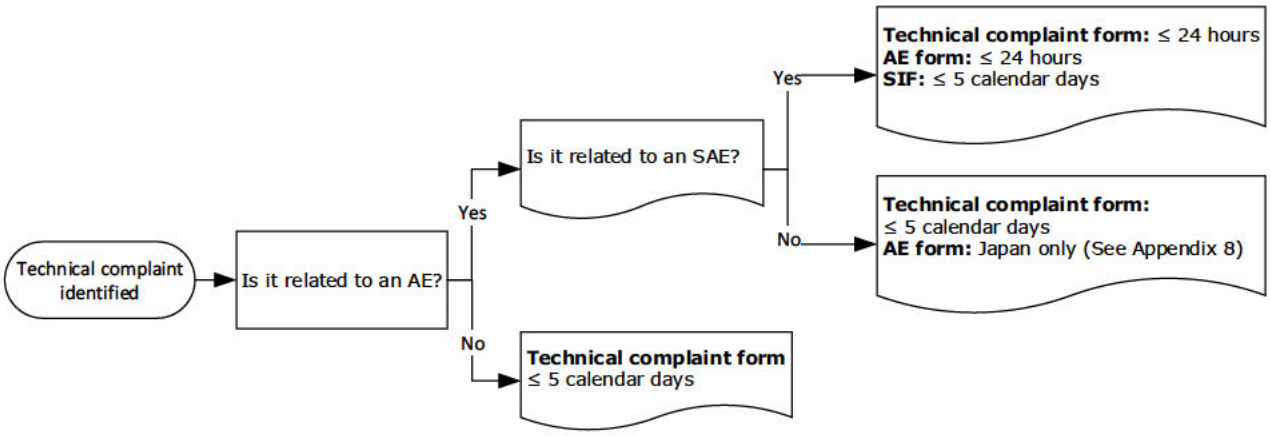
9.3.8 Medical device incidents (including malfunctions)

Not applicable for this trial. Refer to technical complaints in Section 9.3.9.

9.3.9 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.
Timelines for reporting technical complaints are listed in Figure **9-3**.

Figure 9-3 Decision tree for determining the forms to complete with associated timelines for technical complaints



AE: Adverse Event, SAE: Serious Adverse Event, SIF: Safety Information Form

9.4 Treatment of overdose

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

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE and laboratory abnormalities. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of semaglutide of approximately one week. Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the subject.

Overdoses of up to 4 mg in a single dose have been reported in clinical trials. The most commonly reported adverse reaction was nausea. All subjects recovered without complications. For more information on overdose, also consult the current version of the semaglutide Investigator's Brochure.

Accidental overdose must be reported as a medication error. Intentional overdose is considered abuse or misuse of trial product and must be reported as AEs, if qualifying for reporting according to Section 9.3 (SAE or AE leading to discontinuation of trial product). Refer to Section 9.3.1 for further details.

9.5 Safety assessments

Planned time points for all safety assessments are provided in the flowchart (Section 1).

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the first visit) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Medical history is a medical event that the subject has experienced in the past.

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

- T2D including date of diagnosis
- Diabetes complications, including hypoglycaemia unawareness and neuropathy
- History of kidney disease including data on previous eGFR and UACR measurements
- History of CV disease including peripheral artery disease
- History of eye diseases
- History of pancreatitis
- History of gallbladder diseases
- History of malignant neoplasms
- Other relevant concomitant illness/medical history including COVID-19

In case of an abnormal and clinically significant finding, the investigator must record the finding on the Medical History/Concomitant Illness form if it is present at randomisation. Any new finding fulfilling the SAE definition (see Appendix 4) or included in Section 9.3 or Table 9-1 during the trial and any clinically significant worsening from baseline (visit 2) must be reported as an AE (see Section 9.3).

9.5.1 Physical examinations

A physical examination will include assessments of the:

- General appearance
- Thyroid gland
- Respiratory system
- Cardiovascular system
- Abdomen
- Extremities
- Skin
- Central and peripheral nervous system

Relevant findings present at or prior to randomisation should be recorded on the Medical History/Concomitant Illness form in the eCRF in accordance with Section 9.5. Findings not present at randomisation should be reported as AEs according to Section 9.3.

Body measurements (height and weight) will also be measured and recorded as specified in the flowchart (Section 1). Height should be assessed without shoes. Body weight should be assessed in light clothes without shoes.

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

9.5.2 Vital signs

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a sitting position and a quiet setting without distractions (e.g. television, cell phones).
- Blood pressure will consist of 3 diastolic and systolic blood pressure measurements with intervals of at least 1 minute in between. All three readings must be entered in the eCRF and the average of the 3 blood pressure readings will be calculated in the eCRF.

- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- The measured values should be recorded without rounding.

9.5.3 Eye examination

Subjects 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 precorneal 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 subject 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 subject has experienced worsening of visual function since the last examination. If the applicable eye examination was performed before the subject 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 the above must be performed as per the flowchart within visit window (see Section 1) or within 8 weeks before the applicable visit. The investigator should indicate the outcome of each 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, if applicable according to Section 9.3.

The subject must be informed that pharmacologically pupil-dilated fundus examination may make the eyes more sensitive to light and cause blurry vision, and that driving should not take place if the vision is impaired.

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

9.5.4 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the flowchart in Section 1.

9.6 Pharmacokinetics

Not applicable for this trial.

9.7 Pharmacodynamics

Not applicable for this trial.

9.8 Genetics

Not applicable for this trial.

9.9 Biomarkers

Collection of blood and urine samples for future research is part of this trial. Participation in the biobank component is optional and requires separate informed consent. Subjects who do not wish to participate in the biobank component may still participate in the trial. For the biobank, samples will be collected according to the flowchart and stored for future analysis.

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

Analyses of circulating biomarkers may include analysis of hormones, metabolites or other non-genetic plasma or serum parameters with the purpose of understanding and predicting response to semaglutide as well as to increase understanding nephrologic and cardiometabolic diseases.

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

Brazil, China, Israel, South Africa 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 H_0: HR >=1.0 against the one-sided alternative H_a: HR <1.0, where HR represents the hazard ratio comparing semaglutide to placebo. For the group sequential design, an alpha spending function will be used that approximates O'Brian Fleming stopping boundaries for the overall Type I error probability of 2.5% (one-sided). Based on a randomisation ratio of 1:1 and a true HR of 0.8, a total of 854 primary endpoint events are required for 90% power.

The assumptions for all the power calculations below are based on analysis of data from the subpopulation, approximately 5%, from the liraglutide CV outcome trial EX2211-3748 (LEADER), which fulfilled inclusion criteria 2-6 described in Section 6.1. All assumptions are further supported by data from the similar subpopulation in the smaller and shorter semaglutide CV outcome trial NN9535-3744 (SUSTAIN 6).

For the calculation of number of randomised subjects it is assumed that:

- annual primary endpoint rate in the placebo group is 7.5%
- uniform recruitment occurs in 21 months
- annual lost to follow-up rate in both treatment groups is of 1%
- trial duration is five years and five weeks (from first subject randomised to last subject last visit (LSLV))

Under these assumptions a total of 3,508 subjects are needed for randomisation.

Compared to when LEADER was conducted, the use of SGLT-2 inhibitors is anticipated to become more widespread at the time of conduct of this trial. The event rate observed in LEADER for this nephropathy composite outcome was 9.4% in the placebo group. Recently conducted trials with SGLT-2 inhibitors have suggested a beneficial effect on new or worsening nephropathy.[17, 18] Taking this into account, a primary endpoint event rate of 7.5% in the placebo group and hazard ratio of 0.8 is assumed.

The annual loss rate of 2% (considered a worst case scenario) is based on lost to follow-up rates seen in the SUSTAIN 6 and LEADER trials, while also taking into account missing data for eGFR due to e.g. missing blood samples among subjects being followed.

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 that testing is done at a 2.5% level (one-sided).

The confirmatory secondary endpoint, annual rate of change in eGFR, is analysed using a linear random regression model. Under the assumption of a difference in slope of 1mL/min/1.73 m^2 for semaglutide compared to placebo, a between subject variance for the slope of 20 and a residual variance of 45, the marginal power is >99%.

Assuming a hazard ratio of 0.8, an annual loss rate of 1% and an annual event rate of 7% in the placebo group for the confirmatory secondary MACE endpoint, the marginal power for confirming superiority is 89%. With similar assumptions for hazard ratio and loss rate and assuming an event rate of 5% in the placebo group, the marginal power for the third confirmatory secondary endpoint, time to all-cause death, is 78%.

10.2 Definition of analysis sets

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

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

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

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

In line with the estimand for this trial, all endpoints will be evaluated in terms of the in-trial observation period only.

10.3 Statistical analyses

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

Novo Nordisk will perform the statistical analyses except the 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 tests of the hypotheses 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 presented together with two-sided 95% confidence intervals and two-sided p-values corresponding to testing the exploratory hypotheses of no difference.

Unless otherwise mentioned, baseline assessment is defined as the latest available measurement from the randomisation visit (V2) or the screening visit (V1). Thus, if a V2 assessment is missing then the assessment from V1 will be used as the baseline assessment, if available. For eGFR, the

baseline assessment is defined as the mean of the two assessments from the randomisation visit (V2) and the screening visit (V1). If only one of the assessments is available, this will be used as the baseline assessment. For UACR, the baseline assessment is defined as the mean of the two assessments from the randomisation visit (V2). If only one of the assessments is available, this will be used as the baseline assessment.

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 subject experience 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 cannot be systematically collected after withdrawal of consent, lost-to-follow-up, or after end-of-trial follow-up 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 subject is alive at the end of the period. Censoring due to lost to follow-up 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 hazard ratio for comparing semaglutide versus placebo will be estimated from a stratified Cox proportional hazards model with treatment (semaglutide, placebo) as fixed factor together with the 2-sided 95% confidence interval and one-sided p-value for hypothesis testing. Stratification is by use of SGLT-2 inhibitors (yes/no) at baseline. The score test from the Cox model will be used for testing. The following superiority hypothesis will be tested:

$$H_0: HR \geq 1.0 \text{ against } H_a: HR < 1.0.$$

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

In the primary analysis missing data for scheduled central laboratory eGFR values due to e.g. missing blood samples while subjects are still being followed are not imputed, implicitly assuming no eGFR component events observed during the in-trial observation period with missing eGFR values.

Sensitivity analysis
If superiority is established for the primary endpoint, the following sensitivity analysis is performed. The primary analysis assumes independent censoring for subjects who are lost to follow-up or who withdrawn consent. To investigate the impact of this assumption on the

superiority conclusion of the primary analysis, a tipping point analysis will be made. In this analysis, subjects in the semaglutide treatment group will have their event times imputed with an increasing penalty in the sense that their risk of a primary endpoint event is increased (the penalty) following censoring compared to while under observation. The placebo subjects will be imputed with no penalty, i.e. assuming same event rate before and after censoring. Multiple imputed data sets will be analysed with separate stratified Cox regressions as for the primary analysis 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 three confirmatory secondary endpoints under multiplicity control via a hierarchical testing scheme using the following order:

1. Annual rate of change in eGFR (total eGFR slope)
2. Time to first occurrence of MACE
3. Time to occurrence of all-cause death

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 annual rate (slope) of decline in eGFR will be compared between treatment groups based on a linear random regression model on eGFR values with treatment, use of SGLT-2 inhibitors (yes/no) at baseline, time (as a continuous variable) and treatment time interaction as fixed effects, and including subject effect as a random intercept and time as a random slope. The random intercept and slope is assumed to be bivariate normal distributed with mean zero and an unstructured covariance matrix. The independent error term is assumed to be identical univariate normal distributed with mean zero. To estimate the slope the model will be fitted to scheduled central laboratory baseline and post-baseline data. The parameter of interest is the coefficient for the treatment and time interaction term, which measures the slope difference between semaglutide and placebo. The two confirmatory secondary time-to-event endpoints will be analysed using the stratified Cox proportional hazards model as described for the primary endpoint.

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

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

Endpoint	Intercurrent event	Handling
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 and non-CV death in the Cox model
Annual rate of change in eGFR	• Treatment discontinuations • Medication modifying cardio-renal risk	All measurements 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, i.e. no eGFR data available
	• Initiation of chronic renal replacement therapy	Censoring at time of initiation, i.e. eGFR data after initiation are not used in the analysis
	• Death	Censoring at time of death, i.e. no eGFR data available
Time to first occurrence of MACE	• Treatment discontinuations • Medication modifying cardio-renal risk • Initiation of chronic renal replacement therapy	Subjects 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 occurrence of all-cause 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

10.3.2.2 Supportive secondary endpoints

Each of the supportive secondary time-to-event endpoints will be analysed with the same stratified Cox proportional hazards model as the primary endpoint.

Annual rate of change in chronic eGFR slope will be analysed similar to the total eGFR slope.

The continuous supportive secondary endpoints (change from randomisation to week 12 or year 3) will be analysed using multiple imputation. An imputation model is estimated separately for each treatment group including use of SGLT-2 inhibitors (yes/no) as a factor and baseline value as a covariate. Completed data sets will be analysed by an ANCOVA adjusted for treatment and use of SGLT-2 inhibitors (yes/no) at baseline as fixed factors, 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.

In addition, all-cause death is analysed using FAS and an extended in-trial observation period including the follow-up for vital status for subjects who withdraw consent or are lost to follow-up. The stratified Cox proportional hazards model as described for the primary endpoint will be used.

10.3.3 Exploratory endpoints

The exploratory endpoints will be analysed the same way as the supportive secondary continuous endpoints.

10.3.4 Interim testing for efficacy

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

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, as defined in the SAP. 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 subjects in the trial.

10.4 Pharmacokinetic and/or pharmacodynamic modelling

Not applicable for this trial.

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12 Appendices

Appendix 1 Abbreviations and Trademarks

ACE	angiotensin converting enzyme
AE	adverse event
ARB	angiotensin II receptor blocker
BG	blood glucose
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease - epidemiology collaboration
COVID-19	Coronavirus disease 2019
CTR	clinical trial report
CV	cardiovascular
DMC	data monitoring committee
DUN	dispensing unit number
EAC	event adjudication committee
EAS	event adjudication system
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycated haemoglobin
HRT	hormonal replacement therapy
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalised ratio
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
LSLV	last subject last visit
MACE	major adverse cardiovascular event
MALE	major adverse limb event
PCD	primary completion date

PRO	patient reported outcome
RAAS	renin-angiotensin-aldosterone system
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneously
SGLT-2	sodium glucose cotransporter-2
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TMM	trial materials manual
UACR	urinary albumin-to-creatinine ratio
ULN	upper limit of normal
WOCBP	woman of childbearing potential

Appendix 2 Clinical laboratory tests

- The tests detailed in Table 12-1 and Table 12-2 will be performed by the central laboratory, unless otherwise specified. Descriptions of laboratory supplies and procedures for obtaining, handling and transportation of samples will be available in the laboratory manual provided to sites.
- 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, but abnormal values will be reported to the investigator. Brazil: For country specific requirements, please see Appendix 8.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- Laboratory samples will be destroyed no later than at finalisation of the CTR or as required according to local regulations. China: For country specific requirements, please see Appendix 8.
- Human biosamples for retention will be stored as described in Appendix 7.

Table 12-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• HbA_{1c}

Renal function	• Creatinine-based eGFR, calculated per CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation:
	  ◦ eGFR must be calculated using the CKD-EPI using isotope dilution mass spectrometry (IDMS) for serum creatinine measured or a serum creatinine method validated against and traceable to the international standard reference materials and minimal bias compared to IDMS reference methodology.
	  ◦ Sample collection date and unit must be reported in the eCRF.
	• Urinary albumin-to-creatinine ratio (UACR):
	  ◦ For all applicable visits, except for the screening visit (V1), subjects will be asked to collect a first morning urine sample both on the day prior to the visit and on the day of the visit and bring the samples to the site.
	• Cystatin C-based eGFR, calculated per CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.

Biochemistry	• hsCRP • Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides

Table 12-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Biochemistry[1]	• Albumin • Alanine Aminotransferase (ALT) • Alkaline phosphatase • Aspartate Aminotransferase (AST) • Bilirubin • Potassium • Sodium • Bicarbonate • Haemoglobin • Urea
Pregnancy Testing	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]
Notes : [1]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 4 (Hy's Law) and Section 8.1. [2]Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.	

All trial-required laboratory assessments will be performed by a central laboratory, except urine hCG pregnancy testing, which will be performed locally 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[25] and applicable ICH Good Clinical Practice (GCP) Guideline[26].
    - Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements), must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
    - providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
    - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
    - ensuring submission of the CTR synopsis to the IRB/IEC.

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

2) Financial disclosure

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

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

3) Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the subject and answer all questions regarding the trial. This includes the use of an impartial witness where required according to local requirements.

- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[26], Declaration of Helsinki[25] and the IRB/IEC or trial site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the trial.
- The informed consent form will contain a separate form that addresses long-term storage of human samples and the use of samples for optional exploratory research. The investigator must explain to each subject the objectives of the exploratory research. Subjects must be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.
- A separate informed consent form for optional pre-screening is available. This must be signed before any optional pre-screening activities are performed, but it is not necessary to obtain full informed consent for the remaining trial period before pre-screening, see Section 9.1.
- A copy of the informed consent form(s) must be provided to the subject. Brazil: For country specific requirements, please see Appendix 8.

4) Information to subjects during trial

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

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

5) Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or leaving out

certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.

- The subject must be informed that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. United Kingdom: For country specific requirements, please see Appendix 8.

6) Committee structure

Novo Nordisk safety committee

Novo Nordisk will constitute an internal safety committee to evaluate the ongoing safety of semaglutide. 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 (DMC)

The DMC is an independent, external committee composed of members whose expertise cover relevant specialties including statistics. The DMC is established to review and evaluate accumulated data from the trial at predefined time points as well as ad hoc. This is done in order to protect the safety of the subjects and to evaluate the benefit-risk balance. The DMC will have access to unblinded data, and will provide recommendations on trial continuation, modification or termination.

Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

Event adjudication committee

An independent external event adjudication committee (EAC) 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 specialties. EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk. The EAC will have no authorisations to impact on trial conduct, trial protocol or amendments. The assessment made by both the EAC and the investigator will be presented in the CTR.

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

The AEs for adjudication are listed in Section 9.3.

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.

Global expert panel

Global expert panel(s) (GEP) consisting of selected investigators and study coordinators, referred to as National Leaders (NL) and National Study Coordinators (NSC), respectively, will be formed. The panel members will discuss and provide global as well as local, guidance and advice on operational aspects of the trial, including e.g. subject recruitment and retention topics, as well as supporting peer-to-peer communication within the trial.

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 CTR for this trial.

One investigator will be appointed by Novo Nordisk to review and sign the CTR (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 CTR 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.

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

Authorship

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

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[27]

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

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

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

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

Investigator access to data and review of results

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

8) Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[28], the Food and Drug Administration Amendment Act (FDAAA)[29], European Commission Requirements[30, 31] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a

result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this trial Last Subject Last Visit (LSLV). The trial will therefore be registered with an estimated PCD corresponding to the estimated LSLV, which is first subject randomised plus 61 months. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

9) Data quality assurance

Case Report Forms (CRFs)

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The following will be provided as paper CRFs:
    - Pregnancy forms
    - Other CRFs
- The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:
    - AE forms
    - Safety information forms
    - Technical complaint forms (also to be used to report complaints that are not subject related, e.g. discovered at trial site before allocation)
- Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.
- The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

Monitoring

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source

documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

- Monitoring will be conducted using a risk based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to trial sites.
- Monitors will review the subject's medical records and other source data to ensure consistency and/or identify omissions compared to the CRF.

Protocol compliance

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

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

10) Source documents

- All data entered in the CRF must be verifiable in source documentation other than the CRF.
- The original of the completed PROs must not be removed from the trial site, unless they form part of the CRF and a copy is kept at the site.
- Source documents provide evidence for the existence of the subject 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 subject's medical history in source documents such as subject's medical record
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each trial site. There will only be one source document defined at any time for any data element.

11) Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.

  Spain: For country specific requirements, please see Appendix 8.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied

by Novo Nordisk. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the trial site. If the provided electronic data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

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

12) Trial and site closure

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

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

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

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

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

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

13) Responsibilities

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

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

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

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

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

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

14) Indemnity statement

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

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

Belgium, France and Mexico: For country specific indemnity statements, please refer to Appendix 8.

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

Table 12-3 Adverse event definitions

AE definition
• An AE is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • An AE can be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product.
Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, 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 and inappropriately used not in accordance with the protocol or the terms of the marketing authorisation. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms or the clinical sequelae of a suspected overdose of trial product regardless of intent. • A "lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.
Events NOT meeting the AE definition
• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed 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 the first trial related activity after the subject has signed the informed consent.
Definition of an SAE
An SAE is an AE that fulfils at least one of the following criteria:
• **Results in death**
• **Is life-threatening** ◦ The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
• **Requires inpatient hospitalisation or prolongation of existing hospitalisation** ◦ Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. ◦ Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Note: ▪ Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs.

▪ Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.
• **Results in persistent disability/incapacity** • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experience of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
• **Is a congenital anomaly/birth defect**
• **Important medical event:** • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion. • The following AEs 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 ULN and total bilirubin >2 x ULN, where no alternative aetiology exists (Hy's law).

Table 12-4 Recording, reporting and classification of adverse events

Description of AEs requiring additional data collection (via specific event form) and events for adjudication are found in Table 9-1
Definition of 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 subject, such as: • Administration of wrong drug. Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in administration of wrong drug • Wrong route of administration, such as intramuscular instead of subcutaneous. • Accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur. Treatment pauses should not be reported as a medication error.
AE and SAE recording
• All SAEs, AEs leading to discontinuation of trial product, AEs requiring additional data collection and events for adjudication, and other selected AEs (see Section 9.3) 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 subject identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to Novo Nordisk.

- For all non-serious AEs the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE related forms refer to "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 AE to relevant regulatory authorities.

Assessment of severity

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

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

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

Assessment of causality

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

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

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

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

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

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always 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 send a follow-up report with the updated causality assessment.

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

Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
- **Recovering/resolving:** The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
- **Recovered/resolved with sequelae:** The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequelae meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the subject has not improved and the symptoms are unchanged or the outcome is not known.

- **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the subject is lost to follow-up.

Follow-up of AE and SAE

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

If a subject dies during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology, if available.
New or updated information will be recorded in the 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 9.3.1.
- After the trial is completed at a given site, the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after CRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

SAE reporting via paper CRF

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by secure fax line, 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.

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 subjects are of childbearing potential.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

Contraception guidance

Male subjects

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

Female subjects

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

Table 12-5 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) oral, intravaginal or transdermal hormonal contraception associated with inhibition of ovulation
Progestogen only oral or injectable hormonal contraception associated with inhibition of ovulation
Highly effective methods that are user independent[b]
• Implantable progesteron only hormonal contraception associated with inhibition of ovulation • Intrauterine Device (IUD) • Intrauterine hormone-releasing System (IUS) • Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence[b] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.
Notes: [a]Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials. [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 subjects, and/ or
- if the risk of initiating treatment with a specific highly effective method outweigh the predicted benefits of trial participation for the female subject.

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, Germany, Italy, Spain and United Kingdom: For country specific requirements, please see Appendix 8.

Pregnancy testing

- WOCBP should only be included after a negative highly sensitive urine pregnancy test.
- Additional urine pregnancy testing should be performed at monthly intervals during the treatment period, if required locally (Appendix 8).
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- A urine pregnancy test must also be completed for WOCBP at the end of treatment and follow-up visits.

Collection of pregnancy information

Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk via secure fax line, encrypted e-mail or courier within 14 calendar days of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to Novo Nordisk. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to Novo Nordisk as described in Appendix 4. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

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

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

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

Examples of technical complaints:

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

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

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

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within the timelines specified in Figure 9-3. If the CRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

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

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

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

Appendix 7 Retention of human biosamples

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 9.9. The following samples will be stored:

- EDTA plasma (for future analyses of circulating biomarkers)
- Urine (for future analyses of urinary biomarkers)

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

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

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

In the event that the collected biosamples will be used in the future, care will be taken to target analyses within the scope defined in Section 9.9.

Appendix 8 Country-specific requirements

Argentina:

- Appendix 5: Use of barrier contraceptive method with spermicide in combination with another highly effective method as described in Table 12-5 is required for WOCBP.
- Appendix 5: Monthly testing with highly sensitive urine pregnancy tests is required for WOCBP.
- Novo Nordisk will reimburse costs of standard of care treatment for CKD (angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB)), pregnancy tests and contraceptive methods

Belgium:

- Appendix 3, section 14: 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 (according to law concerning experiments on the human person of 07 May 2004 - Article 29: §1).
- Appendix 5: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group) "Recommendations related to contraception and pregnancy testing in clinical trials", as listed in Table 12-5. This means that the use of double barrier methods is not applicable for Belgium.

Brazil:

- Section 6.2, exclusion criterion #4: Participation in other trials within one year prior to screening visit (Visit 1), unless there is a direct benefit to the research subject at the investigator's discretion (according to Resolution 251/97, item III.2.j).
- 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 9.9: No subjects from Brazil will take part in the optional biobank part of the trial and no genetic testing will be performed.
- 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).
- Novo Nordisk will reimburse costs of standard-of-care treatment for CKD.

Bulgaria:

- Collection of age is needed for the calculation of eGFR (CKD-EPI).[24]

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 9.1: Optional pre-screening is not allowed in China.
- Section 9.9: No subjects from China will participate in the optional biobank part of the trial and no genetic testing will be performed.
- 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, section 7: 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.

France

- Appendix 3, section 14: The sponsor is responsible for identification of the harmful consequences of the biomedical the 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 or of 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).
- Collection of age is needed for the calculation of eGFR (CKD-EPI).[24]

Germany:

- Section 9.1: Optional pre-screening is not allowed in Germany
- Appendix 5: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group) "Recommendations related to contraception and pregnancy testing in clinical trials", as listed in Table 12-5. This means that the use of double barrier methods is not applicable for Germany.
- Subject's full date of birth is not allowed to be collected and must be shortened to year of birth. Collection of age is needed for the calculation of eGFR (CKD-EPI).[24]

Hungary:

- Collection of age is needed for the calculation of eGFR (CKD-EPI).[24]

India:

- Section 9.5.3: (additional clarifications in italics)

Subjects 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. *A subject with uncontrolled and potentially unstable retinopathy or maculopathy would be a subject that is not well-controlled in the sense that appropriate treatment and follow-up has not been received.*

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 precorneal 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 subject 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 subject has experienced worsening of visual function since the last examination. If the applicable eye examination was performed before the subject signed the informed consent form, it must be documented that the reason for performing the examination was not related to this trial.

Each eye should be evaluated separately, and presence of the following should be assessed and documented

- *Diabetic retinopathy – using the below staging:*
    - *Mild non-proliferative diabetic retinopathy (only microaneurysms)*
    - *Moderate-severe non-proliferative diabetic retinopathy*
    - *Proliferative diabetic retinopathy*
- *Diabetic macular oedema*
- *Impaired visual acuity (best corrected) – state Snellen grading if assessed*

Israel:

- Section 9.9: No subjects from Israel will take part in the optional biobank part of the trial and no genetic testing will be performed.

Italy:

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

Japan:

- Section 6.1, inclusion criterion #2: Male or female, age above or equal to 20 years at the time of signing informed consent.
- 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 9.3, 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 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 Africa:

- Section 9.9: No subjects from South Africa will participate in the optional biobank part of the trial and no genetic testing will be performed.

Spain:

- Appendix 3, section 11: Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 25 years after end of trial.
- Appendix 5: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group) "Recommendations related to contraception and pregnancy testing in clinical trials", as listed in Table 12-5. This means that the use of double barrier methods is not applicable for Spain.

Turkey:

- Section 9.9: No subjects from Turkey will participate in the optional biobank part of the trial and no genetic testing will be performed.

United Kingdom:

- Appendix 3, section 5: In the United Kingdom the IRB/IEC does not have access to the patients' medical records.
- Appendix 5: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group) "Recommendations related to contraception and pregnancy testing in clinical trials", as listed in Table 12-5. This means that the use of double barrier methods is not applicable for United Kingdom.

Appendix 9 Mitigations to ensure subject safety and data integrity during epidemics/pandemics (e.g. COVID-19)

In case local restrictions due to an epidemic/pandemic leads to lockdown of a site, the site must contact the Sponsor (Novo Nordisk) to allow for implementation of the mitigations mentioned in this appendix based on mutual agreement. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.

If local regulations, requirements and/or guidelines have been issued, these must be complied with.

Assessments

In case local restrictions due to an epidemic/pandemic lead to the lockdown of a site, site visits can be performed as home nursing. On-site visits are always preferred, but trial assessments can be performed by site staff visiting the subject´s home (or at alternative location) if needed. As a pre-requisite it must be ensured that trial site staff is covered by workers' compensation insurance to protect workers. For all assessments done at the subject´s home site specific equipment has to be used and procedures in the lab manual have to be followed. It must be documented in the medical records that the subject has consented to this process, and if any local requirements for informed consent applies, these must be followed. Home nursing may also be performed by a third-party nursing agency, if permissible by local regulation.

Trial product alternative dispensing methods

Alternative dispensing methods of study intervention may be implemented and details will be communicated and documented. The dispensing options will be based on options and requirements at country level and if permitted by local regulations and Novo Nordisk A/S. The trial product should be returned to the trial site or pharmacy when site is open and fully functioning again.

Appendix 10 Protocol amendment history

Protocol amendment no. 1 (dated 24 January 2019, included in version 4.0)

This amendment is considered to be substantial for Argentina 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]

Argentina Local Team noticed post protocol approval that the wording stating what type of standard of care treatment costs will be reimbursed by Novo Nordisk was included by default in Appendix 8, however this wording is not fully applicable due to the trial specific set-up: Novo Nordisk will reimburse standard of care for CKD (treatment with an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) in accordance with inclusion criteria # 6) and not for T2D in this trial.

Section # and name	Description of change	Rationale
Appendix 8 Country-specific requirements for Argentina, amendment 1	Update of requirement: Novo Nordisk will reimburse costs of standard of care treatment for CKD (angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB)), pregnancy tests and contraceptive methods	See overall rationale

Protocol amendment no. 2 (dated 03 June 2019, included in version 4.0)

This amendment is considered to be substantial for Germany 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]

Changes are introduced to fulfil local requirements in Germany due to request of local HA

Section # and name	Description of change	Rationale
Appendix 8 Country-specific requirements for Germany, amendment 2	Update of requirement: Section 9.1: Optional pre-screening is not allowed in Germany	See overall rationale

Protocol amendment no. 3 (dated 01 August 2019, included in version 4.0)

This amendment is considered to be substantial for India 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]

Additional clarification on the eye examination have been added for India only to reflect clarification of the fundus criteria for uncontrolled and potentially unstable retinopathy or maculopathy as required by Central Drug Standard Control Organisation (CDSCO), Office of Drugs Controller General (India).

Section # and name	Description of change	Rationale
Appendix 8 Country-specific requirements for India, amendment 3	Additions to section 9.5.3	See overall rationale

Protocol amendment no. 4 (03-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]

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 COVID-19 postinfectious conditions. In addition, the AE collection have been expanded to reflect these changes.

The sample size has been increased with 348 subjects.

This amendment also addresses changes to the statistical testing strategy, as well as clarifications and administrative changes.

Section # and name	Description of change	Rationale
Section 2 Flowchart	Insertion of subject contact information check	To ensure that the subject contact information is valid
Section 2 Flowchart	Footnote “g” revised	To clarify when the collection of urine samples take place
Section 2 Flowchart	Footnote “k” added	To clarify that yearly visits should take place approximately 13 weeks after the previous visit
Section 3.2 Background	Background section has been elaborated	Background information expanded to provide expected population information captured by inclusion/exclusion criteria and to introduce communication options that may be used to motivate focused recruitment.
Section 3.3.2 Risks related to semaglutide	Removed sentence regarding that semaglutide should be discontinued 2 months before a planned pregnancy. Inserted reference to Appendix 5 in pregnancy, lactation and fertility section.	To align across protocol, appendix and SI-IC form and to specify that semaglutide should be discontinued at least 5 weeks before a planned pregnancy.
Section 4.2 Exploratory endpoints	Statement deleted that eGFR samples meeting a threshold and followed by a non-eGFR component of the primary endpoint before confirmation will have the date of the eGFR sample as event date.	Description corrected because un-confirmed eGFR samples followed by a non-eGFR component of the primary endpoint will not have the eGFR sample as primary endpoint event date. Details on derivation of eGFR components in the presence of intercurrent events are given in the SA

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 COVID-19 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 7.2 Dose modification	Specification of visit periods in Table 7.2	For clarification
Section 7.7 Concomitant medication	Text revised	To specify that if a subject is treated with the maximum tolerated dose but not the maximum labelled dose of the RAAS blocking agent a previous dose escalation attempt is not a requirement, but the reason why the subject is not expected to tolerate a higher dose must be documented in the medical records. Further to specify that in case of intolerance to and ACE-inhibitor due to cough an ARB must have been tried
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 COVID-19 postinfectious conditions is allowed at the investigator discretion without discontinuing trial product.	To allow for co-participation in a COVID-19 trial
Section 8.1 Discontinuation/Withdrawal criteria	Text revised	To clarify that subjects who participate in other trials can resume trial product if the investigational medicinal product of the other trial has been discontinued, if deemed safe by the investigator and the Novo Nordisk medical expert.

Section 8.1 Discontinuation/Withdrawal criteria	Text regarding pregnancy updated	To specify that contraception should be utilised for at least 5 weeks after the last dose of trial product.
Section 9 Trial assessments and procedures	Text regarding review of PROs updated	To specify that the review must be performed by an investigator.
Section 9.2.1 Self-measured plasma glucose	Text revised	To specify that subjects can use either their own BG meter or one provided by Novo Nordisk and to note that it is not necessary to file the measurements at the site.
Section 9.2.2 Clinical efficacy laboratory assessments	Text regarding collection of creatinine values from medical records revised.	For clarification
Section 9.3 Adverse events	Text regarding COVID-19 AEs included. 'including all fatal events', pregnancies and technical complaints deleted on the list	To describe the procedure for collection of COVID-19 AEs Fatal events are per default SAEs, as they fulfil the first seriousness criteria. Hence there is no need to mention this here where it clearly states that all SAEs are collected. Pregnancies and technical complaints are not AEs and the collection and reporting of them is covered elsewhere in the protocol (section 9.3.7 and section 9.3.9, and Appendix 5 and 6).
Section 9.3.1 Adverse events, Figure 2	Text regarding COVID-19 AEs included	To describe the procedure for collection of COVID-19 AEs
Section 9.5 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 9.5.3 Eye examination	Window for eye examination changed from 5 weeks to 8 weeks	To allow more time for performing eye examinations.
Section 10.1 Sample size determination	The event rate for the nephropathy composite outcome in LEADER adjusted to 9.4%	To align with the population fulfilling the inclusion criteria, including UACR<5000mg/g
Section 10.1 Sample size determination	Lowering of expected event rate and dropout and consequently an increase in expected recruitment time and sample size as well as updated power calculations for confirmatory secondary endpoints.	To account for potentially lower event rate than initially expected.
Section 10.1 Sample size determination, confirmatory secondary endpoints	Text updated to reflect analysis on raw eGFR values	Log transformation is not considered necessary in order to achieve the appropriate distributional properties.
Section 10.3.1 Primary endpoint	Description of handling of missing eGFR data updated	Imputation of missing eGFR values is not considered necessary for the primary analysis.

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	Log-transformation prior to analysis of annual change in eGFR removed and baseline included as response variable.	Analysis will be done on raw eGFR value as it is not believed that log transformation is required in order to achieve the appropriate distributional properties.
Section 10.3.2.2 Supportive secondary endpoints	Text revised	Specification of imputation model since reference to primary analysis no longer appropriate after update.
Section 10.3.4 Interim testing for efficacy	The requirement that 60% of the total primary endpoint events are renal events is removed	Requirement not considered necessary for valid interim results
Appendix 2	Text revised	To specify that urine hCG pregnancy testing will be performed locally unless serum testing is required by local regulation or IRB/IEC.
Appendix 2	hsCRP, Cholesterol, High density lipoprotein (HDL) cholesterol, Low density lipoprotein (LDL) cholesterol and Triglycerides moved to efficacy assessments	For correctness
Appendix 5	Changes to formatting	For clarification
Appendix 5	Text revised	To specify that contraception should be utilised for at least 5 weeks after the last dose of trial product.
Appendix 9 Mitigations to ensure subject safety and data integrity during epidemics/pandemics (e.g. COVID-19)	Implementation of mitigations (home nursing and alternative ways of dispensing) in case sites are locked down due to epidemics/pandemics (e.g. COVID-19)	To ensure subject safety and data integrity in case of restrictions due to epidemics/pandemics (e.g. COVID-19)