# Cover Page for Protocol

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| Sponsor name: | Novo Nordisk A/S |
| NCT number | NCT04865770 |
| Sponsor trial ID: | NN9535-4662 |
| Official title of study: | REMODEL - Renal mode of action of semaglutide in patients with type 2 diabetes and chronic kidney disease |
| Document date: | 21 April 2022 |

# Protocol

**Protocol title: REM*O*DEL - Renal mode of action of semaglutide in patients with type 2 diabetes and chronic kidney disease**

**Substance name: once-weekly semaglutide s.c.**

**Universal Trial Number: U1111-1248-7912**

**EudraCT Number: 2020-000828-19**

**Trial phase:** 3b/4

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

# Protocol amendment summary of changes table

| DOCUMENT HISTORY | | |
|---|---|---|
| Document version | Date | Applicable in country(-ies) and/or site(s) |
| Protocol version 3.0 | 21 April 2022 | All |
| Protocol version 2.0 | 29 January 2021 | All |
| Original protocol version 1.0 | 07 September 2020 | All |

### Protocol version 3.0 (21 April 2022)

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

### Overall rationale for preparing protocol, version 3.0:

The overall rationale for the changes implemented in the amended protocol is to update inclusion criteria 6, 7 and 8, as it is expected to beneficially impact on recruitment without compromising the study integrity or subject safety. Changes to the content of the protocol are presented in the table below.

In addition, minor editorial changes were made in Sections 1.2, 4.2, 5.1, 5.4, 8.1.1, 8.1.2, 8.1.4, and in Appendix 2, 8 and 9 to increase consistency and clarity.

Based on evaluation by Novo Nordisk and input from an external Expert Panel, the changes introduced will have no impact on efficacy endpoints or subject safety.

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 1.1 Synopsis | Changes to key inclusion criteria | To align wording with inclusion criteria in section 5.1 |
| Section 1.2 Flowchart | Visit window for the end of trial visit (V12) has been changed from ±7 days to +7 days. | To correct a typo. Based on semaglutide half-life the end of trial visit cannot be earlier than 5 weeks after end of treatment. |
| | On site random spot urine collection added as a separate row in the flowchart. | For clarification purposes only, to clearly differentiate the urine collections (first morning void spot urine, on site random spot urine, and 24-hour urine). |
| Section 4.2 Scientific rationale for trial design | Wording slightly updated to align with changes in inclusion criteria in section 5.1. | To align wording with inclusion criteria in section 5.1 |

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 5.1 Inclusion criteria | Inclusion criterion 6:<br>• For subjects in the non-biopsy population: The lower limit for eGFR has been changed to ≥ 30 mL/min/ 1.73 $m^2$.<br>• For subjects in the biopsy sub-population the value is kept at ≥40 mL/min/ 1.73 $m^2$. | • For subjects in the non-biopsy population, lowering the eGFR to 30 ml/min is not expected to influence MRI endpoints. It is also not likely to impact subject safety nor significantly alter the subject population in the trial but is expected to beneficially affect recruitment.<br>• For subjects in the biopsy sub-population, the lower limit for eGFR is kept unchanged to ensure subject safety. |
| | Inclusion criterion 7:<br>The lower limit for UACR has been changed to ≥ 20 mg/g. | Changing the lower limit for UACR to ≥ 20 mg/g will not impact the subject safety nor alter the subject population in the trial significantly but is expected to beneficially affect recruitment. |
| | Inclusion criterion 8:<br>Criterion updated to allow inclusion of subjects for whom treatment with RAAS blockers is contraindicated or not tolerated. | To align with wording in trial NN9535-4321 (FLOW, a large CVOT investigating the effect of semaglutide in subjects with T2D and CKD) and to allow for the possibility that some subjects do not tolerate RAAS blockers. This is expected to beneficially affect recruitment but not impact subject safety nor alter the subject population in the trial. |
| Section 5.4 Screen failures | Wording updated to put more emphasis on the investigator's evaluation on when it makes medical sense to rescreen a subject. Reference to specific inclusion criteria (5, 6 and/or 7) has been removed.<br><br>Rescreening of previous screen failures is still only allowed twice. | To accommodate that it can make medical sense to re-screen a subject that screen fails on other changeable or fluctuating inclusion/ exclusion criteria than inclusion criteria 5, 6 and/ or 7. This is expected to ease the screening and recruitment process. |
| | A sentence added to specify that subjects who are rescreened are required to sign a new informed consent. | To clarify expectations related to when a subject is rescreened and to align with new protocol template text. |
| Section 8.1.1 Magnetic resonance imaging | Plasma glucose updated to blood glucose. | To clarify, as the glucose measurements are performed with BG meters at site. |
| | Wording slightly updated to clarify investigator responsibilities related to radiology assessment. | For clarification purposes only. |
| Section 8.1.2 Kidney biopsy | Wording slightly updated to clarify investigator responsibilities related to histopathologic report. | For clarification purposes only. |
| Section 8.1.4 Urine collection | A paragraph describing on site random spot urine has been added | Text added for clarification purposes only, to clearly differentiate the urine collections (first morning void spot urine, on site random spot urine, and 24-hour urine). |

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 10.2, Appendix 2 Clinical laboratory tests<br><br>Table 10-1 Protocol-required efficacy laboratory assessments | Renal function:<br>Laboratory parameters related to first morning void spot urine and on site random spot urine split into separate rows in the table.<br><br>Biomarkers:<br>Urine changed to: On site random spot urine. | For clarification purposes only. |
| Section 10.8 Appendix 8 Mitigations to ensure subject safety and data integrity during epidemics/pandemics | Visit window for the end of trial visit (V12) has been changed from ±7 days to +7 days.<br><br>On site random spot urine collection added as a separate row in the flowchart. | To align with changes in the flowchart (Section 1.2). |
| Section 10.9, Appendix 9 Country-specific requirements | Country-specific requirements added for Denmark. | Denmark has been included in the study. |

# Table of Contents

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# 1 Protocol summary

## 1.1 Synopsis

**Rationale:**
In the SUSTAIN 6 trial, once-weekly (OW) subcutaneous (s.c.) semaglutide showed a significant reduction in the risk of new or worsening nephropathy. To confirm the renal benefit suggested by SUSTAIN 6, the FL*O*W trial (NN9535-4321) was initiated, a pivotal phase 3b trial investigating kidney outcomes. The aim of the current trial (the REM*O*DEL trial) is to explore the impact of semaglutide on the underlying kidney-related mechanisms hypothesised to be involved in the kidney protective effect of semaglutide in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). Non-invasive MRI methods will be used, along with urine- and blood-based sampling, kidney biopsies and RNA sequencing to assess changes in the kidney after 52 weeks of treatment with semaglutide compared to placebo.

**Objectives and endpoints:**

***The primary objective:***

- To investigate the effect of OW semaglutide s.c. versus placebo on renal inflammation and haemodynamics, as measured by MRI in patients with T2D and CKD.

***The secondary objective****:*

- To investigate the effect of OW semaglutide s.c. versus placebo on renal oxidative stress, natriuresis, albumin excretion and kidney function in subjects with T2D and CKD.

The following **primary endpoints** are derived from the MRI scan:

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in kidney oxygenation (cortex), BOLD MRI (R2*) | From baseline (week 0) to end of treatment (week 52) | Ratio |
| Change in kidney oxygenation (medulla), BOLD MRI (R2*) | From baseline (week 0) to end of treatment (week 52) | Ratio |
| Change in global kidney perfusion (MRI) | From baseline (week 0) to end of treatment (week 52) | Ratio |
| Change in kidney inflammation (cortex), T1 mapping (MRI) | From baseline (week 0) to end of treatment (week 52) | Ratio |
| Change in kidney inflammation (medulla), T1 mapping (MRI) | From baseline (week 0) to end of treatment (week 52) | Ratio |

BOLD: blood oxygenation-level dependent; MRI: magnetic resonance imaging

The following are **key secondary endpoints**:

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in gene expression assessed by single nucleus RNA sequencing (kidney biopsy) | From baseline (week 0) to end of treatment (week 52) | $log_2$ fold-change |
| Change in glomerular basement membrane width (kidney biopsy) | From baseline (week 0) to end of treatment (week 52) | nm |
| Change in ADC (cortex) (MRI) | From baseline (week 0) to end of treatment (week 52) | Ratio |
| Change in ADC (medulla) (MRI) | From baseline (week 0) to end of treatment (week 52) | Ratio |
| Change in natriuresis (urinary sodium excretion) (urinalysis) | From baseline (week 0) to end of treatment (week 52) | mmol/l |
| Change in albumin excretion rate (urinalysis) | From baseline (week 0) to end of treatment (week 52) | mg/24 h |
| Change in kidney function (creatinine clearance) (urinalysis) | From baseline (week 0) to end of treatment (week 52) | ml/min/1.73 $m^2$ |

ADC: apparent diffusion coefficient.

**Overall design:**

This is a multi-centre, international, randomised, double-blinded, parallel-group, placebo-controlled trial comparing OW semaglutide 1.0 mg s.c. versus placebo, both added to standard-of-care treatment (including antidiabetic medication, CKD medication and CV medication) in subjects with T2D and CKD. Subjects will be randomised 2:1 to receive either OW semaglutide or placebo.

Key inclusion criteria:

- Male or female.
- Age above or equal to 18 years at the time of signing informed consent.
- Diagnosed with T2D ≥180 days prior to the day of screening.
- $HbA_{1c}$ ≤9.0% (≤75 mmol/mol).
- Depending on biopsy/non-biopsy population:
    a. For subjects in the non-biopsy population: Serum creatinine-based eGFR ≥ 30 and ≤75 mL/min/1.73 $m^2$ (CKD-EPI).
    b. For subjects in the biopsy sub-population: Serum creatinine-based eGFR ≥ 40 and ≤75 mL/min/1.73 $m^2$ (CKD-EPI).
- UACR ≥20 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 angiotensin II receptor blocker (ARB)) unless such treatment is contraindicated or not tolerated. Treatment dose must be stable for at least 28 days prior to screening.

Key exclusion criteria:

- Use of any glucagon-like peptide 1 receptor agonist (GLP-1 RA) within 30 days prior to screening.
- A prior solid organ transplant or awaiting solid organ transplant.
- Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.
- Presence or history of malignant neoplasms (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) within 5 years prior to the day of screening.

- Congenital or hereditary kidney diseases including polycystic kidney disease, autoimmune kidney diseases including glomerulonephritis or congenital urinary tract malformations.
- 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 V2. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.
- Treatment with systemic anti-inflammatory or immunosuppressant drugs within 90 days prior to screening. Stable treatment with acetylsalicylic acid for prevention of cardiovascular events and occasional use of propionic acid derivatives drugs (e.g. ibuprofen) is allowed.
- Any contraindication for MRI according to standard checklist used in clinical routine, including claustrophobia or metallic foreign bodies, metallic implants, internal electrical devices, or permanent makeup/tattoos that cannot be declared MR compatible.
- Combination use of an ACE inhibitor and an ARB.

**Number of subjects:**
In this trial, 105 subjects will be randomly assigned to trial product.

**Treatment groups and duration:**
The total duration of trial participation for each subject will be:
- up to 6 weeks for screening and pre-treatment assessments
- 52 weeks of treatment
- 5 weeks follow-up

Trial products are:
- Active trial product: semaglutide 1.34 mg/mL solution for injection in pre-filled PDS290 pen-injector. One pre-filled pen contains 2 mg semaglutide in 1.5 mL solution.
- Reference product: semaglutide placebo, solution for injection in 1.5 mL pre-filled PDS290 pen-injector.

**Data monitoring committee:** No

## 1.2 Flowchart

| Procedure | Protocol section | Information | Screening | Pre-treatment period | Randomisation | Treatment period | | | | | | | End of treatment | End of trial |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit number | | V0 | V1[a] | V2[b] | V3 | V4 | P5 | V6 | P7[c] | V8 | V9 | V10 | V11[d] | V12 |
| Timing of Visit (Weeks) | | Minimum 3 days prior to V1 | Prior to V2 and up to 6 weeks prior to V3 | Up to 5 weeks prior to V3 | 0 | 1 | 2 | 4 | 8 | 12 | 26 | 39 | 52 | End of treatment + 5 weeks |
| Visit Window (Days) | | | | | - | ±3 | ±3 | ±3 | ±3 | ±7 | ±7 | ±7 | ±7[c] | +7 |
| Informed consent and demography[e] | 10.1.3 | X | | | | | | | | | | | | |
| Inclusion and exclusion criteria[f] | 5.1, 5.2 | | X | | | | | | | | | | | |
| Randomisation criteria and randomisation | 5.5, 6.3 | | | | X | | | | | | | | | |
| Concomitant medication | 6.5 | | X | | X | X | X | X | X | X | X | X | X | X |
| Concomitant illness/medical history | 8.2 | | X | | | | | | | | | | | |
| Tobacco and nicotine products use[g] | | | X | | | | | | | | | | | |
| Childbearing potential[h] | 10.4 | | X | | | | | | | | | | | |
| Pregnancy test[h] | 8.3.5 | | X | | X | | | | | | | | X | X |
| Physical examination | 8.2.1 | | X | | | | | | | | | | X | |
| Height | 8.2.1 | | | | X | | | | | | | | | |
| Body weight | 8.2.1 | | | | X | | | X | | X | X | X | X | X |
| Blood pressure | 8.2.2 | | X | | X | X | | X | | X | X | X | X | X |
| Pulse | 8.2.2 | | X | | X | X | | X | | X | X | X | X | X |
| Eye examination[i] | 8.2.3 | | X | | | | | | | | | | X | |
| MRI Scan | 8.1 | | | X | | | | X | | | | | X | |
| Kidney biopsy[j] | 8.1 | | | X | | | | | | | | | X | |
| Laboratory assessments | 8, 10.2 | | X | | X | X | | X | | X | X | X | X | X |

| Procedure | Protocol section | Information | Screening | Pre-treatment period | Randomisation | Treatment period | | | | | | | End of treatment | End of trial |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit number | | V0 | V1[a] | V2[b] | V3 | V4 | P5 | V6 | P7[c] | V8 | V9 | V10 | V11[d] | V12 |
| Timing of Visit (Weeks) | | Minimum 3 days prior to V1 | Prior to V2 and up to 6 weeks prior to V3 | Up to 5 weeks prior to V3 | 0 | 1 | 2 | 4 | 8 | 12 | 26 | 39 | 52 | End of treatment + 5 weeks |
| Visit Window (Days) | | | | | - | ±3 | ±3 | ±3 | ±3 | ±7 | ±7 | ±7 | ±7[c] | +7 |
| 24-hour urine collection[k] | 10.2 | | | | X | | | X | | X | | | X | |
| First morning void collection[l] | 8.1.4 | | X | | X | X | | X | | X | X | X | X | X |
| On site random spot urine collection | 8.1.4 | | | | X | | | X | | X | | | X | |
| Biosamples for future analysis[m] | 10.6 | | | | X | | | X | | X | | | X | |
| Adverse event | 8.3, 10.3 | | | | X | X | X | X | X | X | X | X | X | X |
| Severe hypoglycaemic episodes | 10.7 | | | | X | X | X | X | X | X | X | X | X | X |
| Drug dispensing | 6 | | | | X | | | X | | X | X | X | | |
| Attend visit following dietary requirements[n] | 5.3.1 | | | X | | | | X | | | | | X | |
| Training in devices | 6.1 | | | | X | | | X | | | X | | | |

**a.** The investigator must confirm subject eligibility based on all inclusion and exclusion criteria assessed at V1 (including the eye examination) before the subject can initiate the pre-treatment period (V2).

**b.** Assessments at V2 must be done in the period between V2 and V3. V2 is included to ensure that eligibility has been settled, while treatment with trial drug has not yet been initiated.

**c.** The P7 visit should include a reminder of dose escalation from 0.5 to 1.0 mg.

**d.** The MRI scan and kidney biopsy (for subjects who participate in the biopsy subpopulation) can be performed up to 28 days before V11. For subjects who permanently discontinue treatment early, MRI and kidney biopsy should be performed as presented in Section 8.1.1 and 8.1.2, respectively.

**e.** Demography consists of date of birth, sex, ethnicity and race (according to local regulation).

**f.** Date of informed consent will be captured in CRF during V1.

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

**h.** Only applicable for women of childbearing potential; Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.

**i.** The V1 eye examination can be performed and evaluated 90 days prior to V1 or in the period between V1 and V2 (see Section 8.2.3). The V11 eye examination may be performed on a separate day up to 28 days before V11.

**j.** Kidney biopsies to be performed only in a subset of the population, see Section 4.1. Kidney biopsy should be performed after the MRI scan scheduled at the same visit has been approved.

**k.** Subjects must have collected 24-hour urine prior to the site visit, see Section 8.1.4 for details.

**l.** Subjects must have collected first morning urine samples two days before and one day before the visit; for V1, subjects must additionally collect a first morning urine sample on the day of the visit. See Section 8.1.4 for details.

**m.** Only applicable for subjects that have provided informed consent for biobanking.

**n.** Applicable for the days prior to and the day of the MRI scan (and biopsy, for subjects in the biopsy subpopulation).

# 2 Introduction

Semaglutide is a GLP-1 analogue developed by Novo Nordisk for the treatment of T2D and other diseases. Once weekly semaglutide s.c. has received marketing approval by the U.S. FDA, the European Commission and several other countries (Ozempic®, OW semaglutide s.c.).[2, 3] In the US, OW semaglutide s.c. is also indicated for reduction of MACE in adults with T2D and established CV disease.[2] Semaglutide is currently being investigated for the treatment of CKD in subjects with T2D.

## 2.1 Trial rationale

A statistically significant 36% reduction in the secondary 4-component composite endpoint of new or worsening nephropathy was observed for treatment with OW semaglutide s.c. versus placebo in subjects with T2D and high risk of CV events in the pre-approval CVOT SUSTAIN 6 (NN9535-3744).[4] The 4-component composite endpoint was comprised of 1) death due to renal disease, 2) continuous renal-replacement therapy, 3) new onset of persistent macroalbuminuria and 4) persistent doubling of serum creatinine level. The results of the 4-component endpoint were primarily driven by a reduction in events of new onset of persistent macroalbuminuria in the semaglutide group.

To confirm the renal benefit suggested by SUSTAIN 6, the FL*O*W trial (NN9535-4321) has been initiated. The FL*O*W trial is a pivotal phase 3b trial, aiming to demonstrate that OW semaglutide s.c. 1 mg delays the progression of renal impairment and lowers the risk of renal and CV mortality compared to placebo, both added to standard-of-care, in subjects with T2D and CKD. The primary endpoint in the FL*O*W trial is time to the first occurrence 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

The renal mode of action of semaglutide is not well established. There are a number of proposed direct and indirect mechanisms, including a reduction in inflammation and oxidative stress, and changed haemodynamics (direct mechanisms) as well as via improvement of glycaemic control, blood pressure and body weight (indirect mechanisms). The aim of the current trial is to explore the impact of semaglutide on kidney-related parameters hypothesised to be involved in the kidney protective effect of semaglutide in subjects with T2D and CKD.

## 2.2 Background

CKD is a frequent and severe microvascular complication of diabetes. Diabetes is the single leading cause of ESKD, requiring either chronic dialysis treatment or kidney transplantation. Up to 40% of patients with T2D develop some degree of CKD, and these patients have severely increased cardiovascular morbidity and mortality.[5]

Blocking the RAAS with ACE inhibitors or ARBs is recommended to reduce the progression of CKD.[6] Additionally, treatment with SGLT-2 inhibitors holds the potential to decrease CKD progression rates.[7] Despite optimal standard of care, a major unmet medical need to improve the

treatment of CKD in patients with T2D persists; semaglutide holds the potential to fill in parts of this gap. While the FL*O*W trial will provide such clarification, knowledge of the underlying mechanism of semaglutide's effect in the kidneys remains unknown, and investigation is warranted.

The pathogenesis of CKD progression within T2D is complex. Kidney hypoxia, inflammation, oxidative stress and haemodynamic changes play critical roles and a vicious circle gradually results in fibrosis and loss of kidney function.[8] Current knowledge indicates that the expected kidney protective effect of GLP-1 is caused only to a minor extent by indirect mechanisms including improved glycaemic control, systolic blood pressure reduction and weight loss,[9, 10] suggesting that one or more of the direct mechanisms mentioned above may play a key role. Only few, small non-clinical and clinical studies have focused on the direct renal MoA of GLP-1. These studies have primarily assessed the acute phase following GLP-1 treatment in the setting of normal kidney function with or without diabetes. GLP-1 RA therapy has been shown to reduce systemic markers of inflammation in humans,[11] and the kidney specific marker of inflammation and macrophage activation MCP-1 was significantly reduced by liraglutide in a mice study (data on file). Moreover, in a recent publication, semaglutide was found to downregulate multiple inflammatory genes.[12] Changes in renal haemodynamics have been inconsistent in different studies and seem to depend on baseline renal function,[13-17] whereas change in oxidative stress is only sparsely elucidated. GLP-1 therapy consistently induces natriuresis in the acute phase[18] as well as modulates the RAAS system by suppressing angiotensin II and renin.[13-15, 17] The impact of these findings are unclear and the current trial will investigate the impact of semaglutide on kidney inflammation, kidney oxidative stress, renal haemodynamics and natriuresis in patients with T2D and CKD, who are treated with standard of care for T2D, CVD and CKD. This trial will therefore support and expand the scientific understanding of the results of the FL*O*W trial.

Detailed information for OW semaglutide s.c. is available in the current edition of the IB and in the local labels for Ozempic®.

## 2.3 Benefit-risk assessment

Main benefits and risks are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of OW semaglutide s.c may be found in the investigator's brochure or prescribing information/ summary of product characteristics.[2, 3]

### 2.3.1 Risk assessment

## Table 2-1 Potential risks of clinical significance

| Potential risk of clinical significance | Summary of data/rationale for risk | Mitigation strategy |
|---|---|---|
| **Trial treatment(s) (semaglutide)** | | |
| Gastrointestinal disorders | Consistent with other GLP-1 RAs, the most frequent adverse events (AEs) with semaglutide are gastrointestinal (nausea, vomiting and diarrhoea). In general, these reactions are mild or moderate in severity, of short duration, and dose dependent.<br><br>In subjects treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating subjects with impaired renal function as it may cause a deterioration of renal function. | Clinical trials have shown that a low starting dose and gradual dose escalation mitigates the risk of developing gastrointestinal symptoms.<br><br>Subjects with GI AEs are recommended to drink plenty of fluids, unless medically contraindicated, to avoid volume depletion. |
| Hypoglycaemia | There is a low risk of hypoglycaemic episodes when semaglutide is used as monotherapy. Subjects treated with semaglutide in combination with sulphonylurea or insulin may have an increased risk of hypoglycaemia. | The risk of hypoglycaemia can be lowered by reducing the dose of sulphonylurea and/or insulin when initiating treatment with semaglutide. See Section 6.5. |
| Diabetic retinopathy complications | In a 2-year clinical trial with s.c. semaglutide (NN9535-3744) involving 3,297 subjects with T2D, high CV risk, long duration of diabetes and poorly controlled blood glucose, EAC-confirmed events of diabetic retinopathy complications occurred in more subjects treated with s.c. semaglutide (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among subjects with a history of diabetic retinopathy at baseline. In the subjects who did not have a documented history of diabetic retinopathy the number of events were similar for s.c. semaglutide and placebo. In the other clinical trials up to 1 year involving 4,807 subjects with T2D, AEs related to diabetic retinopathy were reported in similar proportions of subjects treated with s.c. semaglutide (1.7%) and comparators (2.0%). | Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Long-term glycaemic control decreases the risk of diabetic retinopathy. These subjects should be monitored closely and treated according to clinical guidelines. |
| Allergic reactions | As with all protein-based pharmaceuticals, treatment with semaglutide may evoke allergic reactions, including serious allergic reactions such as anaphylactic reactions and angioedema. | As a precaution, subjects with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this trial. In addition, subjects will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the trial product occurs. |

| Potential risk of clinical significance | Summary of data/rationale for risk | Mitigation strategy |
|---|---|---|
| Acute pancreatitis | Acute pancreatitis has been observed with the use of GLP-1 RAs. In the completed phase 3 trials with semaglutide s.c. and oral semaglutide, both the event rate and the proportion of subjects experiencing confirmed pancreatitis were similar with semaglutide and comparator. Few events were confirmed; the events occurred throughout the trial periods and the overall rates were similar to the rates reported in background populations | Subjects 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.<br><br>For details on discontinuation of treatment, see Sections 7.1 and 7.1.1 |
| Neoplasms (malignant and non-malignant) | Patients with T2D, as well as patients with overweight or obesity, have an increased risk of certain types of cancer. There is no evidence from clinical trials that GLP-1-based therapies increase the risk of neoplasms. However, in the semaglutide s.c. as well as oral semaglutide phase 3a trials, the proportion of subjects with neoplasms (malignant and non-malignant) were slightly higher with semaglutide than with comparator. The number of subjects exposed to semaglutide s.c. or oral semaglutide for a longer period is considered insufficient for a thorough assessment of the risk of neoplasms. | Subjects with presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in situ prostate cancer) within 5 years prior to the day of screening will not be enrolled in this trial. |
| Pancreatic cancer | Patients with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from non-clinical studies, clinical trials or post-marketing data that GLP-1 based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies. There is no indication of an increased relative risk in the semaglutide treatment groups vs. comparator, including placebo. The rates of EAC-confirmed events of pancreatic cancer were consistently low across trials. | Subjects with presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, *in situ* carcinomas of the cervix, or *in situ* prostate cancer) within 5 years prior to the day of screening will not be enrolled in this trial. |

| Potential risk of clinical significance | Summary of data/rationale for risk | Mitigation strategy |
|---|---|---|
| Medullary thyroid cancer | Thyroid C-cell tumours were seen in mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. No C-cell tumours were observed in monkeys after 52 weeks exposure up to 52-fold above the clinical plasma exposure at 14 mg/day. The GLP-1 receptor is not expressed in the normal human thyroid, and therefore the clinical relevance of the findings is considered to be low. | To mitigate this risk, subjects with a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2) are excluded from clinical trials with semaglutide. |
| **Trial procedures** | | |
| COVID-19: Risk of COVID-19 infection in relation to participation in trial | Subjects may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country or region/state. | The risk of COVID-19 transmission in relation to site visits is overall considered to be low. To minimize the risk as much as possible, the following measures have been taken:<br>• Cautious subject recruitment planning ensures controlled subject enrollment in countries where the COVID-19 pandemic is evaluated to be sufficiently under control, and at sites where health care resources are evaluated to be adequate.<br>• The number of physical on-site visits has been limited to the extent possible, without risking the scientific value of the trial. Phone visits have to the extent possible replaced on-site visits.<br>• On-site visits will be well prepared and as short as possible. Physical contact between subjects and site staff will be limited to the extent possible, and protective measures will be implemented, if deemed necessary by the investigator. |
| MRI | All medical imaging examinations are carried out using a scanner where the subject lies on a bed that is moved into the scanner so that the head is inside the scanner tunnel. This procedure may be perceived as unpleasant for people suffering from claustrophobia. Further, the MRI examination involves the use of strong magnetic field but does not involve radiation exposure. No contrast agent will be used in this trial. | To minimize the risk of claustrophobia and risks associated with the magnetic field, local guidelines will be followed, and the following subjects have been excluded from the trial:<br>• subjects who might experience claustrophobia<br>• subjects with metal implants of certain types (e.g. pacemakers and cochlear implants) or permanent makeup that cannot be declared MR compatible. |

| Potential risk of clinical significance | Summary of data/rationale for risk | Mitigation strategy |
|---|---|---|
| Kidney biopsy | A kidney biopsy is an invasive procedure, which may cause mild to severe complications. Refer to the biopsy SI/IC for additional details. | A number of initiatives will be taken to minimize the risk for kidney biopsy complications and to ensure proper and immediate handling should they appear:<br>• Only nephrologists, invasive radiologists or other HCPs with extensive experience in performing kidney biopsies will perform the procedure.<br>• Local biopsy guidelines should be strictly adhered to including:<br>o fasting before the biopsy procedure<br>o sufficiently regulated blood pressure<br>o pausing of relevant concomitant medication in advance of the biopsy procedure<br>o monitoring of vital signs before and after the biopsy procedure<br>o imaging guided biopsy procedure<br>o post-biopsy clinical observation<br>o post-biopsy precautions |
| **Other** | | |
| Pregnancy and fertility | Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. | Semaglutide should not be used during pregnancy. Women of childbearing potential are required to use highly effective contraceptive methods when participating in this trial (see Appendix 4, Table 10-3). If a subject wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued (please see Section 7.1 and 8.3.5 for further guidance). The effect of semaglutide on fertility in humans is unknown. |

### 2.3.2 Benefit assessment

In clinical trials, semaglutide has provided superior long-term glycaemic control in subjects with T2D 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.[19]

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 RAs and SGLT-2 inhibitors 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.

### 2.3.3 Overall benefit-risk conclusion

Data from the clinical 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 expected AEs of semaglutide may be found in the investigator's brochure or the locally approved label for Ozempic®.

Considering the measures taken to minimise risk to subjects participating in this trial, the potential risks identified in association with OW semaglutide s.c. are justified by the anticipated benefits that may be afforded to subjects with T2D and CKD.

# 3 Objectives and endpoints

## 3.1 Primary, secondary and exploratory objective(s)

### 3.1.1 Primary objective

To investigate the effect of OW semaglutide s.c. versus placebo on renal inflammation and haemodynamics, as measured by MRI in subjects with T2D and CKD.

### 3.1.2 Secondary objectives

To investigate the effect of OW semaglutide s.c. versus placebo on renal oxidative stress, natriuresis, albumin excretion and kidney function in subjects with T2D and CKD.

### 3.1.3 Exploratory objectives

To explore the effect of OW semaglutide s.c. versus placebo on circulating and urinary biomarkers in subjects with T2D and CKD.

## 3.2 Primary, secondary and exploratory endpoint(s)

For each assessment, the baseline is defined as the latest observed measurement at or before the randomisation visit (V3).

### 3.2.1 Primary endpoints

The following primary endpoints are derived from the MRI scan.

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in kidney oxygenation (cortex), BOLD MRI (R2*) | From baseline (week 0) to end of treatment (week 52) | ratio |
| Change in kidney oxygenation (medulla), BOLD MRI (R2*) | From baseline (week 0) to end of treatment (week 52) | ratio |
| Change in global kidney perfusion (MRI) | From baseline (week 0) to end of treatment (week 52) | ratio |
| Change in kidney inflammation (cortex), T1 mapping (MRI) | From baseline (week 0) to end of treatment (week 52) | ratio |
| Change in kidney inflammation (medulla), T1 mapping (MRI) | From baseline (week 0) to end of treatment (week 52) | ratio |

BOLD: blood oxygenation-level dependent; MRI: magnetic resonance imaging

### 3.2.2 Secondary endpoints

#### 3.2.2.1 Supportive secondary endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in gene expression assessed by single nucleus RNA sequencing (kidney biopsy) | From baseline (week 0) to end of treatment (week 52) | $log_2$ fold-change |
| Change in glomerular basement membrane width (kidney biopsy) | From baseline (week 0) to end of treatment (week 52) | nm |
| Change in ADC (cortex) (MRI) | From baseline (week 0) to end of treatment (week 52) | ratio |
| Change in ADC (medulla) (MRI) | From baseline (week 0) to end of treatment (week 52) | ratio |
| Change in mean RARI (MRI) | From baseline (week 0) to end of treatment (week 52) | ratio |
| Change in mean arterial flow (MRI) | From baseline (week 0) to end of treatment (week 52) | ratio |
| Change in natriuresis (urinary sodium excretion) (urinalysis) | From baseline (week 0) to end of treatment (week 52) | mmol/l |
| Change in albumin excretion rate (urinalysis) | From baseline (week 0) to end of treatment (week 52) | mg/24 h |
| Change in kidney function (creatinine clearance) (urinalysis) | From baseline (week 0) to end of treatment (week 52) | ml/min/1.73 $m^2$ |

ADC: apparent diffusion coefficient; RARI : renal artery resistive index

### 3.2.3 Exploratory endpoint(s)

Exploratory endpoints will be defined in the SAP, and include additional outcomes from the MRI scans, morphometric outcomes from kidney biopsies, 24-hour urine, circulating and urinary biomarkers, and clinical parameters.

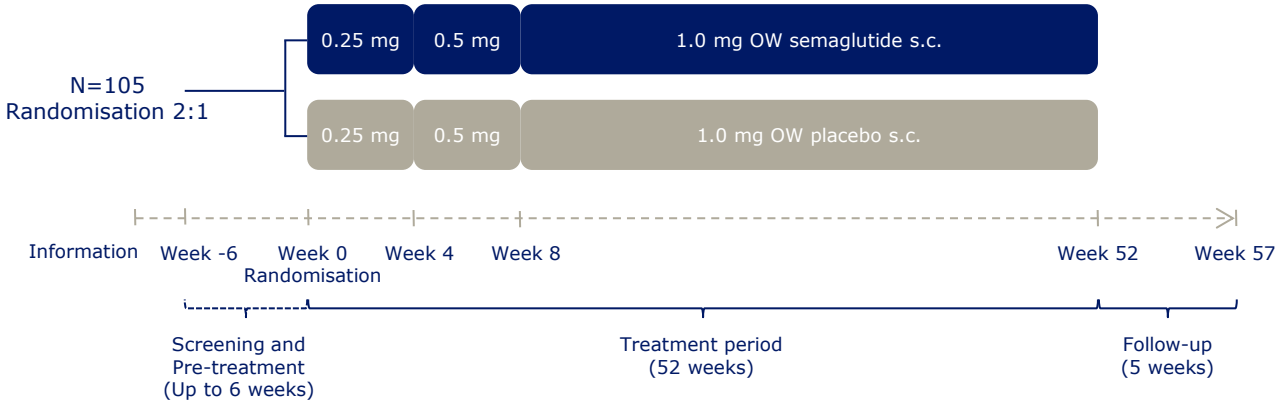
# 4 Trial design

## 4.1 Overall design

This is a multi-centre, international, randomised, double-blinded, parallel-group, placebo-controlled trial comparing OW semaglutide s.c. versus placebo, both added to standard-of-care treatment (including antidiabetic medication, CKD medication and CV medication) in subjects with T2D and CKD. The total treatment duration will be 52 weeks with a follow-up period of 5 weeks. The trial

will include a subpopulation (aiming for 45 subjects or more) undergoing kidney biopsies at baseline and end of treatment. Subjects will be invited to participate in the biopsy subpopulation at sites with the capacity to perform kidney biopsy. The full population (including the biopsy subpopulation) will be randomised 2:1 to semaglutide or placebo, respectively. Standard dose escalation (every 4 weeks) will be applied, until the maximum dose of 1 mg semaglutide or placebo is reached. A schematic illustration of the trial design is shown in Figure 4-1.

**Figure 4-1 Trial design**




## 4.2 Scientific rationale for trial design

Previous data has suggested that GLP-RAs are associated with improvements in renal inflammation, haemodynamics, natriuresis, oxidative stress and the RAAS.[9-16] However, most studies have focused on the acute phase response and been hampered by limited sample size, non-CKD populations and lack of methods to assess the effect on a molecular level.

The REM*O*DEL trial will include subjects with T2D and pre-existing CKD. Subjects who will undergo biopsy will have a minimum baseline eGFR of 40 ml/min/1.73 $m^2$ to ensure the safety of the subjects as well as interpretability of the biopsies due to limited fibrosis. Subjects who will not undergo biopsy will have a minimum baseline eGFR of 30 ml/min/1.73 $m^2$. Overall, subjects will have a UACR ≥20 mg/g; however, in >50% of the trial population, subjects will have a UACR ≥100 mg/g, which is indicative of existing renal damage and significant risk of disease progression. This will also ensure a similar population to the FL*O*W trial. Maximum $HbA_{1c}$ will be 9.0% to minimise the potential impact on inflammatory measures seen following dramatic improvements in glycaemic control.[20] A treatment duration of 52 weeks allows for a thorough assessment of the chronic effects of semaglutide treatment, and it ensures the possibility to correlate changes in renal inflammation, oxygenation, haemodynamics and gene expression with changes in markers of kidney damage (e.g. albuminuria) and kidney function (e.g. eGFR). Frequent visits and assessments during early trial conduct also allows for assessment of the acute effects of semaglutide treatment. A pre-treatment visit (V2) will ensure that the baseline measurements for MRI scan and kidney biopsy are performed before treatment with trial drug is initiated.

SGLT-2 inhibitors have been shown to reduce progression of CKD;[7] and therefore randomisation will be stratified by concomitant treatment with SGLT-2 inhibitors at baseline to ensure representative use in both treatment groups. For the biopsy subpopulation as well as for the total population, there will be a 50% cap on the number of subjects treated with an SLGT-2 inhibitor. To

reduce possible bias with SGLT-2 inhibitor treatment, a stable dose of SGLT-2 inhibitor for a minimum of 90 days is required at screening, while initiation of SGLT-2 inhibitors will not be allowed during the trial. For subjects treated with an SGLT-2 inhibitor at baseline, dose changes during the trial are allowed, however discontinuation is discouraged unless for safety reasons. Dose modification of SGLT-2 inhibitors is considered acceptable because there is no clear dose-response for the kidney-protective effect of SGLT-2 inhibitors.[21-23] These restrictions on SGLT-2 inhibitor treatment are considered ethically acceptable, as other treatments for hyperglycaemia or co-morbidities can be introduced (except GLP-1 RAs) or adjusted throughout the trial based on individual needs and at the investigator's discretion.

To ensure unbiased assessment of the effects and underlying mechanisms of semaglutide on kidneys, the trial is randomised, double-blinded and placebo-controlled.

### 4.3 Justification for dose

A dose of OW semaglutide s.c. 1 mg was chosen similar to the FL*O*W trial. This dose has been tested for glycaemic control in subjects with T2D in a comprehensive phase 3a programme and shown to have a positive benefit-risk balance. The SUSTAIN 6 data indicates that the 1 mg dose provides a slower decline in kidney function compared to the 0.5 mg dose, with a comparable AE profile. For information regarding dose modifications, see Section 6.6.

In order to lower the risk of gastrointestinal AEs, a dose-escalation regimen is applied, in accordance with the prescribing information.[2, 3] For further information on the dose-escalation, see Section 6.1.

### 4.4 End of trial definition

A subject is considered to have completed the trial if he/she has completed all phases of the trial including the last visit (V12, 'end of trial' according to the flowchart).

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

# 5 Trial population

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

Inclusion and exclusion criteria are also referred to as eligibility criteria.

### 5.1 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.
2. Male or female.
3. Age above or equal to 18 years at the time of signing informed consent.
4. Diagnosed with T2D ≥180 days prior to the day of screening.
5. $HbA_{1c}$ ≤9.0% (≤ 75 mmol/mol).

6. Depending on biopsy/non-biopsy population:
    a. For subjects in the non-biopsy population: Serum creatinine-based eGFR ≥30 and ≤75 mL/min/1.73 $m^2$ (CKD-EPI).[a]
    b. For subjects in the biopsy sub-population: Serum creatinine-based eGFR ≥ 40 and ≤75 mL/min/1.73 $m^2$ (CKD-EPI).[a]
7. UACR ≥20 and <5000 mg/g.[a, b]
8. Treatment with maximum labelled or tolerated dose of a RAAS blocking agent including an 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 28 days prior to screening.

**a.** At the time of sample collection, the subject must be in usual health condition as evaluated by the investigator.

**b.** Present in 2 out of 3 first morning void urine samples taken at individual, consecutive days prior to V1 (screening). Screening UACR is defined as the median value of the 3 first morning void urine samples.

## 5.2 Exclusion criteria

The following are general exclusion criteria for all enrolled subjects. Subjects in the biopsy sub-population have additional exclusion criteria, see Section 5.2.1.

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 4 [10.4] for further guidance). For country specific requirements see Appendix 9 (10.9).
4. Receipt of any investigational medicinal product within 60 days before the day of the screening visit.
5. Any disorder, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
6. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.
7. Planned coronary, carotid or peripheral artery revascularisation.
8. Chronic heart failure classified as being in New York Heart Association (NYHA) ≥ Class III at screening.
9. Presence or history of malignant neoplasms (other than basal or squamous cell skin cancer, *in situ* carcinomas of the cervix, or *in situ* prostate cancer) within 5 years prior to the day of screening.
10. Congenital or hereditary kidney diseases including polycystic kidney disease, autoimmune kidney diseases including glomerulonephritis or congenital urinary tract malformations.
11. Use of any GLP-1 receptor agonist within 30 days prior to screening.
12. Use of finerenone within 30 days prior to screening.
13. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 (MEN2) or medullary thyroid carcinoma (MTC).
14. Chronic or intermittent haemodialysis or peritoneal dialysis.
15. 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 V2. Pharmacological pupil-dilation is a requirement unless using a

digital fundus photography camera specified for non-dilated examination.

16. Treatment with systemic anti-inflammatory or immunosuppressant drugs within 90 days prior to screening. Stable treatment with acetylsalicylic acid for prevention of cardiovascular events and occasional use of propionic acid derivatives drugs (e.g. ibuprofen) is allowed.
17. Inadequately treated blood pressure, defined, as systolic ≥180 mmHg or diastolic ≥110 mmHg at screening.[a]
18. Any contraindication for MRI according to standard checklist used in clinical routine, including claustrophobia or metallic foreign bodies, metallic implants, internal electrical devices, or permanent makeup/tattoos that cannot be declared MR compatible.
19. Abdominal height in the supine position >35 cm (>13.8 inch). Abdominal height should be measured as the vertical distance from the back to tallest point on the abdomen while the subject is lying flat on his/her back.
20. A prior solid organ transplant or awaiting solid organ transplant.
21. Combination use of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin II receptor blocker (ARB).
22. Depending on baseline SGLT-2 inhibitor use: [b.]
    a. For subjects not treated with an SGLT-2 inhibitor at baseline:
       Treatment with an SGLT-2 inhibitor within 90 days of screening
    b. For subjects treated with an SGLT-2 inhibitor at baseline:
       Stable dose of SGLT-2 inhibitor for less than 90 days prior to screening

**a.** For patients in the biopsy subpopulations, blood pressure requirements in advance of the kidney biopsy will be more stringent (see Section 8.1.2.1(b)).

**b.** See Section 4.2 on baseline SGLT-2 inhibitor use.

### 5.2.1 Biopsy subpopulation exclusion criteria

Subjects are excluded from the biopsy subpopulation if any of the following criteria apply (however, these subjects may still be eligible for the non-biopsy population of the trial):

1. Not expected to fulfil all of the biochemical, imaging and clinical requirements on the day of the biopsy (see Section 8.1.2.1(b) for details).
2. Any condition with a single kidney.
3. Evidence of bleeding disorder or complications from previous bleeding episodes.
4. Use of aspirin, NSAID, other anti-platelet therapy, fish oil, gabapentin or other drugs that can be associated with bleeding and which cannot be safely stopped for a sufficient time period before and after the biopsy
   - anti-platelet agents (e.g. clopidogrel, aspirin) to be stopped for at least 7 days prior to biopsy
   - regular NSAID to be stopped for at least 4 days prior to biopsy
   - other agents associated with bleeding should be paused at the investigator's discretion, and avoided if possible
5. Use of chronic anticoagulation (e.g. novel oral anticoagulants [NOAC] or warfarin) that cannot be safely stopped for a sufficient time period before and after the biopsy.
6. Unwilling to receive blood transfusion (if needed).
7. Allergy to iodinated contrast, or if allergic, then alternative contrast-free imaging approaches must be available at the biopsy site in case an intervention for bleeding is needed.

## 5.3 Lifestyle considerations

### 5.3.1 Meals and dietary requirements

Subjects must follow these dietary requirements before the MRI scan visits according to the flowchart:

- drinking 250 mL (8.5 oz) of water within one hour before the MRI scan.
- avoid excess intake of sodium during the 3 days before the MRI scan.
- abstaining from caffeine, nicotine, alcohol and protein-rich meals within 6 hours of the MRI scan.

If the subject has not been following the dietary requirements, the subject should be called in for a new visit within the visit window to have the MRI scan performed.

For subjects in the biopsy subpopulation, subjects must adhere to local site regulations for fasting before the kidney biopsy visits.

## 5.4 Screen failures

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

A screen failure session must be made in IWRS.

Subjects who do not meet the criteria for participation in this study may be re-screened twice if the investigator assesses it is reasonable to expect that potential changeable or fluctuating in- or exclusion criteria may change, e.g., biochemical parameters. Previously randomised subjects cannot be re-screened. Subjects who are re-screened are required to sign a new informed consent form and provided with a new subject ID. A new screening session must be made in the IWRS.

If the subject has failed any of the inclusion criteria related to laboratory parameters, re-sampling is not allowed, unless subject is re-screened. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

## 5.5 Randomisation criteria

First dose must only be administered after baseline assessments related to primary and/or secondary endpoints are completed.

To be randomised, all randomisation criteria must be answered "yes".

1. No initiations of the following medications between screening and randomisation: anti-inflammatory drugs, immunosuppressants, finerenone, GLP-1 RAs or SGLT-2 inhibitors.
2. No disorder having arisen since screening that, in the investigator’s opinion, might jeopardise subject’s safety or compliance with the protocol.
3. Acceptable image acquisition at V2 for MRI scan as judged by the centralised imaging core laboratory.

4. Kidney biopsy performed at V2 (applicable only for the biopsy subpopulation).
5. Stable dose of RAAS blocking agent between screening and randomisation.

# 6 Treatments

## 6.1 Treatments administered

### Investigational medicinal products (IMP)

The investigational medicinal products (trial products) provided by Novo Nordisk are listed in Table 6-1. The trial products are packed blinded and are visually identical.

**Table 6-1 Investigational medicinal product provided by Novo Nordisk A/S**

| **Trial product name:** | **Semaglutide B 1.34 mg/ml** | **Semaglutide placebo** |
|---|---|---|
| **Dosage form** | Solution for injection | Solution for injection |
| **Route of administration** | Subcutaneous | Subcutaneous |
| **Recommended dosing (mg)** | 0.25, 0.5, 1 | 0.25, 0.5, 1 |
| **Dosing instructions** | Once weekly | Once weekly |
| **Packaging** | 1.5 ml pre-filled PDS290 pen-injector | 1.5 ml pre-filled PDS290 pen-injector |

Information about the use of the PDS290 pen-injector for semaglutide and placebo can be found in the DFU.

### Dose escalation

Subjects will initiate once weekly 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 6-2. The 4-week dose escalation intervals are applied in order to lower the risk of GI AEs. The investigator should remind subjects when to escalate dose; not all dose escalations are scheduled to occur at site visits.

**Table 6-2 Trial periods and treatment groups**

| **Trial periods** | | **Screening** | **Dose 1** | **Dose 2** | **Maintenance** | **Follow-up** |
|---|---|---|---|---|---|---|
| **Duration of each period** | | Up to 6 weeks | 4 weeks | 4 weeks | 44 weeks | 5 weeks |
| **Treatment** | **N** | | | | | |
| **Semaglutide s.c. OW** | 70 | - | 0.25 mg | 0.5 mg | 1 mg | - |
| **Placebo s.c. OW** | 35 | - | 0.25 mg | 0.5 mg | 1 mg | - |

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

Subjects should remain on the 1 mg dose level until the end of treatment visit; however, dose reductions and extensions of dose escalation intervals are allowed e.g. if treatment with trial product is associated with unacceptable AEs or due to other circumstances. Treatment with trial product should be intensified towards the target dose of 1 mg if/when deemed safe at the discretion of the investigator. Continued maintenance treatment at the 0.25 mg dose level is not acceptable. Subjects who discontinue trial product permanently will be withdrawn from the trial, see Section 7. Date and dose need to be recorded in the eCRF when trial product is initiated and changed.

### Instructions for the subject

The investigator must document that directions for use are given to the subject verbally and in writing as a DFU document at the first dispensing visit (as specified in the flowchart, see Section 1.2). If the investigator finds it relevant, the DFU can also be given at other visits during the trial. Training is the responsibility of the investigator or delegate.

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 investigator may choose to observe the subject when administering the first dose.

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

Auxiliary supplies are provided by Novo Nordisk:

- needles for the PDS290 pen-injector (maximum needle length: 6 mm)
- directions for use (DFU) for the prefilled PDS290 pen-injector
- blood glucose (BG) meters including lancets, test strips, control solutions and instructions for use

Only needles provided by Novo Nordisk may be used for administration of trial product. Auxiliary supplies should be provided at the first dispensing visit and again during the trial as relevant.

## 6.2 Preparation/handling/storage/accountability

Only subjects randomised to treatment may use trial product and only delegated site staff may supply or administer trial product. Information on in-use conditions and in-use time will be available on the trial product label and in the TMM.

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

The following requirements must be followed:

- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the TMM.

- The investigator or designee 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 used/partly used, or unused) or as lost.
- The investigator or designee must instruct the subject in what to return at next visit.
- The investigator or designee must instruct the subject on how to manage the in-use time of dispensed products.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- All returned, expired or damaged trial products (for technical complaint samples, see Appendix 5 [10.5]) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the site.

### 6.3 Measures to minimise bias: randomisation and blinding

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

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.

The IWRS is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subjects' treatment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Novo Nordisk prior to unblinding a subjects' treatment unless this could delay emergency treatment of the subject. If a subject's treatment is unblinded, Novo Nordisk (Global Safety department) must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation. The person breaking the blind must print the "code break confirmation" notification generated by the IWRS, sign and date the document. If IWRS is not accessible at the time of blind break, the IWRS helpdesk should be contacted. Contact details are listed in Attachment I. The subject will continue on trial product if there are no safety concerns at the discretion of the investigator

Randomisation will be stratified by:
- SGLT-2 inhibitor treatment at baseline (yes versus no)
- participation in the biopsy subpopulation (yes versus no)
- MRI field strength (1.5 T versus 3.0 T)

In the overall population, as well as the biopsy subpopulation, the number of subjects on SGLT-2 inhibitor treatment at baseline will be capped at 50%, see Section 4.2 for details.

The number of subjects with screening UACR <100 mg/g will be capped at 50% of the overall population. Screening UACR is defined as the median value of the 3 first morning void urine samples.

## 6.4 Treatment compliance

### Drug treatment compliance

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

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

- Drug accountability information; counting returned trial product, visual inspection of pens
- Discussion with subjects

Treatment start and stop dates will be recorded in the CRF.

### Missed doses

If one semaglutide 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 either case, subjects can then resume their regular once-weekly dosing schedule. A missed dose should not affect the scheduled dosing day of the week.

If 2–3 consecutive doses of trial product are missed, the subject should be encouraged to recommence the treatment if considered safe as per the investigator's discretion and if the subject does not meet any of the discontinuation criteria (Section 7.1). The trial product should be continued as early as the situation allows. The missed doses should not affect the scheduled dosing day of the week. The start dose for re-initiation of trial product is at the investigator's discretion.

If ≥4 consecutive doses of trial product are missed, the investigator should consult Novo Nordisk to decide if the subject can continue treatment. Previous dose and gastrointestinal adverse reactions should be taken into consideration when evaluating whether to repeat dose escalation in case treatment is resumed.

If doses are missed blood glucose should be more closely monitored if judged necessary by the investigator.

## 6.5 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.

Additional anti-hyperglycaemic, CV, and CKD medications may be added or changed during the trial at the discretion of the investigator and in accordance with local treatment guidelines and policies. Investigators are encouraged to optimise standard-of-care treatment for T2D, CKD, and CV risk management according to local treatment practice.

Subjects are not allowed to receive continuous treatment with systemic anti-inflammatory drugs >14 days. Stable treatment with acetylsalicylic acid for prevention of cardiovascular events and occasional use of propionic acid derivatives drugs (e.g. ibuprofen) is allowed. Refer to Section 7.1.

Anti-hyperglycaemic, CV and CKD standard-of-care treatment is considered background treatment and will not be provided by Novo Nordisk A/S.

### 6.5.1 RAAS blocking agent

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. Treatment dose must be stable for at least 28 days prior to screening and kept stable between screening and randomisation.

### 6.5.2 Anti-hyperglycaemic agents

Initiating GLP-1 RAs or SGLT-2 inhibitors (for subjects not on SGLT-2 inhibitors at baseline) is not allowed during the entire trial, refer to Section 7.1. For subjects on SGLT-2 inhibitor treatment at baseline (capped at maximum 50% of subjects), dose modification of the SGLT-2 inhibitor is considered acceptable, however discontinuing SGLT-2 inhibitor treatment during the trial is discouraged, except for safety reasons; these subjects are allowed to re-initiate SGLT-2 inhibitor treatment following temporary termination, at the investigator's discretion. For subjects on SGLT-2 inhibitor treatment at baseline, treatment dose must be stable for at least 90 days prior to screening.

It is recommended that the investigator ensures that subjects taking sulphonylurea or insulin perform adequately frequent blood glucose monitoring to ensure subject safety during trial product initiation and dose escalation. A reduction in the dose of sulphonylurea or insulin should be considered to reduce the risk of hypoglycaemia.

To mitigate risk of hypoglycaemia, consider cautiously lowering the dose of insulin and sulphonylurea when initiating treatment and/or escalating dose of trial product. General recommendations in patients with high risk of hypoglycaemia, well controlled $HbA_{1c}$ (e.g. <8% [64 mmol/mol]) and/or advanced CKD (e.g. eGFR <45 mL/min/1.73 $m^2$) are to reduce the insulin (basal and especially prandial) dose by approximately 20% or more, while 50% dose reduction or pausing of sulphonylurea may be considered. Exact dose reduction should be individualized at the investigator´s discretion. Close monitoring of blood glucose levels during initiation and dose escalation of trial product is important, with further adjustments as appropriate based on changes in blood glucose.

The reduced dose of insulin/sulphonylurea should be maintained or gradually increased towards baseline doses during the titration period at the investigator´s discretion based on blood glucose

measurements. Dose increase of concomitant anti-diabetic therapy should be commenced once target dose of the trial product has been reached to ensure optimal glycaemic control.

### 6.5.3 Data capture of concomitant medications

For randomised subjects, the following medications (not including trial product) that the subject is receiving at the time of screening (V1) or receives during the trial must be recorded in 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 8.3

The medication must be recorded in the eCRF along with dates of administration including start and stop dates or continuation and related AE number when applicable. For anti-hyperglycaemic medication, including SGLT-2 inhibitors if not administered as anti-hyperglycaemic medication, and for RAAS blocking agents (ACE inhibitors and ARBs), the total daily dose needs to be included in the eCRF.

Changes in concomitant medication must be recorded at each visit. Dose changes (lasting 2 weeks or more) should be captured as a new concomitant medication with the new dose and relevant start and stop date. If a change is due to an AE or serious adverse event (SAE), then this must be reported according to Section 8.3.

## 6.6 Dose modification

Not applicable for this trial. Refer to Section 6.1 for description of dose escalation.

## 6.7 Treatment after end of 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 RA and interference with safety data collection, initiating GLP-1 RAs should be avoided between the end of treatment visit (V11) and the end of trial visit (V12). All other medications are allowed during the follow-up period, although it is discouraged that subjects who are not treated with an SGLT-2 inhibitor at screening also do not initiate SGLT-2 inhibitor treatment until after the end of trial visit (V12).

# 7 Discontinuation of trial treatment and subject discontinuation/withdrawal

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

Efforts must be made to have the subjects who discontinue trial product attend the end of treatment visit (V11) as soon as possible, and the end of trial visit (V12) 5 weeks after last treatment. Subjects must be educated about the continued scientific importance of their data, even if they discontinue trial product early.

## 7.1 Discontinuation of trial treatment

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

1. Safety concern as judged by the investigator
2. Confirmation of acute pancreatitis
3. Pregnancy
4. Intention of becoming pregnant
5. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical trial[a]
6. Treatment with another GLP-1 RA[b]
7. Treatment with an SGLT-2 inhibitor (applicable only for subjects not on SGLT-2 inhibitor treatment at baseline)[b]
8. Treatment with finerenone[b]
9. Continuous treatment with systemic anti-inflammatory or immunosuppressant drugs >14 days. Stable treatment with acetylsalicylic acid for prevention of cardiovascular events and occasional use of propionic acid derivatives drugs (e.g. ibuprofen) is allowed.
10. Continuous maintenance treatment of trial product with a dose lower than 0.5 mg.

**a.** Simultaneous participation in a COVID-19 vaccine trial is allowed without discontinuing trial product.

**b.** Initiation of GLP-1 RAs, SGLT-2 inhibitors and/or finerenone is not allowed in the trial. Subjects treated with GLP-1 RAs, SGLT-2 inhibitors and/or finerenone for > 30 days will be discontinued from the trial and the V11 MRI and kidney biopsy should not be performed. Subjects treated with GLP-1 RAs, SGLT-2 inhibitors and/or finerenone for ≤30 days must discontinue treatment with the disallowed medication, and the V11 MRI and kidney biopsy should only be performed if possible within the visit window and after washout (5 half-lives) of the disallowed medication.

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 7.1.1). Subjects who discontinue trial product permanently will be discontinued from the trial.

As soon as possible after the decision to permanently discontinue trial product, the subject should attend the end of treatment visit (V11), followed by the end of trial visit (V12) 5 weeks after treatment discontinuation. A treatment discontinuation session must be made in the IWRS. The primary reason for discontinuation of trial product must be specified in the end of trial form in the eCRF, and final drug accountability must be performed.

For subjects who discontinue before week 26 (V9), the end of treatment (V11) MRI scan and kidney biopsy should not be performed. Subjects who discontinue between V5 and V6 (both inclusive) should have the V6 MRI scan performed.

If a patient intends to become pregnant, trial product must be discontinued at least 5 weeks before the contraceptive method is stopped. If a patient becomes pregnant unintentionally, trial product must be discontinued immediately during pregnancy and during breast feeding.

If the subject does not wish to attend scheduled site visits, efforts should be made to have the remaining visits converted to phone contacts. If a subject is unwilling to attend any of the remaining visits, information about the attempts to follow up with the subject must be documented in the subject's medical record.

### 7.1.1 Temporary discontinuation of trial treatment

If a subject has discontinued trial product temporarily, the guide for missed doses should be followed (Section 6.4). In such cases a treatment discontinuation session should not be made in the IWRS.

In case of suspicion of acute pancreatitis, the trial product should promptly be interrupted. Treatment discontinuation session should not be made in IWRS before diagnosis of acute pancreatitis is confirmed.

## 7.2 Subject discontinuation/withdrawal from the trial

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

If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to the end of treatment visit (V11) and the end of trial visit (V12). See the flowchart for data to be collected. For subjects who discontinue before week 26 (V9), the end of treatment (V11) MRI scan and kidney biopsy should not be performed. Subjects who discontinue between V5 and V6 (both inclusive) should have the V6 MRI scan performed.

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

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

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

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

### 7.2.1 Replacement of subjects

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

## 7.3 Lost to follow-up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if

necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial with a primary reason of `lost to follow-up'.

# 8 Trial assessments and procedures

- The following sections describe the assessments and procedures, while their timing is summarised in the flowchart.
- Informed consent must be obtained before any trial related activity, see Appendix 1 (10.1.3).
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all inclusion and randomisation criteria and none of the exclusion 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 site staff that can be contacted in case of emergency.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- The investigator must ensure to keep regular contact with each subject throughout the entire trial, and always have updated contact information. Even if a visit is missed and it is not possible to reschedule, every effort to have all subjects followed for the primary endpoint and AEs must be made.
- To secure optimal data quality and reduce risk of missing or repeating assessments, the investigator should remind the subjects of upcoming trial visits and requirements for these e.g. via a telephone call or a text message.
- Review of laboratory reports, MRI scans and kidney biopsy reports (where applicable) must be documented either on the documents or in the subject's medical records.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 (10.2) for further details on laboratory samples.
- The investigator must confirm subject eligibility based on all inclusion and exclusion criteria assessed at the screening visit (V1) (including the eye examination) before the subject can attend the pre-treatment visit (V2). All V2 assessments must be evaluated before the subject can be randomised at V3.

## 8.1 Efficacy assessments

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

### 8.1.1 Magnetic resonance imaging

The MRI scans will be performed at selected MRI units and images will be analysed by a centralised imaging core laboratory. For standardisation purposes the imaging core laboratory will train the MRI units as applicable, and the imaging core laboratory will do centralised blinded (blinded to treatment allocation) image analysis.

Information on the imaging processes and analysis will be described in the documents prepared by the imaging core laboratory. Results from the imaging analyses will be electronically transferred directly from the centralised imaging core laboratory to Novo Nordisk.

To account for the impact of circadian rhythm, the three MRI scans should be performed at the same time of the day (± 2 hours). On the day of each MRI scan, the subject should have blood glucose measured and documented in the eCRF. Blood glucose should be measured shortly before the MRI scan, and the subject should avoid food and carbohydrate-containing beverages between the measurement of blood glucose and the MRI scan. If the first MRI scan at any visit does not pass quality control checks, an additional MRI scan should be performed once more only. The imaging site should use the same approved MR scanner for all scheduled MRI scans.

An MRI scan should be performed for all subjects during the V2 pre-treatment period. A subject cannot be randomised without an acceptable MRI scan as judged by the centralised imaging core laboratory.

The end of treatment MRI can be performed up to 28 days before V11 (if the subject has remained on trial product), or as soon as possible after treatment discontinuation. If trial product is permanently discontinued before V9 (week 26), the end of treatment MRI should not be performed. If the subject permanently discontinues treatment during week 3 (the week leading up to the V6 (week 4) MRI assessment), a V6 MRI should be performed as soon as possible after treatment discontinuation.

The investigator must ensure that a standard radiology assessment of the MR images is performed by a qualified radiologist. In case of any incidental findings, the investigator must assess if any adverse event reporting is required (please refer to Section 8.3). It is the responsibility of the investigator to refer the subject to further examination and treatment based on the incidental findings as medically indicated. Continued trial participation or discontinuation must be considered by the investigator.

To calibrate the MRI, the imaging core laboratory will test the imaging protocol in healthy volunteers. This test will check the MRI settings and the quality of the images generated. Novo Nordisk will not have access to any data generated from the MRI examination on the healthy volunteers and these subjects are therefore not considered part of the trial.

### 8.1.2 Kidney biopsy

The kidney biopsies will be performed in a subpopulation of subjects. The aim is for 45 subjects or more to have kidney biopsies performed.

Kidney biopsies will be analysed for histopathology, morphometry and snRNAseq at a centralised kidney biopsy laboratory.

All subjects in the biopsy subpopulation should have acceptable MRI acquisition before performing the kidney biopsy scheduled for the same visit. The end of treatment biopsy can be performed up to 28 days before V11 (if the subject has remained on trial product), or as soon as possible after treatment discontinuation. If trial product is permanently discontinued before week 26 (V9), the kidney biopsy at V11 (week 52) should not be performed.

In case conclusive evaluation of pre-randomisation biopsy or end of treatment biopsy is not possible due to technical issues with the biopsy sample, the subject should not be asked to have another kidney biopsy performed. The investigator will be notified if a subject's pre-treatment biopsy is not usable for subsequent analysis. These subjects should not undergo the V11 biopsy.

The histopathologic assessment will be performed after processing of the kidney biopsy. A report based on the histopathological assessment will be send to the investigator. It is the responsibility of the investigator to inform the trial subject and to take appropriate action should the outcome of the report indicate a need for further examinations. In case of any incidental findings, the investigator must assess if any adverse event reporting is required (please refer to Section 8.3).

Kidney samples will be stored until CTR, except for subjects who have consented to biobanking (see Appendix 6 [10.6]).

#### 8.1.2.1 Requirements for the kidney biopsy

Local site clinical practice procedures should be followed as the underlying basis for the kidney biopsy procedure and post-biopsy regimen. Tissue handling and transportation of the kidney biopsy will be described in a kidney biopsy manual.

The below requirements are minimum requirements; in case of stricter requirements defined in local site procedures, the stricter requirements should be followed.

**(a) Requirements for the kidney biopsy operator**

Kidney biopsies must be performed at sites with extensive experience with this procedure and subsequent post-biopsy observation regimen. The kidney biopsy procedure must be performed by a highly experienced nephrologist or intervention radiologist.

The biopsy operators must be credentialed (e.g. Licensed Independent Providers), and meet the following minimum requirements:

- minimum experience of 35 kidney biopsies over a 2-year period within the past 5 years, with at least 25 kidney biopsies as the primary operator
- an overall major complication rate (complications requiring acute or subacute intervention) of less than 10%, as assessed at the discretion of the operator's institution

**(b) Pre-biopsy requirements**

In advance of the biopsy, the subject must fulfil the following minimum biochemical, imaging and clinical requirements. These must be documented in source data files.

**Biochemical requirements**

Biochemical requirements must be assessed locally in advance of the biopsy procedure and in accordance with local site clinical practice procedures. If the requirements are not immediately met, re-tests can be done in accordance with local site clinical practice procedures.

The following minimum requirements must be met and documented:

- Blood urea nitrogen ≤80 mg/dL (≤28.6 mmol/L)
- eGFR (creatinine-based, according to CKD-EPI formula) ≥40 mL/min/1.73 $m^2$

- INR (international normalised ratio) ≤1.4
- Haemoglobin (Hgb) ≥10 mg/dL (≥6.2 mmol/L)
- Platelet count ≥100,000/μL
- aPTT/PTT ≤35 s
- in WOCBP: negative pregnancy test

**Imaging requirements**

Imaging (ultrasound or CT scan) requirements must be assessed locally in advance of the biopsy procedure and in accordance with local site clinical practice procedures.

The following minimum requirements must be met and documented:

- 2 kidneys (i.e., subjects with single kidney are excluded from the trial)
- Kidney cortex ≥1 cm (both kidneys)
- Kidney length ≥8 cm (both kidneys)
- Absence of any anatomical abnormalities that, at the operator's discretion, would render the kidney biopsy unsafe

**Clinical requirements**

Clinical requirements must be assessed locally in advance of the biopsy procedure and in accordance with local site clinical practice procedures.

The following minimum requirements must be met and documented:

- No evidence of urinary tract infection
- Systolic blood pressure ≤150 mmHg and diastolic blood pressure ≤100 mmHg on the day of the biopsy
  - Blood pressure lowering medication may be given to achieve required blood pressure at the clinical discretion of the investigator.
- Absence of any disorder or condition that, at the operator's discretion, would render the kidney biopsy unsafe
- Fasting requirements, in accordance with local site clinical practice procedures.

**(c) Post-biopsy regimen and information**

Post-biopsy observation should be performed according to local site clinical practice procedures. The patient should be kept for on-site observation for at least 8 hours following the procedure.

Local clinical practice procedures should specify the following:

- Timing and frequency for monitoring of pulse, blood pressure and symptoms (including pain and swelling)
- Timing for strict bedrest and mobilisation
- Timing and frequency for testing of blood haemoglobin (and haematocrit, if tested)
- Requirements for observation of post-biopsy void, including assessment for haematuria

The biopsy site must have a setup in place for observation, monitoring and potential interventions for biopsy complications, including:

- Kidney imaging

- Consultation with a surgeon or interventional radiologist, in case haematuria, falling serum haemoglobin or other symptoms suggest a haematoma,
- Embolization or surgical intervention in case of excessive bleeding

Before discharge, subjects must receive instructions for home care according to local site clinical practice procedures. The instructions must include a telephone number to call for questions or to report new symptoms, as well as instructions not to lift heavy objects and to avoid strenuous activities after discharge.

### 8.1.3 Clinical efficacy laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (10.2), must be conducted in accordance with the flowchart and the laboratory manual.

### 8.1.4 Urine collection

**First morning void spot urine**

Subjects must collect first morning void urine samples in accordance with the flowchart. Urine must be collected in the containers which are to be provided at the previous visit. The investigator should remind the subject to collect first morning void samples e.g. via a telephone call or a text message.

For the applicable visits, subjects must collect 2 first morning void samples: Two days before and on the day before the visit. For the screening visit (V1), subjects must also collect the first morning void sample on the day of the visit.

If the subject has not collected the required first morning void urine samples, the subject must be asked to provide new samples (within the visit window) to replace the missed samples.

**On site random spot urine**

Subjects must collect on site random spot urine samples in accordance with the flowchart. Urine must be collected in a container, which will be provided at the applicable visit. The urine collection is independent of time of the day.

**24-hour urine**

Subjects must collect 24-hour urine samples in accordance with the flowchart. Urine must be collected in the container which is to be provided at the previous visit. The investigator should remind the subject to start collecting 24-hour urine e.g. via a telephone call or a text message. Subject must be instructed to keep the 24-hour urine samples refrigerated at home if possible, and cooled during transit to site in the provided cooler bag.

The first morning void should be collected as described above. For the following 24 hours after the first void, all urine (including the first morning void of the following day) must be collected in the container. Collection of 24-hour urine should end on the day of the visit.

If the subject has not collected the required 24-hour urine samples, the subject must be asked to provide a new 24-hour urine sample within the visit window. For the randomisation visit (V3), the first dose of trial medication must be postponed until 24-hour urine has been collected.

## 8.2 Safety assessments

Planned time points for all safety assessments are provided in the flowchart. Time period and frequency for collecting AEs and SAEs are described in Section 8.3.1.

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

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

The following concomitant illness/medical history should be reported in the eCRF:
- T2D including date of diagnosis
- History of neuropathy
- History of kidney disease
- History of CV disease
- History of eye diseases
- History of pancreatitis
- History of gallbladder diseases
- History of neoplasms
- Other relevant concomitant illness/medical history

In case of an abnormal and clinically significant finding fulfilling the definition of a concomitant illness or medical history, the investigator must record the finding on the Medical History/ Concomitant Illness form.

### 8.2.1 Physical examinations

A physical examination will include assessments of the
- General appearance
- Thyroid gland
- Respiratory system
- Cardiovascular system
- Abdomen
- Extremities

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

Body measurements will also be measured and recorded as specified in the flowchart:
- Height, without shoes
- Body weight, without shoes and only wearing light clothing

### 8.2.2 Vital signs

- Pulse, systolic and diastolic blood pressure will be assessed.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. no use of television, cell phones).

- Blood pressure and pulse measurements will be assessed sitting with a completely automated device. Manual techniques must be used only if an automated device is not available.
- Blood pressure will consist of 3 systolic and diastolic blood pressure measurements with intervals of at least 1–2 minutes. An additional fourth blood pressure measurement must be performed if the first two readings on systolic or diastolic blood pressure differ by >10 mmHg.
  - The mean systolic and diastolic blood pressure values are calculated based on the last 2 systolic and diastolic blood pressure measurements, respectively. The mean pulse value is calculated based on the last 2 pulse measurements.
  - Record the last 2 systolic and the last 2 diastolic blood pressure measurements in the eCRF. The eCRF will calculate the mean of the last 2 systolic blood pressure measurements and the mean of the last 2 diastolic blood pressure measurements.
- Pulse will be measured in connection to the blood pressure measurements.
  - Record the pulse for the last 2 blood pressure measurements in the eCRF. The eCRF will calculate the mean of the last 2 pulse measurements.

### 8.2.3 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 V2 to assess eligibility. The eye examination should be performed as a fundus photography (e.g. 2-field 60 degree or better, colour or red-free) or by slit-lamp biomicroscopy examination (e.g. using a pre-corneal or corneal contact lens examination). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

If the 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 V2 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 V2, an eye examination performed according to above must be performed as per protocol flowchart. The investigator should indicate the outcome of each eye examination. Relevant findings prior to randomisation must be recorded as concomitant illness/medical history. Relevant findings occurring after randomisation should be reported only if it is an SAE, please refer to Section 8.3.

### 8.2.4 Self-measured plasma glucose

Subjects will be provided with a BG meter including auxiliaries as well as instructions for use. The subjects 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 at the discretion of the investigator. The measurements are meant to support the investigator's treatment decisions when optimising glycaemic control.

### 8.2.5 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (10.2), must be conducted in accordance with the laboratory manual and the protocol flowchart.

## 8.3 Adverse events and serious adverse events

The investigator is responsible for detecting, documenting, recording and following up on all the events listed below:

- SAEs
- AEs leading to discontinuation of trial product
- Severe hypoglycaemic episodes
- Selected types of AEs (SAEs and non-SAEs) requiring additional data collection (Table 8-1)

The definition of AEs and SAEs can be found in Appendix 3 (10.3), along with a description of AEs requiring additional data collection.

Some AEs require additional data collection on a specific event form. The relevant events are listed below in Table 8-1.

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

| Event type | AE requiring additional data collection |
|---|---|
| Medication error | Specific event form |
| Misuse and abuse of IMP | Specific event form |
| Neoplasms (malignant and non-malignant) | Specific event form |

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

**Severe hypoglycaemic episodes**

Severe hypoglycaemic episodes require data collection on a severe hypoglycaemic episode form. Non-serious severe hypoglycaemic episodes do not require an AE form to be filled in. If the severe hypoglycaemic episode fulfils the criteria for an SAE, then, in addition to the severe hypoglycaemic episode form, an AE form and a SIF must be filled in, please see Appendix 3 (10.3).

For more information on severe hypoglycaemic episodes, please refer to Appendix 7 (10.7).

Non-serious, non-severe hypoglycaemic episodes are not collected in this trial.

### 8.3.1 Time period and frequency for collecting AE and SAE information

All events specified in Section 8.3 (for events related to pregnancy, see Appendix 4 [10.4]) must be collected and reported. Events must be collected from the screening visit (V1) and until the end of trial visit (V12), at the time points specified in the flowchart.

Medical occurrences that take place or have onset prior to the time point from which AEs are collected will be recorded as concomitant illness/medical history. AE and SAE reporting timelines can be found in Appendix 3 (10.3). All SAEs must be recorded and reported to Novo Nordisk

within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

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

### 8.3.2 Method of detecting AEs and SAEs

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

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

### 8.3.3 Follow-up of AEs and SAEs

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

### 8.3.4 Regulatory reporting requirements for SAEs

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

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

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.

### 8.3.5 Pregnancy

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

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

### 8.3.6 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to Section 8.3.

### 8.3.7 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form.

Instructions for reporting technical complaints can be found in Appendix 5 (10.5).

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

## 8.4 Treatment of overdose

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

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.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.3 and Appendix 3 (10.3) for further details

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE.

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

For more information on overdose, also consult the current version of the IB for OW semaglutide s.c.

## 8.5 Pharmacokinetics

- Single blood samples for measuring plasma concentration of semaglutide will be drawn on visits specified in Appendix 2 (10.2)
- The exact timing of obtaining the PK sample must be recorded on the laboratory form. In addition, dose details (date, time and dose) will be collected for the last 2 doses before each visit with PK samples. The investigator must ensure that the correct information is collected, e.g. by asking the subject to note the dosing details after injection, instructing the subject to dose at the same time each day, or by calling the subject on the planned day of dosing.
- PK samples may be taken at any time in relation to trial product administration.
- Blood samples for PK assessments must be collected, handled and shipped according to the description in the laboratory manual supplied by the central laboratory. The bioanalysis of semaglutide PK will be performed by a special laboratory. Semaglutide PK samples will be stored at the special laboratory responsible for PK until final CTR, in case Novo Nordisk requests further analysis of the PK samples. Details of the bioanalysis will be outlined in a

bioanalytical study plan issued by the special laboratory. Bioanalysis of plasma samples for semaglutide will be carried out using a validated LC-MS/MS assay.

## 8.6 Pharmacodynamics

Not applicable for this trial.

## 8.7 Genetics

Not applicable for this trial.

## 8.8 Biomarkers

Collection and storage of serum, plasma, urine and kidney tissue for future research (biobanking) 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 analyses.

Storage of kidney tissue is only applicable to subjects who consent to both kidney biopsy and biobanking. No additional biopsy will be performed, and no additional biopsy core will be acquired from the planned biopsies; only potential surplus kidney tissue sample will be stored.

Sampling must be recorded in the CRF. The samples are collected for the purpose of allowing future analyses of 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 biomarkers may include analysis of hormones, metabolites or other nongenetic markers with the purpose of understanding how semaglutide cardiometabolic parameters.

Circulating and urinary 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 secure central biorepositories. For further details on retention of human samples for subjects who consented to biobanking, see Appendix 6 (10.6).

Clinical laboratory assessments for efficacy and safety are described in Sections 8.1.3 and 8.2.5, respectively.

### 8.8.1 RNA transcriptome research

Tissue samples from the kidney biopsies will be used for snRNAseq.

Kidney biopsies are described in Section 8.1.2.

Information on the sequencing process will be described in the documents prepared by the kidney biopsy core laboratory.

The analysis of snRNAseq data is described in Section 9.4.3.1 and in the bioinformatics analysis plan.

# 9 Statistical considerations

## 9.1 Statistical hypotheses

The trial is explorative, and no confirmatory hypothesis testing is planned. Analyses and p-values from statistical models are considered descriptive in nature. No adjustment for multiple testing will be performed, except separately in connection with analyses of gene expression data where methods for controlling false discovery rates will be applied as needed.

## 9.2 Sample size determination

Due to the exploratory nature of this trial, the sample size has been determined in a more heuristic manner, by arguing that the trial would be able to detect changes in R2* that are considered clinically important. This sample size is also considered sufficient for the analyses of the remaining primary endpoints.

Specifically, the trial is designed to have at least 80% marginal power to detect a relative treatment difference of 10% for R2* cortex and medulla, respectively, after 52 weeks treatment. This treatment difference is considered clinically relevant but is hypothetical, as no previous studies have assessed whether semaglutide changes renal tissue oxygenation. However, relative differences in R2* of this magnitude (~5-15%) have been observed in various intervention studies of short duration.[24-26]

Limited data is available on the variation of R2* (cortex as well as medulla) in a diabetic CKD population. In a large trial in CKD patients, the CV for R2* cortex varied between 0.11 and 0.15 depending on time of assessments, whereas the CV for R2* medulla varied between 0.09 and 0.11.[27] In the proposed analysis where baseline is included as a covariate the CV should be smaller. CVs of 0.09, 0.12, 0.15 have been examined in the power calculations seen below. The power calculation is for each endpoint based on a two-sided test at the 5% significance level, with no adjustment for multiplicity.

**Table 9-1 R2* (cortex or medulla): Number of subjects with primary endpoint data needed to obtain 80% marginal power based on 2:1 randomisation**

| | Treatment ratio | | |
|---|---|---|---|
| **CV** | **1.05** | **1.10** | **1.15** |
| **0.09** | 123 | 36 | 18 |
| **0.12** | 216 | 60 | 30 |
| **0.15** | 333 | **90** | 45 |

There is no correction for multiplicity in the power calculation

Hence, with a CV of e.g. 0.15 and 90 subjects with primary endpoint data, the trial will with 80% power be able to detect a treatment ratio of 1.10 corresponding to a relative treatment difference of 10%, see Table 9-1.

Based on “Multiparametric Renal Magnetic Resonance Imaging: Validation, Interventions, and Alterations in Chronic Kidney Disease”,[28] the CV of global kidney perfusion is assumed to be 0.8, whereas the CV of T1 mapping is assumed to be 0.06 and 0.05 for cortex and medulla, respectively.

With data from 90 subjects, the detectable treatment ratio corresponding to 80% marginal power is then 1.56 for global kidney perfusion and 1.04 for T1 mapping (cortex as well as medulla). The expected treatment ratios between semaglutide and placebo are not known. However, in Cox et al, 2017 [28] the ratio of the estimated means in global cortical perfusion for healthy subjects versus CKD patients was approximately 2.8, whereas the ratio between the estimated means in T1 mapping in CKD patients versus healthy subjects was approximately 1.09 (cortex) and 1.02 (medulla). Hence, for two of the endpoints these treatment ratios are well above the detectable treatment ratios presented above. Due to the explorative nature of the trial, this is considered acceptable.

Based on the above, 90 subjects with primary endpoint data is needed. Assuming approximately 15% of randomised subjects will have missing data (mainly due to treatment discontinuation prior to the week 39 visit (V10)), 105 subjects will be randomly assigned to trial product.

## 9.3 Populations for analyses

The following populations are defined:

| Population | Description |
|---|---|
| Randomised | All subjects randomised. |
| Full analysis set (FAS) | All subjects randomly assigned to trial treatment and who take at least 1 dose of trial product. Exclusion of data from analyses should be used restrictively, and normally no data should be excluded from the FAS. Subjects will be analysed according to the treatment they actually received. |
| Safety analysis set (SAS) | All subjects randomly assigned to trial treatment and who take at least 1 dose of trial product. Subjects are analysed according to the treatment they actually received. |

Analyses of efficacy endpoints will be analysed based on the full analysis set and safety will be analysed based on the safety analysis set.

## 9.4 Statistical analyses

The first draft of the statistical analysis plan (SAP) will be finalised prior to first subject first visit (FSFV), and it will include a more technical and detailed description of the statistical analyses described in this section. Any changes will be documented in the change-log.

This section provides a description of the planned statistical analyses of the primary endpoints and a short summary of the analyses of gene-expression data. All analyses of gene-expression data will be described in detail in a separate bioinformatics analysis plan prepared by Bioinformatics & Data Mining, Novo Nordisk, which will be finalised prior to database lock.

### 9.4.1 General considerations

The comparison presented from a statistical analysis will be semaglutide versus placebo.

The randomisation is stratified by use of SGLT-2 inhibitors at baseline (yes/no), MRI field strength (1.5/3.0 T), as well as whether subjects participate in the biopsy subpopulation (yes/no). Stratification for biopsy subpopulation is done purely for administrative reasons, to balance the subpopulation treatment allocation and not because subpopulation membership is expected to be associated with the outcome. Accordingly, it will not be accounted for in the statistical analyses.[29]

When the term 'stratification' factor is applied it refers to use of SGLT-2 inhibitors at baseline (yes/no) and MRI field strength (1.5/3.0 T).

### 9.4.2 Primary endpoints

The primary endpoints are derived from the MRI scan. They are defined as the ratio of baseline to week 52 in:

- kidney oxygenation (cortex), R2* (no unit)
- kidney oxygenation (medulla), R2* (no unit)
- global kidney perfusion (no unit)
- kidney inflammation (cortex), T1 mapping (no unit)
- kidney inflammation (medulla), T1 mapping (no unit)

**Primary analysis, if all subjects had adhered to the randomised treatment, without initiation of disallowed medication**

The aim of the analysis is for each of the endpoints to estimate the treatment ratio between semaglutide and placebo after 52 weeks of treatment if all subjects had adhered to the randomised treatment of semaglutide/placebo, without initiation of disallowed medication.
The following intercurrent events are considered:

- Permanent discontinuations of treatment prior to the week 39 visit:
  - When subjects discontinue treatment, the end of treatment visit (V11) will be scheduled as soon as possible thereafter. Unless subjects have discontinued treatment prior to the week 26 visit (V9), the MRI scan and biopsy will be performed. However, data collected for subjects who discontinue treatment prior to the week 39 visit (V10) will not be applied in the analysis. For this intercurrent event a hypothetical strategy is applied, and data will be imputed as described below.
- Permanent discontinuation of treatment at or after the week 39 visit:
  - Data collected after this intercurrent event will be used in the analysis as week 52 assessments.
- Maintenance treatment at 0.5 mg or 1 mg semaglutide/placebo is not reached:
  - A continued maintenance treatment at the 0.25 mg semaglutide/placebo is not allowed. Subjects who cannot tolerate a dose of at least 0.5 mg as a maintenance dose should discontinue treatment and data will be handled as described above.
- Initiation of GLP-1 RA, SGLT-2 inhibitor (only for subjects not on SGLT-2 at baseline) and/or finerenone:
  - Initiation of GLP-1 RAs, SGLT-2 inhibitors and/or finerenone is not allowed. Data collected after these intercurrent events from subjects that fulfil discontinuation criteria 6, 7, or 8 will not be used in the analysis, regardless of continued trial participation.
- Discontinuation or change of dose of SGLT-2 inhibitors (only for subjects on SGLT-2 inhibitors at baseline):
  - Discontinuation of SGLT-2 inhibitors is discouraged unless due to safety reasons. Change of dose of SGLT-2 inhibitors is allowed during the trial, because this is expected to have little effect on the MRI and biopsy endpoints. Therefore, data collected after these intercurrent events will be applied in the analysis.

Change from baseline analyses will be done on log scale based on the FAS. The log treatment differences will be back transformed in order to obtain treatment ratios for reporting. Imputation of

missing data (either truly missing or omitted from analysis due to the hypothetical strategy) will be handled by multiple imputations assuming that the missing data are missing at random (MAR). Missing data will be imputed using observed data within the same actual treatment group. It is thereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who receive the same actual treatment.

A sequential regression approach for imputing missing values at planned visits will be implemented for each endpoint starting with V6 and continuing to the planned end of treatment visit at week 52 (V11). For each actual treatment group an analysis of covariance (ANCOVA) model will be used to impute missing values at the planned post-baseline visits. The model will include region and stratification factors as categorical effects and baseline and, (when applicable) the post-baseline value prior to the visit in question as covariates. A total of 500 copies of the dataset will be generated.

An ANCOVA with actual treatment, region and the stratification factors as categorical effects and the endpoint baseline value as a covariate will for each endpoint be used to estimate the treatment difference on the log scale at week 52 for each of the 500 complete data sets generated as part of the imputation of missing values. Rubin's rule will be used to combine the estimates, which will then be backtransformed in order to draw inference on the relative scale.

The estimated treatment ratio between semaglutide and placebo will be presented together with the associated two-sided 95% confidence interval and a two-sided p-value. Due to the explorative nature of the trial, no adjustment for multiplicity is made.

**Sensitivity analysis, delta-adjustment**
The aim of the analysis is to assess the sensitivity of results to the missing at random assumption. The analysis address if discontinued subject had adhered to the treatment regimen but would have responded less favourably than adherent subjects.

The delta adjustment analysis is based on the FAS. In this analysis, subjects from the semaglutide group with missing observations will be given a penalty (a delta value), i.e., it is assumed that subjects with missing observations who are treated with semaglutide will have less favourable outcomes than subjects with observed values who are treated with semaglutide.

The 500 complete datasets created for the primary analysis will be re-used for the delta adjustment analysis. For each of these datasets, a penalty is added to the imputed log-change from baseline at week 52 for subjects with actual treatment semaglutide, followed by performing the ANCOVA applied for the primary analysis. A range of penalties will be applied to assess the impact on the results.

**Additional analysis, while on treatment after week 26 if all subjects had adhered to the randomised treatment at least until week 26, without initiation of disallowed medication**
The aim of the analysis is to estimate the treatment ratio between semaglutide and placebo while on treatment after week 26 if all subjects had adhered to the randomised treatment at least until week 26, without initiation of disallowed medication.
The following intercurrent events are considered:

- Permanent discontinuations of treatment prior to the week 26 visit (V9):

- For subjects who discontinue treatment prior to the week 26 data, the final MRI scan and biopsy will not be performed. For this intercurrent event a hypothetical strategy is applied, and data will be imputed from the 'while-on treatment after week 26' values.

- Permanent discontinuation of treatment at or after the week 26 visit:
  - Data collected after this intercurrent event will be used in the analysis. A while on treatment strategy is applied.
- Maintenance treatment at 0.5 mg or 1 mg semaglutide/placebo is not reached:
  - A continued maintenance treatment at the 0.25 mg semaglutide/placebo is not allowed. Subjects who cannot tolerate a dose of at least 0.5 mg as a maintenance dose should discontinue treatment and data will be handled as described above.
- Initiation of GLP-1 RA, SGLT-2 inhibitor (only for subjects not on SGLT-2 at baseline) and/or finerenone:
  - As for the primary analysis, data collected after these intercurrent events from subjects that fulfil discontinuation criteria 6, 7, or 8 will not be used in the analysis, regardless of continued trial participation.
- Discontinuation or change of dose of SGLT-2 inhibitors (only for subjects on SGLT-2 inhibitors at baseline):
  - As for the primary analysis, data collected after these intercurrent events will be applied in the analysis.

The analysis will, as the primary analysis, be done on log scale based on the FAS. The imputation of missing values will be further described in the SAP.

### 9.4.3 Secondary endpoints

#### 9.4.3.1 Supportive secondary endpoints

**Relative change in gene expression as fold change from kidney biopsy generated snRNAseq**

A secondary endpoint is the fold change values derived from the changes in the gene expression within relevant cell types comparing different conditions. In order to achieve this, first, a dimensionality reduction and clustering of the abundance data will be performed. Annotation of clusters will be done manually or via a state-of-the-art classification tool. In order to accurately annotate cell types and ensure comparability with existing studies, available data sets will be compared (or integrated) with the REM*O*DEL data. After successful annotation of cell types, differences in cell type composition between placebo and semaglutide can be explored using differential abundance testing. For all cell types of interest, changes in gene expression within that cell type but between the different comparisons can be explored. In order to test for significance, state-of-the-art methods accounting for sample variation (pseudo-bulk, linear mixed models) will be used. Subsequent analysis could include trajectory inference and analysis of gene dynamics.

All analyses of the single nucleus RNA sequencing of cells from the kidney biopsies will be described in detail in the bioinformatics analysis plan.

**Remaining supportive secondary endpoints**

For details on the analyses of all other supportive endpoints, please refer to the SAP.

### 9.4.4 Exploratory endpoints

For details on analyses of exploratory endpoints, please refer to the SAP.

### 9.4.5 Other safety analyses

All safety analyses will be made on the safety analysis set. The standard safety assessments (AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively; including any notable changes of clinical interest in laboratory parameters.

### 9.4.6 Other analyses

The primary endpoints may be affected by differences in blood glucose. Exploratory analyses will therefore be performed to evaluate the association between the pre-scan plasma glucose levels and the primary endpoints.

For other analyses, please refer to the SAP.

#### 9.4.6.1 Pharmacokinetic and/or pharmacodynamic modelling

PK modelling based on the data from the current trial may be carried out, e.g. as a joint analysis of PK data from multiple trials. Other exploratory PK/PD and exposure-response analyses for this trial may be performed if deemed relevant. If PK and/or PK/PD modelling is performed, it will be carried out by Quantitative Clinical Pharmacology, Novo Nordisk, and the results will be reported separately from the CTR.

Individual drug concentration data will be tabulated in the CTR.

## 9.5 Interim analyses

No interim analysis is planned for this trial.

## 9.6 Data monitoring committee

Not applicable for this trial.

## 9.7 Reporting of the main part of the trial

Not applicable for this trial.

# 10 Supporting documentation and operational considerations

## 10.1 Appendix 1: Regulatory, ethical, and trial oversight considerations

### 10.1.1 Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[30] and applicable ICH Good Clinical Practice (GCP) Guideline[31]
    - Applicable laws and regulations

- The analysis of kidney biopsies (snRNAseq and histopathology assessments), which are solely analysed by laboratories at Michigan University, are exploratory in nature, and hence not considered fully GCP-applicable. The rights, safety and well-being of the subject will be protected, and data integrity will be assured.
    - The lab responsible for snRNAseq is heading the NIH-funded (National Institute of Health) KPMP (kidney precision medicine project).
    - The lab responsible for the histopathology assessments is CLIA-certified (Clinical Laboratory Improvement Act) and CAP-accredited (College of American Pathologists).
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
    - providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
    - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
    - ensuring submission of the CTR synopsis to the IRB/IEC
    - reporting any potential serious breaches to the sponsor immediately after discovery

### 10.1.2 Financial disclosure

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

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

### 10.1.3 Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the subject and answer all questions regarding the trial.

- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.
- Subjects must be informed about their privacy rights.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[31], Declaration of Helsinki[30] and the IRB/IEC or site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent forms during their participation in the trial.
- A copy of the informed consent forms must be provided to the subject.

### 10.1.4 Information to subjects during trial

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

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

### 10.1.5 Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the subject are transferred to Novo Nordisk.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.
- The subject must be informed about his/her privacy rights, including that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

### 10.1.6 Committees structure

#### 10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee.

### 10.1.7 Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements, such as those of the International Committee of Medical Journal Editors (ICMJE),[32] the Food and Drug Administration Amendment Act (FDAAA),[33] European Commission Requirements[1, 34, 35] 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 PCD is the last assessment of the primary endpoint, and is for this trial last subject first treatment (LSFT) + 52 weeks corresponding to visit 11. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed the end of treatment visit (V11). The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

### 10.1.8 Data quality assurance

#### 10.1.8.1 Case report forms

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on 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
- 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 on trial product not yet allocated to a subject)
- 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.

#### 10.1.8.2 Monitoring

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

#### 10.1.8.3 Protocol compliance

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

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

### 10.1.9 Source documents

- All data entered in the CRF must be verifiable in source documentation other than the CRF.
- If source data is entered directly in a paper CRF, each data entry or clear series of data entries must be signed and dated separately by the trial staff making the entry.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data reported on the paper CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify subject's medical history in source documents, such as subject's medical record.

- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

### 10.1.10 Retention of clinical trial documentation

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

### 10.1.11 Trial and site closure

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

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

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

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

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

### 10.1.12 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate and documented training for all

staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

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

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

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. This also includes ensuring that no indirect sharing of user credentials for IT systems used in this study takes place (e.g., by not sharing IT equipment with others in a way where user credentials have the possibility of being shared). The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

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

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

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

### 10.1.13 Indemnity statement

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

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

### 10.1.14 Publication policy

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

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

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

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

One or more investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators.

#### 10.1.14.1 Communication of results

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

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

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

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

#### 10.1.14.2 Authorship

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

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[36]

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

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

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

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

### 10.1.14.4 Investigator access to data and review of results

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

## 10.2 Appendix 2: Clinical laboratory tests

- The tests in Table 10-1 and Table 10-2 will be performed by the central laboratory with the exception of F2-isoprostanes per unit creatinine and semaglutide plasma concentration, which will be performed by the special laboratory, and urine pregnancy tests, which will be performed locally (at trial sites or at home).
- 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 central laboratory will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their lab SOPs. These data will not be transferred to the trial database. The investigator should review such values for AEs and report these according to this protocol.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- Laboratory samples will be destroyed no later than at finalisation of the CTR.
    - For subjects who consent to biobanking, human biosamples for future research will be stored as described in Appendix 6 (10.6).
- Laboratory results that could unblind the trial (e.g. PK data) will not be reported to the trial sites until the trial has been unblinded.

## Table 10-1 Protocol-required efficacy laboratory assessments

| Laboratory assessments | Parameters | Visit |
|---|---|---|
| Renal function | Serum/plasma:<br>• Creatinine<br>• Creatinine-based eGFR, calculated per CKD-EPI equation<br>• Cystatin C<br>• Cystatin C-based eGFR, calculated per CKD-EPI equation | V1, V3, V4, V6, V8, V9, V10, V11, V12 |
| | First morning void spot urine:<br>• Urinary albumin-to-creatinine ratio (UACR) | UACR:<br>V1, V3, V4, V6, V8, V9, V10, V11, V12 |
| | On site random spot urine:<br>• Sodium and fractional sodium excretion | Sodium and fractional sodium excretion:<br>V3, V6, V8, V11 |
| | 24-hour urine:<br>• Volume<br>• Creatinine clearance<br>• Albumin excretion rate<br>• Sodium excretion rate<br>• pH | V3, V6, V8, V11 |
| Biomarkers | Serum/plasma:<br>*Inflammation:*<br>• High-sensitivity C-reactive Protein (hs-CRP)<br>• Interleukin 6 (IL-6)<br>• Soluble Tumour Necrosis Factor Receptor-1 (sTNFR1)<br>• Soluble Tumour Necrosis Factor Receptor-2 (sTNFR2)<br>• Tumour Necrosis Factor Alpha (TNF-α)<br>• uric acid<br>*Renal injury:*<br>• Fibrinogen<br>On site random spot urine:<br>*Inflammation*:<br>• Monocyte Chemoattractant Protein-1 (MCP-1)<br>*Renal injury:*<br>• Kidney Injury Molecule-1 (KIM-1)<br>• Neutrophil Gelatinase-associated Lipocalin (NGAL)<br>*Oxidative stress*:<br>• F2-isoprostanes per unit creatinine<br>• 8-oxo-2'-deoxyguanosine (8-OHdG) | hs-CRP:<br>V1, V3, V4, V6, V8, V9, V10, V11, V12<br><br>All other biomarkers (serum/plasma and on site random spot urine):<br>V3, V6, V8, V11 |
| Glucose metabolism | • $HbA_{1c}$ | V1, V3, V4, V6, V8, V9, V10, V11, V12 |
| Lipids | • Cholesterol<br>• HDL cholesterol<br>• LDL cholesterol<br>• Triglycerides | V3, V6, V8, V11 |
| Pharmacokinetics | • Semaglutide plasma concentrations | V6, V8, V9, V11 |

## Table 10-2 Protocol-required safety laboratory assessments

| Laboratory assessments | Parameters | Visit |
|---|---|---|
| Haematology | • Haemoglobin<br>• Haematocrit | V3, V6, V8, V11 |
| Biochemistry | • Albumin<br>• Potassium<br>• Sodium<br>• Calcium<br>• Albumin-corrected calcium<br>• Urea<br>• Bicarbonate | V3, V6, V8, V11 |
| Pregnancy Testing | • Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP)[a] | V1, V3, V11, V12 |

**a.** Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.

WOCBP: woman of child-bearing potential.

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

### 10.3.1 Definition of AE

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

| **Events meeting the AE definition** |
|---|
| • Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected<br>• Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected<br>• Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition<br>• Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction<br>• Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent<br><br>A "lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition. |
| **Events NOT meeting the AE definition** |
| • Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or other trial procedures performed before exposure to IMP.<br>Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.<br>• Medical or surgical procedures (e.g. endoscopy, appendectomy). The condition that leads to the procedure is the AE.<br>• Medical or surgical procedures not preceded by an AE or worsening of a known condition. |

### 10.3.2 Definition of an SAE

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

**a. Results in death**

**b. Is life-threatening**

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

**c. Requires inpatient hospitalisation or prolongation of existing hospitalisation**

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

Note:

- Hospitalisations for administrative, trial related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs.
- Hospital admissions for medical or surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

**d. Results in persistent or significant disability/incapacity**

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

**e. Is a congenital anomaly/birth defect**

**f. Important medical event:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
- The following adverse events must always be reported as SAEs using the important medical event criterion if no other seriousness criteria are applicable:
    - Suspicion of transmission of infectious agents via the IMP
    - Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL where no alternative aetiology exists (Hy's law). Please see the box 'Follow-up of an AE and SAE' in Section 10.3.4.

### 10.3.3 Description of AEs requiring additional data collection

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

**Adverse events requiring additional data collection**
AEs requiring additional data collection on a specific event form are listed in Table 8-1.

**Medication error**
A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the subject, such as:

- administration of wrong drug:
  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- wrong route of administration, such as intramuscular instead of subcutaneous
- accidental administration of 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.

**Misuse and abuse**

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

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

**Neoplasms (malignant and non-malignant)**

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

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

**AE and SAE recording**

- SAEs and AEs listed in Section 8.3 and AEs/SAEs in connection with pregnancies, must be recorded by the investigator in the CRF. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to Novo Nordisk.

- For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE related forms, refer to "AE and SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

**Assessment of severity**

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

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

**Assessment of causality**

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

| **Final outcome** |
|---|
| The investigator will select the most appropriate outcome:<br>• **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented<br>• **Recovering/resolving:** The condition is improving, and the subject is expected to recover from the event. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).<br>Note: For SAEs, this term is only applicable if the subject has completed the follow-up period and is expected to recover.<br>• **Recovered/resolved with sequelae:** The subject has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.<br>• **Not recovered/not resolved:** The condition of the subject has not improved, and the symptoms are unchanged, or the outcome is not known.<br>Note: This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).<br>• **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.<br>• **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 or Hy's law. Please see seriousness criteria f). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.<br><br>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.<br><br>New or updated information will be recorded in the CRF. |

### 10.3.5 Reporting of SAEs

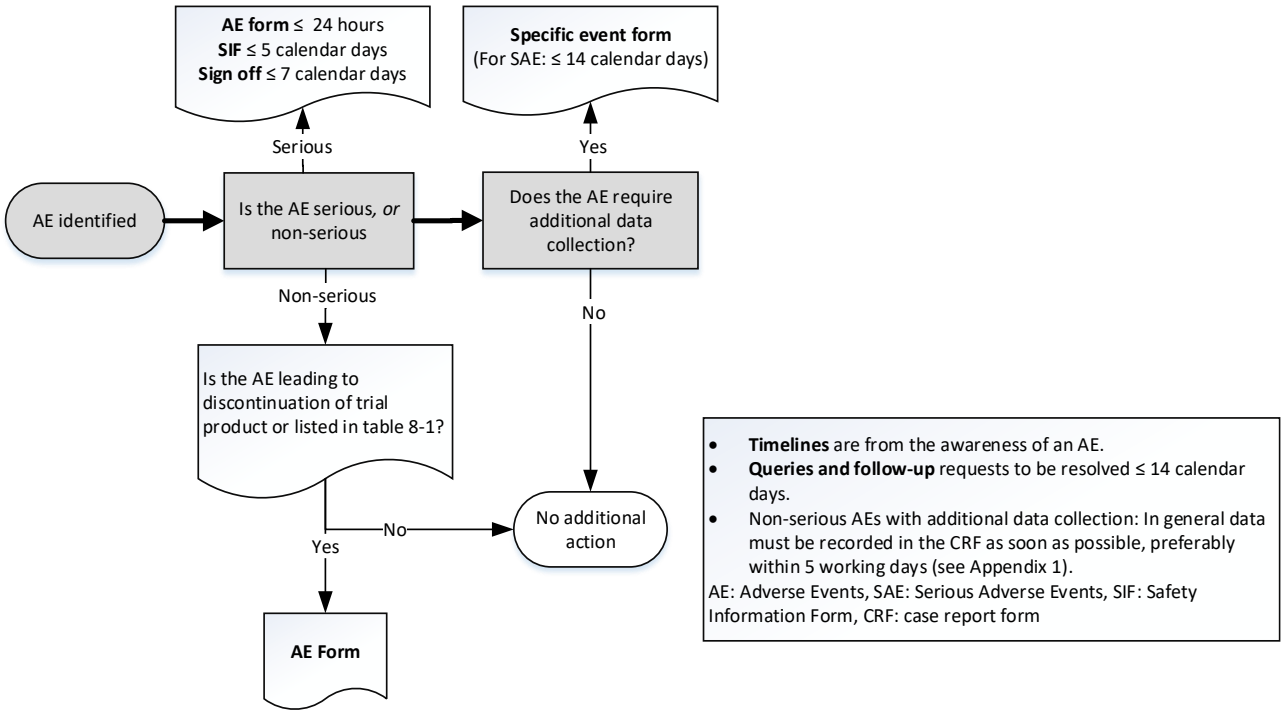
**SAE reporting via electronic CRF**

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

**AE and SAE reporting via paper CRF**

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

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




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

## 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

**Definitions**

### Woman of childbearing potential (WOCBP)

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

If fertility is unclear (e.g. amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of trial treatment, additional evaluation should be considered.

### Females in the following categories are not considered WOCBP

1. Premenarcheal
2. Females with one or more of the following:
   - Documented total hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

11. Females with permanent infertility due to an alternate medical cause other than the above (e.g. Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining trial enrolment.

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

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

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

### Contraception guidance

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 10-3:

**Table 10-3 Highly effective contraceptive methods**

| **CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:** |
|---|
| **Highly effective methods[b, d] that have low user dependency**:<br>• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]<br>• Intrauterine device (IUD)<br>• Intrauterine hormone-releasing system (IUS)[b]<br>• Bilateral tubal occlusion<br>• Vasectomized partner<br>(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)<br><br>**Highly effective methods[b,d] that are user dependent**:<br>• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]<br>o oral<br>o intravaginal<br>o transdermal<br>o injectable<br>• Sexual abstinence<br>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 treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject. |
| *NOTES*<br>a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical trials.<br>b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.<br>c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.<br>d) Contraception should be utilised during the treatment period and for at least 35 days (corresponding to time needed to eliminate trial product) 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 in Table 10-3 or where the use of any of the listed highly effective contraceptive measures are contraindicated in the individual subject, and/or
- if the risk of initiating treatment with a specific highly effective method outweighs the benefit for the female.

Justification for accepting double barrier method should be at the discretion of the investigator taking into consideration his/her knowledge about the female's medical history, concomitant illness, concomitant medication and observed AEs. The justification must be stated in the medical records.

**Pregnancy testing**

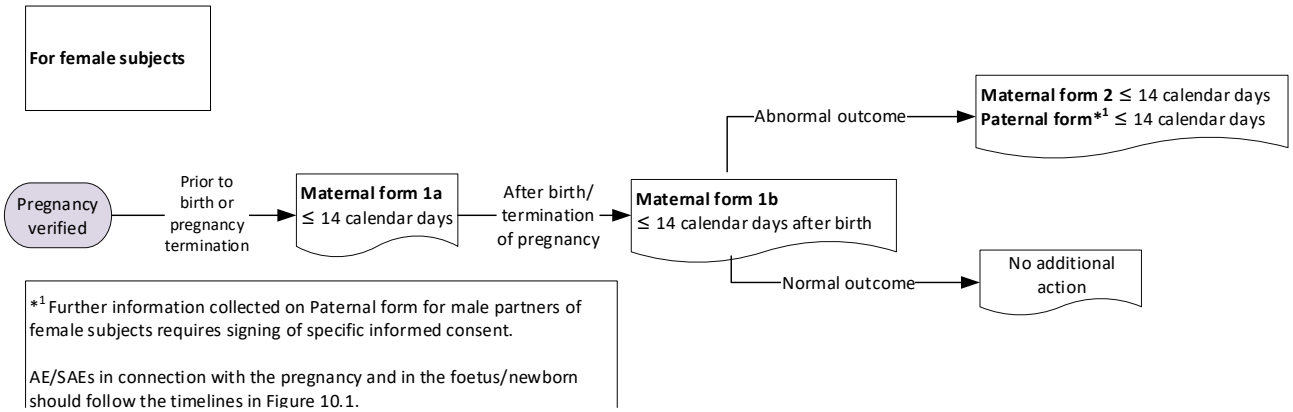
- Additional pregnancy testing should be performed during the treatment period, if required locally (Appendix 9 [10.9]).
- WOCBP should only be included after a negative highly sensitive urine pregnancy test (refer to Appendix 2 [10.2]).
- A pregnancy test should be performed at the end of relevant systemic exposure (refer to Appendix 2 [10.2]).
- Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.

**Collection of pregnancy information**

***F****emale subjects who become pregnant*

- Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy (see Figure 10-2).
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate which will be forwarded to Novo Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding 'gestational', 'pregnancy related' or a similar term when reporting the AE/SAE.
- Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the IMP by the investigator will be reported to Novo Nordisk as described in Appendix 3 (10.3). While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.
- In case of abnormal pregnancy outcome, the male partner will be asked to sign a specific informed consent form for further collection of paternal information

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




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

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

### 10.5.1 Definition of technical complaint

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

Examples of technical complaints:

- Problems with the physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- Problems with packaging material including labelling
- Problems related to 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 site until the time of the last usage of the product must be collected for products predefined on the technical complaint form. |

### 10.5.2 Recording and follow-up of technical complaints

| Reporting of technical complaints to Novo Nordisk |
|---|
| Contact details for Customer Complaint Center, please refer to Attachment I.<br><br>Technical complaints must be reported on a separate technical complaint form:<br>1. One technical complaint form must be completed for each affected DUN.<br>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:<br>• 24 hours if related to an SAE<br>• 5 days calendar for all other technical complaints<br><br>If the CRF is unavailable, or when reporting a technical complaint on a trial product that is not yet allocated to subject, the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the 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 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.<br>Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product. |

### 10.5.3 Reporting of technical complaints

| **Reporting of technical complaints for Novo Nordisk products not included in technical complaint form** |
|---|
| Technical complaints on Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk. |

## 10.6 Appendix 6: Retention of human biosamples

For patients who consent, the trial will involve collection of human biosamples to be stored in central archives for future use as noted in Section 8.8. The following samples will be stored:

- Plasma (for future analyses of circulating biomarkers)
- Serum (for future analyses of circulating biomarkers)
- Urine (for future analyses of urinary biomarkers)
- Kidney tissue (applicable to subjects who consent to both kidney biopsy and biobanking). No additional biopsy will be performed, and no additional biopsy core will be acquired from the planned biopsies; only potential surplus kidney tissue sample will be stored.

As new biomarkers related to the disease and/or safety, efficacy or mechanism of action of semaglutide within T2D and CKD may evolve during the conduct of the trial, the analyses of the stored biosamples may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial.

The samples will be transferred and stored at a secure central biorepository 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. Only Novo Nordisk staff and biorepository personnel will have access to the stored samples.

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

Confidentiality and personal data protection will be ensured during storage after the end of trial. The subject's identity will remain confidential and the samples will be identified only by subject number, visit number, and trial identification number. No direct identification of the subject will be stored together with the samples.

In the event that the collected biosamples will be used in the future, the investigator will become directly informed by Novo Nordisk about the results, if the findings are deemed clinically relevant and analytically valid and quantifiable. In such case, a written summary of the findings, including listings of subject specific values, will be provided once a firm conclusion from the results has been drawn by Novo Nordisk. Potentially, observations of neoplastic diseases, serious hereditary diseases, other un-treatable diseases or any other abnormal findings could be part of the observations.

## 10.7 Appendix 7: Severe hypoglycaemic episodes

Only severe hypoglycaemic episodes are to be collected in this trial.

### Severe hypoglycaemia

Severe hypoglycaemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[37]

### Nocturnal hypoglycaemia

Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.

### Reporting of severe hypoglycaemic episodes

Reporting of severe hypoglycaemic episodes by BG meters:
Plasma glucose (PG) should always be recorded in the eCRF when a severe hypoglycaemic episode is suspected.

If the severe hypoglycaemic episode fulfils the criteria for an SAE then, an AE form and a safety information form must also be filled in. One AE form and safety information form can cover several hypoglycaemic episode forms, if the subject has not recovered between the episodes, see Section 8.3.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the PG value is ≥3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines.[37]

Repeated PG measurements and/or symptoms will by default be considered as one hypoglycaemic episode until a succeeding PG value is ≥3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved and should be reported as only one hypoglycaemic episode. In case of several low PG values within the hypoglycaemic episode, the lowest value is the one that will be reported as the PG value for the hypoglycaemic episode, but the start time of the episode will remain as the time for the first low PG value and/or symptom. The remaining values will be kept as source data.

## 10.8 Appendix 8: Mitigations to ensure subject safety and data integrity during epidemics/pandemics (e.g. COVID-19)

In case local restrictions due to COVID-19 lead to lockdown of a site, the investigator must contact the sponsor (Novo Nordisk) to allow for implementation of the mitigations mentioned in this appendix based on mutual agreement.

The assessments listed in Table 10-4 indicate the minimum requirements that should be performed during a lockdown, although investigators should always aim to follow the assessments outlined in the protocol flowchart to the extent possible. Implementation of specific mitigations should be based on a feasibility assessment at the individual site.

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

### 10.8.1 Site visits

- The information visit (Visit 0), screening visit (Visit 1) and randomisation (Visit 3) must always be performed as physical on-site visits. If a site is unable to perform these visits on-site, screening and randomisation of new subjects at that site should be on hold until on-site visits can be conducted.
- Visit including MRI scans (Visit 2, 6 and 11) and kidney biopsies (Visit 2 and 11) (relevant for the biopsy sub-population only) should always be performed as physical on-site visits at respective imaging and biopsy sites.
- Efforts to assess and collect as much data as possible to the flowchart must always be ensured. Visit 4, 8, 9, 10 and 12 can however be converted to phone visits, if deemed necessary because of the lockdown. Minimum requirements for assessments during a phone visit are shown in Table 10-4. Visit 5 and 7 are already phone visits as per protocol.
- At each visit the investigator must indicate in the eCRF how the visit was performed and specify the reason for the preferred assessment method.

### 10.8.2 Assessments

- Assessments used for the primary and supportive secondary endpoints (i.e. MRI scans, kidney biopsies, first morning void spot urine, and 24-hour urine) should be prioritised.
- First morning void spot urine and 24-hour urine can be shipped to the site if on-site visits are not possible. The site is responsible for contracting a suitable courier and costs will be reimbursed by Novo Nordisk. It must be documented in medical records that the subject has consented to this process, and, if required locally, the subject might have to sign a separate informed consent form.
- Local laboratories or diagnostic facilities can be used for safety laboratory assessments if on-site visits cannot be conducted or in case of temporary lockdown of the central laboratory. Such data should not be entered in the eCRF.

### 10.8.3 Alternative dispensing methods of trial product

Alternative dispensing methods of study intervention may be implemented, and details will be communicated and documented. The dispensing options will eb based on options and requirements at country level and if permitted by local regulations and Novo Nordisk A/S.

### 10.8.4 Minimum assessments to be performed during lockdown

**Table 10-4 Minimum requirements that should be performed during a lockdown**

Please see Section 1.2 for the full flowchart. Procedures marked with a black X should be prioritised. If deemed necessary because of the lockdown, procedures marked with a red □ can be cancelled and Visit 4, 8, 9, 10 and 12 can be fully converted to phone visits.

| **Procedure** | **Information** | **Screening** | **Pre-treatment period** | **Randomisation** | **Treatment period** | | | | | | | **End of treatment** | **End of trial** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit number | V0 | V1 | V2 | V3 | V4 | P5 | V6 | P7 | V8 | V9 | V10 | V11 | V12 |
| Timing of Visit (Weeks) | Minimum 3 days prior to V1 | Prior to V2 and up to 6 weeks prior to V3 | Up to 5 weeks prior to V3 | 0 | 1 | 2 | 4 | 8 | 12 | 26 | 39 | 52 | End of treatment + 5 weeks |
| Visit Window (Days) | | | | - | ±3 | ±3 | ±3 | ±3 | ±7 | ±7 | ±7 | ±7[c] | +7 |
| Informed consent and demography | X | | | | | | | | | | | | |
| Inclusion and exclusion criteria | | X | | | | | | | | | | | |
| Randomisation criteria and randomisation | | | | X | | | | | | | | | |
| Concomitant medication | | X | | X | X | X | X | X | X | X | X | X | X |
| Concomitant illness/medical history | | X | | | | | | | | | | | |
| Tobacco and nicotine products use | | X | | | | | | | | | | | |
| Childbearing potential | | X | | | | | | | | | | | |
| Pregnancy test | | X | | X | | | | | | | | X | X |
| Physical examination | | X | | | | | | | | | | X | |
| Height | | | | X | | | | | | | | | |
| Body weight | | | | X | | | X | | □ | □ | □ | X | □ |
| Blood pressure | | X | | X | □ | | X | | □ | □ | □ | X | □ |
| Pulse | | X | | X | □ | | X | | □ | □ | □ | X | □ |
| Eye examination | | X | | | | | | | | | | X | |

| **Procedure** | **Information** | **Screening** | **Pre-treatment period** | **Randomisation** | **Treatment period** | | | | | | | **End of treatment** | **End of trial** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit number | V0 | V1 | V2 | V3 | V4 | P5 | V6 | P7 | V8 | V9 | V10 | V11 | V12 |
| Timing of Visit (Weeks) | Minimum 3 days prior to V1 | Prior to V2 and up to 6 weeks prior to V3 | Up to 5 weeks prior to V3 | 0 | 1 | 2 | 4 | 8 | 12 | 26 | 39 | 52 | End of treatment + 5 weeks |
| Visit Window (Days) | | | | - | ±3 | ±3 | ±3 | ±3 | ±7 | ±7 | ±7 | ±7[c] | +7 |
| MRI Scan | | | X | | | | X | | | | | X | |
| Kidney biopsy | | | X | | | | | | | | | X | |
| Laboratory assessments | | X | | X | □ | | X | | □ | □ | □ | X | □ |
| 24-hour urine collection | | | | X | | | X | | X | | | X | |
| First morning void collection | | X | | X | □ | | X | | □ | □ | □ | X | □ |
| On site random spot urine collection | | | | X | | | X | | □ | | | X | |
| Biosamples for future analysis | | | | X | | | X | | X | | | X | |
| Adverse event | | | | X | X | X | X | X | X | X | X | X | X |
| Severe hypoglycaemic episodes | | | | X | X | X | X | X | X | X | X | X | X |
| Drug dispensing | | | | X | | | X | | X[a] | X[a] | X[a] | | |
| Attend visit following dietary requirements | | | X | | | | X | | | | | X | |
| Training in devices | | | | X | | | X | | | □ | | | |

**a.** Trial product could if possible be dispensed via alternative methods listed in Section 10.8.3.

## 10.9 Appendix 9: Country-specific requirements

### Canada

- Appendix 1, Section 10 (10.1.10): Part C, Division 5 of the Food and Drug Regulations [C.05.012] requires a 25 year retention period

### Denmark

- Section 5.2, exclusion criterion 3; and Appendix 4 (Section 10.4): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG: Recommendations related to contraception and pregnancy testing in clinical studies. This means use of double barrier methods is not applicable for Denmark.
- Appendix 1 (Section 10.1.5), Data protection: The participant must be informed about his/her privacy rights, including that his/her personal study-related data will be used by Novo Nordisk in accordance with local data protection law in the given country of data handling.

### France

- Appendix 1, Section 13 (10.1.13): The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I,IX, Journal Officiel of 11 August 2004. "The sponsor is responsible for identification of the harmful consequences of the biomedical 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 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."
- Collection of age is needed for the calculation of eGFR per CDK-EPI.[38]
- Collection of race and ethnic origin will not be collected in the eCRF. This will only be recorded in the central laboratory requisition form for eGFR calculation.

### Poland

- Section 5.2, exclusion criteria 3; and Appendix 4 (10.4): Contraceptive measures according to the EU CTFG guideline.[39] This means use of double barrier methods is not applicable for Poland.
- **Indemnity statement**: Novo Nordisk carries liability for the Trial exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal of Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the Trial, Novo Nordisk and Investigator are covered by the Insurance Policy issued according to applicable Polish law.

### Spain

- Section 5.2, exclusion criteria 3; and Appendix 4 (10.4): Contraceptive measures according to the EU CTFG guideline.[39]
- Appendix 1, Section 10 (10.1.10): 25 years according to the Spanish Royal Decree 1090/2015.

**USA**

- Section 8.2.3 (eye examinations): Funduscopy/fundusphotography will be performed by the investigator or a local ophthalmologist/optometrist according to local practice

## 10.10 Appendix 10: Abbreviations

| | |
|---|---|
| ACE | angiotensin-converting enzyme |
| ADC | apparent diffusion coefficient |
| AE | adverse event |
| ANCOVA | analysis of covariance |
| aPTT/PTT | activated prothromboplastin time / thromboplastin time |
| ARB | angiotensin II receptor blockers |
| BG | blood glucose |
| CKD | chronic kidney disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| COVID-19 | coronavirus disease 2019 |
| CRF | case report form |
| CTFG | Clinical Trial Facilitation Group |
| CTR | clinical trial report |
| CVOT | cardiovascular outcome trial |
| DFU | directions for use |
| DUN | dispensing unit number |
| EAC | event adjudication committee |
| eCRF | electronic case report form |
| ESKD | end stage kidney disease |
| FAS | full analysis set |
| FDA | U.S. Food and Drug Administration |
| FDAAA | FDA Amendments Act |
| GLP-1 | glucagon-like peptide 1 |
| GLP-1 RA | glucagon-like peptide 1 receptor agonist |
| $HbA1_c$ | glycated haemoglobin |
| HDL | high-density lipoprotein |
| HRT | hormone replacement therapy |
| hsCRP | high-sensitivity C-reactive protein |
| ICH | International Council for Harmonisation |
| IEC | independent ethics committee |
| IMP | investigational medicinal product |
| IRB | institutional review board |
| IWRS | interactive web response system |
| LDL | low-density lipoprotein |
| LSLV | last subject last visit |

| | |
|---|---|
| MACE | major adverse cardiovascular event |
| MCP-1 | monocyte chemoattractant protein 1 (also known as CCL2) |
| MOA | mode of action |
| MRI | magnetic resonance imaging |
| mRNA | messenger ribonucleic acid |
| NSAID | nonsteroidal anti-inflammatory drug |
| OW | once-weekly |
| PCD | primary completion date |
| PG | plasma glucose |
| RAAS | renin-angiotensin-aldosterone system |
| RARI | renal artery resistive index |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGLT-2 | sodium glucose cotransporter-2 |
| snRNAseq | single nucleus RNA sequencing |
| SOP | standard operating procedure |
| SUSAR | suspected unexpected serious adverse reaction |
| SUSTAIN | Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes |
| TMM | trial materials manual |
| T2D | type 2 diabetes |
| WOCBP | woman of child-bearing potential |

## 10.11 Appendix 11: Protocol amendment history

The Protocol amendment summary of changes table for the current protocol version is located directly before the table of contents.

### Protocol version 2.0, including version 1: (29 January 2021), global

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

### Overall rationale for preparing protocol, version 2.0:

To align minimum requirements for the kidney biopsy sites, kidney biopsy procedure and sponsor oversight. In addition, randomisation criterion no. 5 was added to ensure stable dose of RAAS blocking agent between screening and randomisation. Changes to the content of the protocol are presented in the table below.

To increase consistency and clarity, semantic changes were introduced in Sections 1.2, 5.3.1, 6.1, 6.3, 7.1, 8.2.1, 8.8, 8.8.1, and in Appendix 6.

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 1.1 Synopsis | Small changes to key inclusion and exclusion criteria, and minor editorial changes | To align wording with eligibility criteria in section 5.1 and 5.2; and for clarity. |
| Section 1.2 Flowchart | Included X for concomitant medication at V1 | To align with text in Section 6.5 |
| Section 2.3.1 Risk assessment | Addition of 'angioedema' to 'Allergic reactions' in Table 2-1 | The template text for the benefit-risk section for protocols has been updated with angioedema for trials with OW semaglutide |
| Section 5.1 Inclusion criteria | Definition of 'screening UACR' moved from Section 6.3 to this section, from 6.3 | To define screening UACR where it is most applicable. |
| Section 5.2 Exclusion criteria | 1. Reference added to the additional exclusion criteria specific for the biopsy subpopulation<br>2. Criteria 15 corrected<br>3. Criteria 22 corrected | 1. To align minimum requirements for the biopsy subpopulation across sites<br>2. To align with timing of the eye examination specified in the flowchart and in Section 8.2.3<br>3. To align SGLT-2i requirements with Section 4.2 |
| Section 5.2.1 Biopsy subpopulation exclusion criteria | Entire section 5.2.1 added. | To align minimum safety requirements for subjects enrolled in the kidney biopsy subpopulation across all sites. |
| Section 5.4 | Correction of which screening criteria can be re-screened. | To align incorrect numbers with the correctly written text |
| Section 5.5 Randomisation criteria | Added criterion no 5 regarding stable dose of RAAS blocking agent | To ensure subject is on stable treatment of RAAS blocking agent between screening and randomisation. |

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 6.5 Concomitant medication | Section restructured and split into sub-sections. The following text was added:<br>1. Clarify that RAAS blocking agent must be kept stable between 'screening and randomisation'<br>2. Correct the number of days subjects can be treated with systemic anti-inflammatory drugs<br>3. Recommendations on dose reductions of sulphonylurea and insulin when initiating treatment with trial product. | For clarity<br>1. To align with the new randomisation criterion no 5.<br>2. To align with section 7.1<br>3. To reduce the risk of hypoglycaemia is subjects treated with sulphonylurea or insulin. |
| Section 8.1.1 Magnetic resonance imaging | 1. Text on where to find information on MRI setup, conduct, analysis and archiving updated<br>2. Details added on plasma glucose measurement before MRI<br>3. Update to description of subjects discontinuing during week 3.<br>4. Explanation on medical reading of MRI updated<br>5. Text about informed consent form for MRI test person removed | 1. To clarify that information on imaging processes and analysis can be found in more than 2 documents<br>2. To clarify where to document the glucose measurement, and to describe dietary requirements<br>3. To improve clarity<br>4. To ensure medical reading of MRI and reporting of potential SAEs<br>5. To correct a mistake (not all MRI sites will have this informed consent form) |
| Section 8.1.2 Kidney biopsy | New section (including 3 sub-sections) added to describe:<br>• minimum requirements for the kidney biopsy operator<br>• minimum biochemical, imaging and clinical requirements that subjects must fulfil in advance of the biopsy<br>• minimum requirements for the post-biopsy regimen and information to be provided to subjects<br><br>Text regarding requirements for kidney biopsy operator moved to new section 8.1.2.1.1. In addition, minor editorial changes to text. | To align minimum safety requirements for the kidney biopsy across all sites, and to improve readability of document |
| Section 8.1.4 Urine collection | Text added to ensure subject is instructed to keep 24-hour urine samples refrigerated at home and cooled during transit to site | To increase reliability of pH assessment of urine samples |
| Appendix 1 Regulatory, ethical and trial oversight<br><br>Section 10.1.12 Responsibilities | Text added to clarify investigator's responsibilities with regards to confidential information on shared IT equipment | To reduce the risk of unauthorised access to subject's confidential information. |
| Appendix 2 Clinical laboratory tests<br><br>Table 10-1 Protocol-required efficacy laboratory assessments | Update of visit numbers for assessments of UACR, sodium and fractional sodium excretion. | Correction, to align with planned assessments. According to the flowchart, first morning void (for UACR assessment) was to be collected at V4, but this was not correctly listed in Appendix 2. |

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Appendix 7 Severe hypoglycaemic episodes | Text added on reporting of severe hypoglycaemic episodes | To clarify reporting requirements |
| Appendix 8 Mitigations to ensure subject safety and data integrity in the case of a local or country-wide COVID-19 lockdown | Appendix added. The content of this memo was previously included in a memo, finalised in September 2020. | To ensure transparent and consistent handling of mitigations for COVID-19 pandemic |
| Appendix 9 Country-specific requirements | Removed requirements for Denmark | No sites from Denmark are planned to be included in REM*O*DEL. |
| Appendix 10 Abbreviations | New abbreviations included | Maintain readability of the document |

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