# Cover Page for Protocol

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| Document date: | 25 October 2018 |

### 16.1.1 Protocol and protocol amendments

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*Redacted protocol*
*includes redaction of personal identifiable and company confidential information.*

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# Protocol

## Trial ID: NN9924-4257

## PIONEER 7 – Flexible dose adjustment

## Efficacy and Safety of Oral Semaglutide Using a Flexible Dose Adjustment Based on Clinical Evaluation versus Sitagliptin in Subjects with Type 2 Diabetes Mellitus

*A 52-week Randomised, Open-label, Active-controlled Trial*

**Trial phase:** 3a

**Protocol originator**

[redacted]

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# List of abbreviations

| | |
|---|---|
| AACE | American Association of Clinical Endocrinologists |
| ADA | American Diabetes Association |
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| BG | blood glucose |
| BMI | body mass index |
| CFR | Code of Federal Regulations |
| CK | creatine kinase |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CLAE | clinical laboratory adverse event |
| CRF | case report form |
| DPP-4 | dipeptidyl peptidase-4 |
| DTSQ | Diabetes Treatment Satisfaction Questionnaire |
| DUN | dispensing unit number |
| EAC | event adjudication committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eGFR | Estimated Glomerular Filtration rate |
| FAS | full analysis set |
| FDA | U.S. Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendment Act |
| FPG | fasting plasma glucose |
| FSFV | first subject first visit |

| | |
|---|---|
| GCP | Good Clinical Practice |
| GLP-1 | glucagon-like peptide-1 |
| GLP-1 RA | glucagon-like peptide-1 receptor agonist |
| $HbA_{1c}$ | glycosylated haemoglobin |
| HDL | high density lipoprotein |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | independent ethics committee |
| IMP | investigational medicinal product |
| IRB | institutional review board |
| IWRS | interactive web response system |
| LDL | low density lipoprotein |
| LLoQ | lower limit of quantification |
| LOCF | last observation carried forward |
| LSFV | last subject first visit |
| LSLV | last subject last visit |
| MAR | missing at random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MEN 2 | Multiple Endocrine Neoplasia Type 2 |
| MI | myocardial infarction |
| MMRM | mixed model for repeated measurements |
| MTC | Medullary Thyroid Carcinoma |
| NIMP | non-investigational medicinal product |
| NSTEMI | Non-ST elevation acute myocardial infarction |
| NYHA | New York Heart Association |
| OAD | oral anti-diabetic drug |
| PG | plasma glucose |
| PK | pharmacokinetics |

| | |
|---|---|
| PRO | patient reported outcome |
| REML | restricted maximum likelihood |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | safety analysis set |
| s.c. | subcutaneous |
| SF-36v2™ | Short Form-36 version 2 |
| SGLT-2 | sodium glucose co-transporter 2 |
| SIF | safety information form |
| SmPC | summary of product characteristics |
| SMPG | self-measured plasma glucose |
| SNAC | absorption-enhancing excipient sodium N-[8-(2-hydroxybenzoyl)amino]caprylate |
| STEMI | ST-elevation acute myocardial infarction |
| SU | sulfonylureas |
| SUSAR | suspected unexpected serious adverse reactions |
| T2DM | Type 2 diabetes mellitus |
| TEAE | treatment-emergent adverse event |
| TIA | transient ischaemic attack |
| TMM | Trial Materials Manual |
| TZD | thiazolidinediones |
| UNL | upper normal limit |
| UTN | Universal Trial Number |

# 1 Summary

**Objectives and endpoints:**

**Primary objective**

To compare the effect of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once-daily, both in combination with 1-2 oral anti-diabetic drugs (OADs) on glycaemic control in subjects with Type 2 diabetes mellitus (T2DM).

**Secondary objectives**

To compare the effect of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once-daily, both in combination with 1-2 OADs on body weight in subjects with T2DM.

To compare the safety and tolerability of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once-daily, both in combination with 1-2 OADs in subjects with T2DM.

**Primary endpoint**

If a subject after week 52 achieves (yes/no) glycosylated haemoglobin ($HbA_{1c}$) < 7% (53 mmol/mol) American Diabetes Association target.

**Key secondary endpoints**

Change from baseline to week 52 in:

- Body weight (kg)
- $HbA_{1c}$
- Fasting plasma glucose

Number of treatment-emergent adverse events during exposure to trial product, assessed up to approximately 57 weeks.

Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks.

**Trial design:**

This is a 52-week randomised, open-label, active-controlled, parallel-group, multi-centre, multi-national trial with two arms comparing the efficacy and safety of oral semaglutide using a flexible dose adjustment versus sitagliptin, in subjects with T2DM treated with 1-2 OADs.

Subjects will be randomised 1:1 to receive one of the following treatments as add-on to their anti-diabetic background medication:

- flexible dosing (3, 7 or 14 mg) of oral semaglutide once-daily
- 100 mg sitagliptin once-daily

In this trial the dosing of oral semaglutide is flexible, following predefined dose adjustment criteria which are based on the subject's individual $HbA_{1c}$ and tolerability (nausea/vomiting). Sitagliptin should be taken once-daily on a fixed dose of 100 mg throughout the trial.

The total trial duration for the individual subject will be approximately 59 weeks. The trial includes a 2-week screening period, a 52-week treatment period and a 5-week follow-up period. The trial is designed to have visits every 8 weeks, including a phone contact at week 4.

**Trial population:**

Number of subjects planned to be randomised: 500

***Key inclusion criteria***

- 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.
- Male or female, age above or equal to 18 years at the time of signing informed consent.
  *For Korea only: Male or female, age above or equal to 19 years at the time of signing informed consent.*
- Diagnosed with type 2 diabetes mellitus ≥ 90 days prior to day of screening.
- $HbA_{1c}$ 7.5-9.5% (58-80 mmol/mol) (both inclusive).
- Treatment target of $HbA_{1c}$ < 7.0% (53 mmol/mol), as judged by the investigator.
- Stable daily dose(s) of 1-2 of the following anti-diabetic drugs within 90 days prior to the day of screening:
  - Metformin (≥1500 mg or maximum tolerated dose as documented in the subject medical record).
  - Sulfonylureas (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record).
  - Sodium glucose co-transporter 2 inhibitors.
  - Thiazolidinediones (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record).

***Key exclusion criteria***

- Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).
  *For certain specific countries: Additional specific requirements apply.*
- Any disorder, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
- Family or personal history of Multiple Endocrine Neoplasia Type 2 or Medullary Thyroid Carcinoma.
- History of pancreatitis (acute or chronic).
- History of major surgical procedures involving the stomach potentially affecting absorption of trial product (e.g. subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery).
- Any of the following: myocardial infarction, stroke or hospitalisation for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening and randomisation.
- Subjects presently classified as being in New York Heart Association Class IV.
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
- Subjects with alanine aminotransferase > 2.5 x upper normal limit.
- Renal impairment defined as Estimated Glomerular Filtration rate < 60 mL/min/1.73 $m^2$ as per Chronic Kidney Disease Epidemiology Collaboration formula.
- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before the day of screening. An exception is short-term insulin treatment for acute illness for a total of ≤ 14 days.
- Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomisation.
- History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and carcinoma *in situ*).
- History of diabetic ketoacidosis.

**Key assessments:**

***Efficacy:***

- $HbA_{1c}$
- Fasting plasma glucose
- Body weight

***Safety:***

- Adverse events
- Hypoglycaemic episodes

**Trial products:**

Investigational medicinal products:

- Test product:
  - semaglutide, 3 mg tablet
  - semaglutide, 7 mg tablet
  - semaglutide, 14 mg tablet
- Reference therapy:
  - sitagliptin (Januvia®), 100 mg tablet

# 2 Flow chart

| **Trial Periods** | Screening [a] | Randomisation | Treatment | | | | | | | End-of-treatment (EoT) | Follow-up [b] | EoT premature discontinuation [c] | Follow-up premature discontinuation [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit (V), Phone contact (P)** | V1 | V2 | P3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V10A | V11A |
| **Timing of visit (weeks)** | Up to -2 wks | 0 | 4 | 8 | 16 | 24 | 32 | 40 | 48 | 52 | 57 | Day of discontinuation of trial product | 5 weeks after discontinuation of trial product |
| **Visit window (days)** | | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | +3 | +3 | +3 |
| **SUBJECT RELATED INFO/ASSESSMENTS** | | | | | | | | | | | | | |
| Informed consent | x | | | | | | | | | | | | |
| In/exclusion criteria | x | x | | | | | | | | | | | |
| Concomitant medication | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Concomitant illness and medical history | x | | | | | | | | | | | | |
| Demography | x | | | | | | | | | | | | |
| Diagnosis of diabetes/diabetes complications | x | | | | | | | | | | | | |
| Hypoglycaemia unawareness | x | | | | | | | | | | | | |

| **Trial Periods** | Screening [a] | Randomisation | Treatment | | | | | | | End-of-treatment (EoT) | Follow-up [b] | EoT premature discontinuation [c] | Follow-up premature discontinuation [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
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| **Timing of visit (weeks)** | Up to -2 wks | 0 | 4 | 8 | 16 | 24 | 32 | 40 | 48 | 52 | 57 | Day of discontinuation of trial product | 5 weeks after discontinuation of trial product |
| **Visit window (days)** | | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | +3 | +3 | +3 |
| Tobacco use | x | | | | | | | | | | | | |
| History of cardiovascular disease | x | | | | | | | | | | | | |
| History of gallbladder disease | x | | | | | | | | | | | | |
| History of gastrointestinal disease | x | | | | | | | | | | | | |
| Randomisation | | x | | | | | | | | | | | |
| Criteria for premature discontinuation of trial product | | | x | x | x | x | x | x | x | | | | |
| **EFFICACY** | | | | | | | | | | | | | |
| Height | | x | | | | | | | | | | | |
| Body weight | | x | | x | x | x | x | x | x | x | | x | |
| Waist circumference | | x | | | x | | x | | | x | | x | |

| **Trial Periods** | Screening [a] | Randomisation | Treatment | | | | | | | End-of-treatment (EoT) | Follow-up [b] | EoT premature discontinuation [c] | Follow-up premature discontinuation [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
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| **Timing of visit (weeks)** | Up to -2 wks | 0 | 4 | 8 | 16 | 24 | 32 | 40 | 48 | 52 | 57 | Day of discontinuation of trial product | 5 weeks after discontinuation of trial product |
| **Visit window (days)** | | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | +3 | +3 | +3 |
| PRO questionnaires | | x | | x | x | | x | | | x | | x | |
| Dose adjustment criteria[d] | | | | x | x | x | x | x | x | | | | |
| Fasting plasma glucose | | x | | | | x | | | | x | | x | |
| $HbA_{1c}$[e] | x | x | | x | x | x | x | x | x | x | | x | |
| Lipids | | x | | | | x | | | | x | | x | |
| **SAFETY** | | | | | | | | | | | | | |
| Adverse events[f] | | x | x | x | x | x | x | x | x | x | x | x | x |
| ECG | | x | | | | x | | | | x | x | x | x |
| Eye examination[g] | x | | | | | | | | | | | | |
| Physical examination | x | | | | | | | | | x | | x | |
| Vital signs | | x | | x | x | x | x | x | x | x | x | x | x |

| **Trial Periods** | Screening [a] | Randomisation | Treatment | | | | | | | End-of-treatment (EoT) | Follow-up [b] | EoT premature discontinuation [c] | Follow-up premature discontinuation [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
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| **Timing of visit (weeks)** | Up to -2 wks | 0 | 4 | 8 | 16 | 24 | 32 | 40 | 48 | 52 | 57 | Day of discontinuation of trial product | 5 weeks after discontinuation of trial product |
| **Visit window (days)** | | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | +3 | +3 | +3 |
| Biochemistry[h] | x | x | | x | x | x | x | x | | x | x | x | x |
| Haematology | | x | | x | x | x | x | x | | x | x | x | x |
| Calcitonin | | x | | | | x | | | | x | x | x | x |
| Pregnancy test[i] | x | x | | x | x | x | x | x | x | x | x | x | x |
| Technical complaints | | | x | x | x | x | x | x | x | x | | x | |
| Hypoglycaemic episodes | | x | x | x | x | x | x | x | x | x | x | x | x |
| **TRIAL MATERIAL** | | | | | | | | | | | | | |
| Dispensing visit | | x | | x | x | x | x | x | x | | | | |
| Drug accountability | | x | | x | x | x | x | x | x | x | | x | |
| IWRS call | x | x | | x | x | x | x | x | x | x | | x | |
| | | | | | | | | | | | | | |

| **Trial Periods** | Screening [a] | Randomisation | Treatment | | | | | | | End-of-treatment (EoT) | Follow-up [b] | EoT premature discontinuation [c] | Follow-up premature discontinuation [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit (V), Phone contact (P)** | V1 | V2 | P3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V10A | V11A |
| **Timing of visit (weeks)** | Up to -2 wks | 0 | 4 | 8 | 16 | 24 | 32 | 40 | 48 | 52 | 57 | Day of discontinuation of trial product | 5 weeks after discontinuation of trial product |
| **Visit window (days)** | | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | +3 | +3 | +3 |
| **REMINDERS** | | | | | | | | | | | | | |
| Attend visit fasting[j] | | x | | | | x | | | | x | | x | |
| Handout and instruct in BG meter use | | x | | | | | | | | | | | |
| Handout ID card | x | | | | | | | | | | | | |
| Training in dosing instructions | x | x | x | x | x | x | x | x | x | | | | |
| Dispense and/or collect diary | x | x | | x | x | x | x | x | x | x | x | x | x |

| Footer | Description |
|---|---|
| x[a] | Subject can be randomised as soon as all inclusion and exclusion criteria are confirmed. The screening assessments must not exceed 2 weeks prior to randomisation (V2). |
| x[b] | Subjects who have discontinued trial product prematurely are not required to attend V11 (Follow-up). |
| x[c] | V10A and V11A are only applicable for subjects who have discontinued trial product prematurely. |
| x[d] | Dose adjustment criteria are subject's $HbA_{1c}$ (measured by point-of-care device) and tolerability (nausea/vomiting) |
| x[e] | Assessed at central laboratory |
| x[f] | Adverse events reporting includes adverse events from the first trial-related activity after the subject has signed the informed consent at V1. Pre-existing conditions identified as a result of the screening procedures should be reported as medical history. |
| x[g] | Fundus photography or dilated fundoscopy performed within 90 days before randomisation is acceptable if results are available for evaluation at visit 2 and no deterioration in visual function since last examination. |
| x[h] | At V1, only ALT, creatinine and eGFR will be assessed as part of Biochemistry. |
| x[i] | For women of child-bearing potential: Urine pregnancy test should also be performed at any time during the trial if menstrual period is missed, and/or according to local regulations/law. For details regarding local regulations/law see Section 6.3 |
| x[j] | Fasting for blood sampling is defined as no food or liquid within the last 8 hours prior to blood sampling, however water is allowed up until 2 hours prior to blood sampling. Trial product must be taken after blood sampling. Other oral medication can be taken 30 minutes after trial product (for subjects randomised to oral semaglutide only). Injectable medications can be administered after blood sampling. |

# 3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP)[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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

## 3.1 Background information

For an assessment of benefits and risks of the trial, see Section 18.1.

### 3.1.1 Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disease primarily characterised by abnormal glucose metabolism. The pathogenesis is heterogeneous involving environmental, lifestyle and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver[3].

Optimal glycaemic control is the treatment goal in subjects with T2DM in order to prevent long-term complications associated with chronic hyperglycaemia[4]. Despite the availability of several anti-diabetic drugs, a significant proportion of subjects with T2DM do not achieve the recommended targets for glycaemic control[5, 6].

### 3.1.2 Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone with a glucose-dependent stimulatory effect on insulin and inhibitory effect on glucagon secretion from the pancreatic islets[7, 8]. Subjects with T2DM have a decreased incretin effect[9-12]. However, the insulinotropic action of GLP-1 and thus, the ability to lower blood glucose (BG) levels, is preserved when GLP-1 is administered at supraphysiological levels[13]. In addition, supraphysiological levels of GLP-1 induce reduction in body weight[14]. GLP-1 is a physiological regulator of appetite and food intake and GLP-1 receptors are present in several areas of the brain involved in appetite regulation[15, 16]. Physiologically, GLP-1 also has a pronounced inhibitory effect on gastric emptying; however this effect seems to diminish upon chronic exposure[14-16]. These mechanisms of action make GLP-1 receptor agonists (GLP-1 RAs) an attractive pharmacological treatment for T2DM[17-19].

### 3.1.3 Oral semaglutide

Semaglutide is a long-acting GLP-1 RA structurally similar to liraglutide (Victoza®), a once-daily GLP-1 RA developed by Novo Nordisk and approved worldwide for the treatment of T2DM. Compared to human native GLP-1, which has a short half-life, the semaglutide molecule has three

minor but important modifications ensuring protraction of its action: amino acid substitutions at position 8 (alanine to alfa-aminoisobutyric acid, a synthetic amino acid) and position 34 (lysine to arginine), and acylation of the peptide backbone with a spacer and C-18 fatty di-acid chain to lysine in position 26[20]. The fatty di-acid side chain and the spacer mediate strong binding to albumin, thereby reducing renal clearance. The amino acid substitution at position 8 makes semaglutide less susceptible to degradation by dipeptidyl peptidase-4 (DPP-4). The change in position 34 from a lysine to an arginine is included to have only one lysine in the sequence where to a spacer can be attached.

Semaglutide is in development for oral once-daily treatment of T2DM. As the bioavailability of GLP-1 RAs is low when administered orally, semaglutide has been co-formulated with the absorption-enhancing excipient sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (SNAC) to increase the bioavailability of semaglutide. The absorption-enhancing properties of SNAC co-formulation is based on the [redacted] concept developed by [redacted]

SNAC facilitates the absorption of semaglutide in a strictly time- and size dependent manner, primarily via the transcellular route. The available data for semaglutide co-formulated with SNAC support that the absorption takes place in the stomach in a localised, buffered environment in close proximity of the tablet erosion. The absorption process is hampered if dosed with food, liquid or in the presence of significant stomach content.

The absorption enhancement requires co-formulation between semaglutide and SNAC. Throughout this document “oral semaglutide” will refer to the drug product, that is, semaglutide co-formulated with 300 mg SNAC.

### 3.1.4 Nonclinical data

#### 3.1.4.1 Semaglutide

The nonclinical programme for semaglutide was designed according to the ICH M3 guideline[21] to support the clinical development. The standard nonclinical data package required to support phase 3 clinical trials has been completed. In addition, 2-year carcinogenicity studies and a pre- and postnatal development toxicity study have been completed. Semaglutide was generally well tolerated in animals (mice, rats and cynomolgus monkeys). Two potential safety issues have been identified and these are detailed below.

**Thyroid C-cell tumours in rodents**
Treatment-related non-genotoxic proliferative changes in the thyroid C-cells of mice and rats were observed in 2-year carcinogenicity studies with semaglutide; thyroid hyperplasia was preceded by an increase in serum calcitonin. C-cell changes have not been observed in long-term studies in non-human primate. The observed pattern of effects in mice and rats and lack of these effects in the non-

human primate and in man suggest that the mechanism by which semaglutide acts on the thyroid C-cells in rodents is the same as has been demonstrated for other GLP-1 RAs, including liraglutide.

According to this mechanism, C-cell hyperplasia is mediated by the GLP-1 receptor and is not associated with RET (re-arranged during transfection) gene activation and rodents appear to be particularly sensitive, whereas humans are not. The relevance for human subjects is currently unknown, but considered to be low[22].

**Embryo−foetal development toxicity**
Semaglutide caused embryo-foetal development toxicity in the rat through a GLP-1 receptor mediated effect on the inverted yolk sac placenta leading to impaired nutrient supply to the developing embryo. Primates do not have an inverted yolk sac placenta which makes this mechanism unlikely to be of relevance to humans and cynomolgus monkeys. In the developmental toxicity studies in cynomolgus monkey, a marked maternal body weight loss associated with the pharmacological effect of semaglutide coincided with increased early foetal loss; however, there was no indication of a teratogenic potential of semaglutide in this species.

A review of the results from the nonclinical studies can be found in the investigator's brochure (IB) for semaglutide (subcutaneous (s.c.) administration), edition 10[23] and the IB for oral administration of semaglutide (NN9924), edition 6[24], or any updates of these documents.

### 3.1.4.2 SNAC

SNAC was developed as an absorption-enhancing excipient for the oral route of administration. The nonclinical programme to support clinical phase 3 development and marketing authorisation application submission has been conducted including a 26-week carcinogenicity study in transgenic rasH2 mice and a 2-year carcinogenicity study in Sprague-Dawley rats.

Measurements of lactate levels have been included at selected time points around peak concentrations of SNAC in two of the phase 3a trials in the PIONEER programme (PIONEER 1 and 2) with the intention to document that SNAC does not impair cellular respiration in humans. In addition, events of lactic acidosis must be reported as an adverse event (AE) requiring additional data collection, please refer to Section 8.4.1.2, Section 12.1.5 and appendix B.

The carcinogenicity studies demonstrated that SNAC was not carcinogenic to the transgenic rasH2 mouse or the Sprague-Dawley rat. The doses tested covered total exposures of SNAC in plasma (in terms of area under the curve [AUC]) of 2-fold in the mouse and up to 44-fold in the rat when compared to the mean total exposure of SNAC in humans following a clinical dose of 300 mg SNAC/day.

A review of the SNAC results from the nonclinical studies can be found in the IB for oral administration of semaglutide (NN9924), edition 6[24], or any updates hereof.

### 3.1.5 Clinical data for oral semaglutide

A comprehensive clinical pharmacology programme including 12 trials has been completed, as well as a 26-week phase 2 dose-finding trial involving more than 600 subjects with T2DM.

For details on the individual trials, please see the IB for oral administration of semaglutide (NN9924) edition 6[24], or any updates hereof.

#### 3.1.5.1 Pharmacokinetics

In the multiple-dose trial (NN9924-3991), oral semaglutide has demonstrated a long mean terminal half life ($t_{½}$) ranging from 153 to 161 hours (~1 week) and a median time to reach maximum observed concentration ($t_{max}$) ranging from 1 to 2 hours in healthy subjects.

In multiple-dose pharmacokinetics (PK) trials, the exposure to oral semaglutide increased with increasing dose. Overall, the pharmacokinetic properties of semaglutide appeared similar in healthy subjects and in subjects with T2DM.

Exposure of semaglutide exhibits a substantially greater dose-to-dose variation following oral administration compared to s.c. administration. However, when administered orally once-daily the PK properties of semaglutide, i.e. low clearance and long half-life, will limit the variation in exposure at steady state.

Data obtained following investigation of different dosing conditions for oral semaglutide have demonstrated that subjects should take the oral semaglutide tablet in the morning in a fasting state and at least 30 minutes before the first meal of the day.

[redacted]

In subjects with mild to severe hepatic impairment, the exposure to semaglutide appeared to be unaffected by the degree of hepatic impairment, whereas the exposure to SNAC (in terms of both AUC and $C_{max}$) was increased for subjects with hepatic impairment as compared to subjects with normal hepatic function.

All tablets of oral semaglutide contain 300 mg of SNAC regardless of the semaglutide dose. SNAC is rapidly absorbed with a median $t_{max}$ ranging from 0.35−0.5 hours in healthy subjects and from 0.52−1.43 hours in subjects with T2DM. It is extensively metabolised and no accumulation of SNAC has been observed in clinical trials.

#### 3.1.5.2 Efficacy

The efficacy of oral semaglutide in adult subjects with T2DM was investigated in a 26-week phase 2 dose-finding trial (NN9924-3790). In this trial, placebo or one of the following doses of oral semaglutide were administered once-daily: 2.5, 5, 10, 20 and 40 mg.

Results from the trial showed that oral semaglutide effectively lowered glycosylated haemoglobin ($HbA_{1c}$) and body weight. Placebo adjusted reductions in $HbA_{1c}$ were dose-dependent and statistically significant for all oral semaglutide treatment arms at week 26 (range: -0.40% to -1.59%). Placebo adjusted reductions in body weight were dose-dependent and statistically significant for oral semaglutide treatment doses of 10 mg and above at week 26 (range: -3.61 kg to -6.98 kg).

#### 3.1.5.3 Safety

In the clinical trials completed so far, no unexpected safety findings have been identified for oral semaglutide administered up to 40 mg once-daily. Consistent with other GLP-1 RAs, commonly reported AEs included nausea and vomiting, most of them were mild to moderate in severity. In line with findings for other GLP-1 RAs, an increase in heart rate and serum levels of lipase and amylase has also been observed in subjects exposed to oral semaglutide.

In addition to the 13 completed clinical trials with oral semaglutide, SNAC has been investigated in the programme of orally administrated heparin in combination with SNAC (heparin/SNAC). The

heparin/SNAC programme ([redacted]) included 29 phase 1 trials (SNAC doses ranged from 0.172-10.5 g). In three of these trials, SNAC alone was investigated (to a maximum dose of 10.5 g). The trials covered formulation development, food effect, hepatic and renal impairment, age-effect and drug-drug interaction. The programme also included a total of three phase 2 and 3 trials in which the effects of orally delivered heparin solution (with >1.5 g SNAC three times a day) was investigated. The overall safety profile of oral semaglutide and heparin/SNAC indicates that SNAC is safe and well-tolerated.

For further details, please see the IB for oral administration of semaglutide (NN9924) edition 6[24], or any updates hereof.

### 3.1.6 Sitagliptin

The selected active comparator in this trial is sitagliptin, an oral anti-diabetic drug (OAD) of the DPP-4 inhibitor class suitable for once-daily oral administration. Sitagliptin was developed by Merck & Co and has been marketed since 2006 under the trade name Januvia®. By inhibition of the enzyme DPP-4, which breaks down GLP-1 and gastric inhibitory polypeptide, secretion of insulin is increased and release of glucagon is suppressed.

Further information can be obtained in the current locally approved label for Januvia®.

## 3.2 Rationale for the trial

Many patients with T2DM are not in glycaemic control with the currently marketed OADs. Nevertheless, treatment with more efficacious injectable therapies such as GLP-1 RAs and insulin are rarely added during the early stages of the disease. Oral semaglutide is the first GLP-1 RA in development in a tablet formulation and it has the potential of becoming a new attractive treatment option early in the treatment cascade due to its effects on both hyperglycaemia and body weight.

The rationale for this trial is to compare the efficacy and safety of oral semaglutide employing a treatment regimen with a flexible dose adjustment of oral semaglutide according to pre-specified criteria. Oral semaglutide will be evaluated versus an established active comparator within the DPP-4 inhibitor drug class (sitagliptin) in subjects with T2DM. The pre-specified criteria for dose adjustment of oral semaglutide are based on the subject's individual $HbA_{1c}$ and tolerability (nausea/vomiting) evaluated every 8 weeks in the trial period. The individualised and flexible dosing strategy of oral semaglutide will ensure that each subject is treated with the optimal therapeutic dose. Hence, the trial is expected to provide data guiding the physicians on the use of oral semaglutide in subject with T2DM.

# 4 Objectives and endpoints

## 4.1 Objectives

### 4.1.1 Primary objective

To compare the effect of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once-daily, both in combination with 1-2 OADs on glycaemic control in subjects with T2DM.

### 4.1.2 Secondary objectives

To compare the effect of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once-daily, both in combination with 1-2 OADs on body weight in subjects with T2DM.

To compare the safety and tolerability of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once-daily, both in combination with 1-2 OADs in subjects with T2DM.

## 4.2 Endpoints

Baseline refers to randomisation, and week 52 refers to 52 weeks after randomisation.

### 4.2.1 Primary endpoint

If a subject after week 52 achieves (yes/no) $HbA_{1c} < 7\%$ (53 mmol/mol) American Diabetes Association (ADA) target.

### 4.2.2 Secondary endpoints

#### 4.2.2.1 Confirmatory secondary endpoints

Change from baseline to week 52 in body weight (kg)

#### 4.2.2.2 Supportive secondary endpoints

Key supportive secondary endpoints prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT) are marked with an asterisk (*).

**Supportive secondary efficacy endpoints**

Change from baseline to week 52 in:

- $HbA_{1c}$*
- Fasting plasma glucose (FPG)*
- Body weight (%)
- Body mass index (BMI)
- Waist circumference
- Fasting lipid profile (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides)
- Patient reported outcomes (PROs):
  - Short Form-36 version 2 (SF-36v2$^{TM}$) (acute version) health survey
  - Diabetes Treatment Satisfaction Questionnaire (DTSQs)

If a subject after week 52 achieves (yes/no):

- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) American Association of Clinical Endocrinologists (AACE) target
- $HbA_{1c}$ reduction $\geq$ 1%-point (10.9 mmol/mol)
- Weight loss $\geq$ 3%
- Weight loss $\geq$ 5%
- Weight loss $\geq$ 10%
- $HbA_{1c} < 7.0\%$ (53 mmol/mol) without hypoglycaemia (treatment-emergent severe or BG-confirmed symptomatic hypoglycaemia) and no weight gain
- $HbA_{1c}$ reduction $\geq$ 1%-point (10.9 mmol/mol) and weight loss $\geq$ 3%

Time to event:

- Time to rescue medication

**Supportive secondary safety endpoints**

- Number of treatment-emergent adverse events (TEAEs) during exposure to trial product, assessed up to approximately 57 weeks*
- Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks*
- Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks (yes/no)

Change from baseline to week 52 in:

- Haematology
- Biochemistry
- Calcitonin
- Pulse
- Systolic blood pressure
- Diastolic blood pressure
- Electrocardiogram (ECG) category
- Physical examination

# 5 Trial design

## 5.1 Type of trial

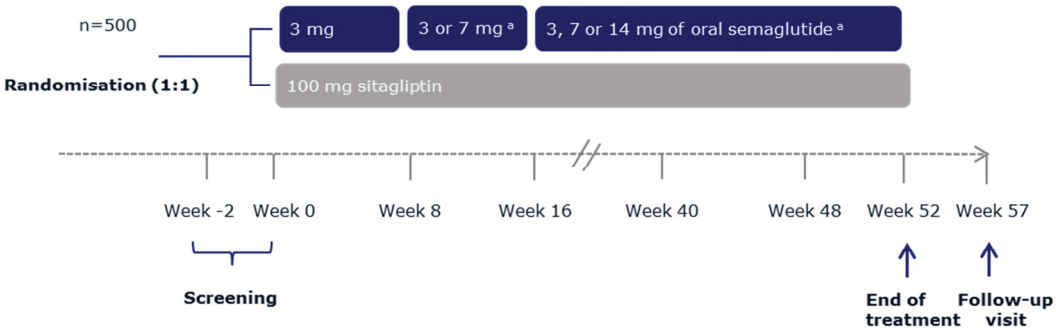
This is a 52-week randomised, open-label, active-controlled, parallel-group, multi-centre, multi-national trial with two arms comparing the efficacy and safety of oral semaglutide using a flexible dose adjustment versus sitagliptin 100 mg once-daily, in subjects with T2DM treated with 1-2 OADs (metformin, sulfonylureas [SU], thiazolidinediones [TZD], sodium glucose co-transporter 2 [SGLT-2] inhibitors).

Subjects will be randomised 1:1 to receive one of the following treatments as add-on to their anti-diabetic background medication:

- flexible dosing (3, 7 or 14 mg) of oral semaglutide once-daily
- 100 mg sitagliptin once-daily

The total trial duration for the individual subject will be approximately 59 weeks. The trial includes a 2-week screening period, a 52-week treatment period and a 5-week follow-up period. The trial is designed to have visits every 8 weeks, including a phone contact at week 4.

A schematic illustration of the trial design is shown in Figure 5–1.




a Dose of oral semaglutide is flexible and will be adjusted at week 8, 16, 24, 32, 40 and 48 based on the subject's $HbA_{1c}$ and tolerability (nausea/vomiting).

**Figure 5–1 Trial design**

## 5.2 Rationale for trial design

The trial has been designed as an open-label, parallel-group, 2-arm superiority trial, where oral semaglutide will be compared with the DPP-4 inhibitor sitagliptin. Visits have been planned every 8 weeks, including a phone contact at week 4. At the visits, the dose of oral semaglutide will be adjusted according to the subject's $HbA_{1c}$ (measured by a point-of-care $HbA_{1c}$ device) and tolerability (nausea/vomiting). Accordingly, after the initial first 8 weeks on 3 mg, the dose of oral

semaglutide is flexible throughout the trial, depending on the subject's individual needs (see Section 5.3.1). The trial is open-label as the dose of sitagliptin is fixed and cannot be changed during the trial. Treatment duration is 52 weeks to ensure adequate time to compare the full effect and sustainability of both treatments on glycaemic control and weight. Randomisation will be stratified (two strata) according to anti-diabetic background medication (with and without SU).

## 5.3 Treatment of subjects

Treatment of subjects is summarised in Table 5–1.

**Table 5–1 Treatment of subjects**

| Trial periods | | Screening | Treatment period 1 | Treatment period 2 | Treatment period 3 | Follow-up |
|---|---|---|---|---|---|---|
| **First visit in each period** | | V1 | V2 | V4 | V5 | V11 |
| **Duration of each period** | | 2 weeks | 8 weeks | 8 weeks | 36 weeks | 5 weeks |
| **Treatment arm** | **N** | | | | | |
| Oral semaglutide | 250 | Screening | 3 mg | flexible dosing (3 or 7 mg) | flexible dosing (3, 7 or 14 mg) | Follow-up |
| Sitagliptin | 250 | Screening | 100 mg | 100 mg | 100 mg | Follow-up |

### 5.3.1 Oral semaglutide treatment

Oral semaglutide is a long-acting GLP-1 RA to be administered orally once-daily. Dose-escalation of oral semaglutide is recommended to mitigate gastrointestinal AEs.

***Dose adjustment of oral semaglutide***

The treatment target is $HbA_{1c}$ < 7.0% (53 mmol/mol). Subjects randomised to oral semaglutide will initiate treatment on the 3 mg dose level and maintain this dose for the first 8 weeks. Thereafter, the dose of oral semaglutide will be adjusted based on the subject's $HbA_{1c}$ (measured by a point-of-care device) and tolerability of oral semaglutide according to the dose adjustment criteria detailed below (see Section 2). The basis for the assessment and the resulting dose of oral semaglutide must be documented in the medical records and entered into the electronic case report form (eCRF).

**The dose adjustment criteria are:**

1. **$HbA_{1c}$**
   - When $HbA_{1c}$ < 7.0% (53 mmol/mol), the current dose of oral semaglutide should be continued
   - When $HbA_{1c}$ ≥ 7.0% (53 mmol/mol), the dose of oral semaglutide should be escalated to the next dose level

**and**

2. **tolerability**
   - In case the subject reports moderate to severe nausea or vomiting for 3 or more days in the week prior to the scheduled visit, the dose of oral semaglutide should be maintained or reduced, at the investigator's discretion, irrespectively of the level of $HbA_{1c}$.

Subjects on 3 mg of oral semaglutide cannot have their dose reduced.

The point-of-care $HbA_{1c}$ device must be used to measure the subject's $HbA_{1c}$ prior to evaluation of the dose adjustment criteria (see Section 2 and 8.3.5).

### 5.3.2 Sitagliptin treatment

The selected active comparator in this trial is sitagliptin, an OAD of the DPP-4 inhibitor class suitable for once-daily oral administration. Subjects randomised to sitagliptin will receive 100 mg once-daily throughout the trial with no dose adjustment.

### 5.3.3 Dosing instructions

**Oral semaglutide**
Absorption of oral semaglutide is significantly affected by food and fluid in the stomach, hence dosing should be once-daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. Oral semaglutide tablet can be taken with up to half a glass of water (approximately 120 mL/4 fluid oz). The tablets must be swallowed whole by the subject and must not be broken or chewed (see Table 9–2). Furthermore, other oral medication can be taken 30 minutes after administration of trial product.

**Sitagliptin**
Sitagliptin tablet should be taken once-daily, with or without food.

### 5.3.4 Background medication

After signing the informed consent, subjects must continue their anti-diabetic background medication throughout the entire trial. The background medication must be maintained at the same dose level as given at trial entrance and with the same frequency during the entire treatment period

unless rescue medication is needed (see Section 6.4), any safety concerns related to the background medication arises or if the subject has unacceptable hypoglycaemia on a background of SU in which case the dose of SU can be reduced.

In addition, all background medication:

- is considered to be non-investigational medicinal product (NIMP)
- will not be provided by Novo Nordisk A/S, except if required by local regulations
- should be used in accordance with standard of care and current approved label in the individual country
- should not exceed the maximum approved dose in the individual country

[redacted]

## 5.4 Treatment after discontinuation of trial product

When discontinuing trial products, either at the scheduled end-of-treatment visit (see Section 8.1.4) or if trial product is discontinued prematurely (see Section 8.1.5), the subject should be switched to a suitable marketed product at the discretion of the investigator *(for Brazil only: or it will be made available according to local regulations)*.

As this trial is a phase 3a trial, oral semaglutide will not be available for prescription until after marketing authorisation.

## 5.5 Rationale for treatment

The doses of oral semaglutide have been chosen based on the data from the phase 2 dose-finding trial. The selected doses are expected to have the optimal benefit risk profile for further development for treatment of T2DM.

Sitagliptin has been chosen as comparator since it is an established OAD within DPP-4 inhibitor drug class.

The duration and doses of randomised treatments are considered adequate to collect sufficient data on efficacy and safety in accordance with the trial objectives.

# 6 Trial population

## 6.1 Number of subjects

Number of subjects planned to be screened: 830

Number of subjects planned to be randomised: 500

Number of subjects expected to complete the trial on or off trial product: 425

## 6.2 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered "yes".

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age above or equal to 18 years at the time of signing informed consent
   *<u>For Korea only:</u> Male or female, age above or equal to 19 years at the time of signing informed consent.*
3. Diagnosed with type 2 diabetes mellitus ≥ 90 days prior to day of screening.
4. $HbA_{1c}$ 7.5-9.5% (58-80 mmol/mol) (both inclusive).
5. Treatment target of $HbA_{1c}$ < 7.0% (53 mmol/mol), as judged by the investigator.
6. Stable daily dose(s) of 1-2 of the following anti-diabetic drugs within 90 days prior to the day of screening:
   a. Metformin (≥1500 mg or maximum tolerated dose documented in the subject medical record).
   b. Sulfonylureas (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record).
   c. Sodium glucose co-transporter 2 inhibitors.
   d. Thiazolidinediones (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record).

## 6.3 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered "no".

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).

*For Argentina only: Birth control methods will be reimbursed by Novo Nordisk Pharma Argentina S.A.*
*For Austria only: A monthly pregnancy test is mandatory for female subjects of childbearing potential*
*For Belgium only: Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly; such as implants, injectables, combined oral contraceptives, some IUDs, true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) or vasectomised partner.*
*For Brazil only: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.*
*For Norway only: Highly effective methods are defined as established use of oral, injectable, transdermal, implantable or intravaginal hormonal methods of contraception associated with inhibition of ovulation, placement of an intrauterine device, female sterilisation, male sterilisation (where partner is sole partner of subject), or true abstinence (when in line with preferred and usual lifestyle).*

4. Receipt of any investigational medicinal product within 90 days before screening.
   *For Brazil only: Participation in other clinical trials within one year prior to screening visit unless there is a direct benefit to the research subject at the investigator´s discretion*
5. Any disorder, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
6. Family or personal history of Multiple Endocrine Neoplasia Type 2 (MEN 2) or Medullary Thyroid Carcinoma (MTC).
7. History of pancreatitis (acute or chronic).
8. History of major surgical procedures involving the stomach potentially affecting absorption of trial product (e.g. subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery).
9. Any of the following: myocardial infarction, stroke or hospitalisation for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening and randomisation.
10. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
11. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
12. Subjects with alanine aminotransferase (ALT) > 2.5 x upper normal limit (UNL)
13. Renal impairment defined as Estimated Glomerular Filtration rate (eGFR) < 60 mL/min/1.73 $m^2$ as per Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI).
14. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before the day of screening. An exception is short-term insulin treatment for acute illness for a total of ≤ 14 days.
15. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomisation.

16. History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and carcinoma *in situ*).
17. History of diabetic ketoacidosis.

### 6.4 Rescue criteria

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification with rescue medication. It is important for trial integrity that only subjects actually needing treatment intensification (i.e. intensification of existing anti-diabetic medication and/or initiation of new anti-diabetic medication) are started on rescue medication.

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification if:
$HbA_{1c}$ (central laboratory) > 8.5% (69.4 mmol/mol) from week 32 to end of treatment.

Rescue medication should be prescribed at the investigator's discretion as add-on to randomised treatment and according to ADA/European Association for the Study of Diabetes guidelines[25, 26] (excluding GLP-RAs, DPP-4 inhibitors and amylin analogues). Subjects that are started on rescue medication should continue to follow the protocol-specified visit schedule.

Rescue medication and any changes hereto should be captured on the concomitant medication form in the eCRF, see Section 8.2.5. Rescue medication is considered to be NIMP and will not be provided by Novo Nordisk, unless required by local regulations.

[redacted]

### 6.5 Criteria for premature discontinuation of trial product

All efforts should be made to keep the subject on trial product. However, the subject may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

The subject must be prematurely discontinued from trial product if the following applies:
- Safety concern related to trial product or unacceptable intolerability
- Included in the trial in violation of the inclusion and/or exclusion criteria
- Pregnancy
- Intention of becoming pregnant
- Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product (IMP)
- Calcitonin ≥ 100 ng/L

If a criterion for premature discontinuation of trial product is met, trial product should not be re-initiated but subjects should continue with the scheduled site contacts.

See Section 8.1.5 for procedures to be performed for subjects discontinuing trial product prematurely.

## 6.6 Withdrawal from trial

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected. Only subjects who withdraw consent should be considered as withdrawn from trial.

See Section 8.1.6 for procedures to be performed for subjects withdrawing consent.

## 6.7 Subject replacement

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

## 6.8 Rationale for trial population

Subjects with T2DM inadequately controlled on 1-2 OADs (metformin, SU, TZD, SGLT-2 inhibitors) will be included in the trial. To ensure unbiased results, the background medication should be stable within 90 days prior to screening. The $HbA_{1c}$ limits of 7.5-9.5% (58-80 mmol/mol) have been chosen to include subjects needing intensification of their anti-diabetic medication. FPG and $HbA_{1c}$ will be monitored throughout the trial and rescue medication should be initiated in subjects with persistent, unacceptable hyperglycaemia. No BMI or blood pressure restrictions will be applied. Subjects with liver test abnormalities (ALT > 2.5 x UNL) will be excluded to avoid potential confounding of liver safety assessments. In addition, subjects with moderate, severe or end-stage-renal disease will be excluded due to restrictions in the labelling of background medications. As SGLT-2 inhibitors have been associated with euglycaemic diabetic ketoacidosis, subjects with a history of diabetic ketoacidosis will be excluded from this trial. The dose of oral semaglutide will be based on the subject's individual needs and only subjects with a treatment target of $HbA_{1c}$ < 7% (53 mmol/mol) will be randomised. Overall, the eligibility criteria will allow for enrolment of a relatively broad trial population, resembling the target population in common practice.

# 7 Milestones

Planned duration of recruitment period FSFV-LSFV: 18 weeks

Planned FSFV: 20-Sep-2016

Planned LSLV: 19-Mar-2018

End of trial is defined as: LSLV

**Recruitment:**
The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening.

**Trial registration:**
Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[27], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[28], the Food and Drug Administration Amendment Act (FDAAA)[29], European Commission Requirements[30, 31] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

# 8 Methods and assessments

## 8.1 Visit procedures

The following sections describe the assessments and procedures. These are also included in the flow chart (see Section 2). Informed consent must be obtained before any trial-related activity, see Section 18.2.

Refer to the flow chart (Section 2) for number and timing of visits and specific assessments to be performed.

Each subject will have 10 site visits and 1 phone contact. It is the responsibility of the investigator to ensure that all visits/pone contact occur according to the flow chart (see Section 2).

Planned visits can be conducted and re-scheduled within the allowed visit window. If a visit is missed and it is not possible to re-schedule, every effort should be made to ensure information is collected at a telephone contact (within the visit window) and entered into the eCRF. Subjects will be invited for the next scheduled visit according to the visit schedule.

The investigator must keep a log of staff and a delegation of task(s) list at site. Investigator must sign the log of staff and the delegation of task(s) at site prior to the delegation of tasks.

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. Only subjects who have signed the informed consent form should be included on the logs. The subject screening log and subject enrolment log may be combined in one log.

### 8.1.1 Screening, visit 1

At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff. Subjects should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

A screening session must be made in the IWRS. Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

Once all data relating to V1 have been obtained, these must be reviewed, dated and signed by the investigator and/or documented in medical records to assess that the subject is eligible to continue in the trial.

**Screening failures:** For screening failures the screening failure form in the eCRF must be completed with the reason for not continuing in the trial. Serious adverse events (SAEs) from

screening failures must be transcribed by the investigator into the eCRF. Follow-up on SAEs must be carried out according to Section 12.1.

A screening failure session must be made in the IWRS. The case book must be signed.

Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria; this includes re-sampling if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters. However, in case laboratory samples are lost (e.g. haemolysed or displaced), re-sampling is allowed.

### 8.1.2 Fasting visits

The subjects must attend some visits in a fasting state (see Section 2).

Fasting for blood sampling is defined as no food or liquid within the last 8 hours prior to blood sampling, however water is allowed up until 2 hours prior to blood sampling

Trial product must be taken after blood sampling (see Section 5.3.1 for dosing instructions). Other oral medication can be taken 30 minutes after trial product (for subjects randomised to oral semaglutide only). Injectable medications can be administered after blood sampling.

In case a subject attends a fasting visit in a non-fasting state, all non-fasting measurements should be performed. The subject should return to the site in a fasting state to have fasting blood samples done within the visit window for the relevant visit.

**Fasting samples:**

- FPG
- fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)

### 8.1.3 Randomisation and trial products administration

Eligible subjects will be randomised into one of two treatment arms. The randomisation session must be made in the IWRS which will allocate the dispensing unit number (DUN) of trial product to be dispensed to the subject.

All V2 assessments must be performed before administration of first dose of trial product.

Trial products (see Section 9) will be dispensed to the subject by the site, hospital pharmacy or equivalent at each site visit during the trial from randomisation to last visit before the end-of-treatment visit (see Section 2). The investigator must document that subjects are trained in the dosing instructions at every dispensing visit, see Section 5.3.1.

Date of first administration of trial product will be captured in the eCRF.

### 8.1.4 End-of-treatment (visit 10) and Follow-up (visit 11)

Subjects, who stay on trial product throughout the trial, must attend the end-of-treatment visit (V10) 52 weeks after randomisation and the follow-up visit (V11) 5 weeks after the last date on trial product (+3 days visit window). Throughout the protocol, last date on trial product is defined as date of the subject's last dosage of trial product. A completion call must be performed in the IWRS after completion of V10 (see Section 10).

In case the subject cannot be reached (by clinic visit or phone contact) at the scheduled V11, the site should consult the contacts provided by the subject (e.g. close relatives), relevant physicians, medical records and locator agencies (if allowed according to local law) to collect health status. If no health status can be collected, the subject should be considered lost to follow up and this should be specified in the end-of-trial form.

### 8.1.5 Premature discontinuation of trial product and follow-up (visits 10A and 11A)

Subjects, who discontinue trial product prematurely, should attend V10A, scheduled to take place on the day of discontinuation of trial product (+ 3 days visit window). V11A should be scheduled 5 weeks (+3 days visit window) after the last date on trial product. The primary reason for premature discontinuation of trial product must be specified in the end-of-trial form in the eCRF, and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS at V10A (see Section 10).

If premature discontinuation of trial product is decided during a scheduled visit, the visit will be converted into a V10A and trial procedures must be performed accordingly.

Subjects should continue with the originally scheduled site contacts after V11A and up to and including V10. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after V11A. However, if a subject is unable or unwilling to attend all subsequent visit(s), the investigator should at least aim to have the subject attend V10 (end-of-treatment) at week 52 as this visit should be performed for all subjects, if at all possible (except subjects who withdraw informed consent, see Section 8.1.6).

Subjects, who only agree to attend or provide health status at the planned V10, should not be considered withdrawn from the trial. In case the subject cannot be reached (by clinic visit or phone contact) at the scheduled V10, the site should consult the contacts provided by the subject (e.g. close relatives), relevant physicians, medical records and locator agencies (if allowed according to local law) to collect health status. If no health status can be collected, the subject should be considered lost to follow-up and this should be specified in the end-of-trial form.

In summary, subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule, missing assessments or trial product discontinuation

for any reason. Only subjects who decline any further contact with the site in relation to the trial should be considered as withdrawn from the trial (see Section 8.1.6).

### 8.1.6 Withdrawal from trial

If a subject considers withdrawing from the trial, the investigator must aim to undertake procedures for V10A as soon as possible and V11A should be scheduled 5 weeks (+3 days visit window) after the last date on trial product, if the subject agrees to it.

The end-of-trial form must be completed and final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be made in the IWRS (see Section 10). The case book must be signed.

Although a subject is not obliged to give his/her reason(s) for withdrawing consent, 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 withdrawing consent must be specified in the end-of-trial form in the eCRF.

### 8.1.7 Investigator assessments

Review of diaries, PROs, laboratory reports, ECGs, fundus photography or dilated fundoscopy, and point-of-care $HbA_{1c}$ measurements must be documented either on the documents or in the subject's medical record.

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

The documents must be retained at the site as source documentation.

For ECGs, physical examinations and eye examinations the evaluations must follow the categories:

- Normal
- Abnormal
  - Was the result clinically significant? (yes/no)

The evaluation should be based on investigator's judgement.

For laboratory report values outside the reference range, the investigator must specify whether the value is clinically significant or not clinically significant. All laboratory printouts must be signed and dated by the investigator prior to the following visit. The signed laboratory report is retained at the site as source documentation.

In case of abnormal clinically significant findings found as a result of screening procedures conducted at V1 or assessments revealing baseline conditions at V2, the investigator must state a comment in the subject's medical record and record this in the medical history/concomitant illness form in the eCRF.

The investigator or his/her delegate must collect and review the PROs and diaries for completeness and to ensure that AEs are reported.

## 8.2 Subject related information/assessments

### 8.2.1 Demography

Demography will be recorded in the eCRF at screening and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

### 8.2.2 Diabetes history and diabetes complications

Diabetes history and diabetes complications will be recorded on a disease specific form at screening and consists of:

- Date of diagnosis of type 2 diabetes
- Information regarding diabetes complications including date of onset
  - Diabetic retinopathy
  - Diabetic neuropathy
  - Diabetic nephropathy

Please note that macroangiopathy (including peripheral arterial disease) should be reported on the disease specific form **History of cardiovascular disease** (see Section 8.2.4).

### 8.2.3 Hypoglycaemia unawareness

Information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8[32]. The investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" The subject can answer never, rarely, sometimes, often or always. Subjects answering 'never, rarely or sometimes' are considered as having impaired awareness of hypoglycaemia.

### 8.2.4 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (V1) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

**Medical history** is a medical event that the subject has experienced in the past. Only relevant medical history as judged by the investigator should be reported.

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

The following must be recorded in the eCRF on the disease specific forms only, i.e. not on the medical history/concomitant illness form:

- **History of cardiovascular disease** (e.g. ischaemic heart disease, myocardial infarction (MI), heart failure including NYHA class, hypertension, stroke, peripheral arterial disease)
- **History of gallbladder disease** (e.g. gallstone, cholecystitis, cholecystectomy)
- **History of gastrointestinal disease** (e.g. gastroesophageal reflux disease, ulcer disease, chronic gastritis)

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE (see Section 12).

It must be possible to verify the subject's medical history, treatment target of $HbA_{1c} < 7.0\%$ (53 mmol/mol) and a valid fundus photography or dilated fundoscopy measurement in source documents such as subject's medical record. If a subject is not from the investigators own practice; the investigator must make reasonable effort to obtain a copy of subject's medical record from relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

### 8.2.5 Concomitant medication

A **concomitant medication** is any medication, other than the trial products, which is taken during the trial, including the screening and follow-up periods.

Details of any concomitant medication must be recorded at the first visit. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes: trade name or generic name; indication; start date and stop date or continuation; and start date of current dose and total daily dose (only applicable for anti-diabetic medication).

If a change is due to an AE, then this must be reported according to Section 12. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

### 8.2.6 Childbearing potential

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

Pregnancy testing must be performed on female subjects of childbearing potential as described in Section 8.4.7 (pregnancy testing). Female subjects of childbearing potential must be instructed to use an adequate contraceptive method throughout the trial and until 5 weeks after end of treatment.

Female of non-childbearing potential is defined as:

- Female who has undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation
- Postmenopausal defined as no menses for 12 months without an alternative medical cause
- Other medical reasons preventing childbearing potential

*For Argentina only: Birth control methods will be reimbursed by Novo Nordisk Pharma Argentina S.A.*
*For Austria only: A monthly pregnancy test is mandatory for female subjects of childbearing potential*
*For Belgium only: Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly; such as implants, injectables, combined oral contraceptives, some IUDs, true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) or vasectomised partner.*
*For Brazil only: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.*
*For Norway only: Highly effective methods are defined as established use of oral, injectable, transdermal, implantable or intravaginal hormonal methods of contraception associated with inhibition of ovulation, placement of an intrauterine device, female sterilisation, male sterilisation (where partner is sole partner of subject), or true abstinence (when in line with preferred and usual lifestyle).*

### 8.2.7 Tobacco use

Details of tobacco use must be recorded at V1. Smoking is defined as smoking at least one cigarette or equivalent daily.

Smoking status:

- Never smoked
- Previous smoker, smoking stop date
- Current smoker

## 8.3 Efficacy assessments

### 8.3.1 Laboratory assessments for efficacy

For overall description of laboratory assessments see Section 8.5.

Blood samples will be drawn according to the flow chart (see Section 2) and will be analysed at the central laboratory to determine levels of the following efficacy laboratory parameters:

**Glucose metabolism:**

- $HbA_{1c}$
- FPG

FPG is measured at central laboratory in order to evaluate glycaemic control. The subject must attend these visits fasting (see Section 8.1.2).

A central FPG result ≤ 3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator (see Section 12.1.1).

**Fasting lipid profile:**

- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides

### 8.3.2 Self-measured plasma glucose

At V2, 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 the instruction will be repeated as necessary during the trial. In case a hypoglycaemic episode is suspected, the provided BG meter should be used for measurement of self-measured plasma glucose (SMPG) (see Section 8.4.8)

The BG meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display. Only the BG meters provided by Novo Nordisk A/S should be used for the measurements required in the protocol.

Subjects should be instructed in how to record the results of the SMPG values in the diaries. The record of each SMPG value should include date, time and value. All data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected between the diary and the SMPG data obtained at the phone contact, the values in the eCRF must be corrected.

Occasional review by the investigator of the values stored in the memory of the BG meter and correct reporting of these in the diary is advised in order to ensure adequacy of the data reported in the trial database.

### 8.3.3 Body weight and height

**Body weight** must be measured and recorded in the eCRF in kilogram or pound (kg or lb), with one decimal (with an empty bladder, without shoes and only wearing light clothing). The body weight should be assessed on the same calibrated weighing scale equipment throughout the trial, if possible.

**Height** is measured without shoes in centimetres or inches and recorded in the eCRF to nearest ½ cm or ¼ inch.

### 8.3.4 Waist circumference

The waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest.

The measurement of waist circumference must be performed and recorded in the eCRF. Waist circumference is measured in the horizontal plane and rounded up or down to the nearest ½ cm or ¼ inch using a non-stretchable measuring tape. The same measuring tape should be used throughout the trial.

The circumference should be measured when the subject is in a standing position, with an empty bladder and wearing light clothing. The subject should be standing, feet together with arms down their side and waist accessible. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

### 8.3.5 Point-of-care $HbA_{1c}$ measurement

The investigator must measure the subject's $HbA_{1c}$ by using a point-of-care device provided by Novo Nordisk A/S prior to adjustment of the oral semaglutide dose (see Section 2, Section 5.3.1 and Section 8.1.7). The $HbA_{1c}$ value must be used for evaluation of the dose adjustment criteria and reported into the eCRF. It is the investigator's responsibility to set-up, calibrate and perform a quality control of the point-of-care $HbA_{1c}$ device.

### 8.3.6 Patient reported outcomes questionnaires

PRO will be assessed using the questionnaires:

- SF-36v2™ (acute version) health survey[33-35]
- DTSQs[36]

The questionnaires must be completed by the subject as specified in the flow chart, see Section 2, preferably before any other trial-related activities for that visit. It takes approximately ten minutes to complete the two questionnaires. Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. The completed questionnaires must be reviewed

for potential adverse events and missing data while the subject is still at the site. All results from the PRO questionnaires must be transferred into the eCRF.

All the questionnaires will be translated to local languages, and also be linguistically validated before being handed out to the subjects participating in the trial.

**SF-36v2™**

SF-36v2™ (acute version) health survey measures the individual overall health related quality of life on 8 domains; Physical functioning, Role physical, Bodily pain, General health, Vitality, Social functioning, Role emotional and Mental health. The acute version's questions are based on a recall period of one week. SF-36v2™ (acute version) health survey contains 36 items.

**DTSQs**

The DTSQs questionnaire will be used to assess subject's treatment satisfaction. This questionnaire contains 8 items and measures subject's diabetes treatment in terms of convenience, flexibility and general feelings regarding treatment.

## 8.4 Safety assessments

### 8.4.1 Adverse events

Adverse events (AEs) must be reported at each visit in accordance with the procedures outlined in Section 12 and appendix B.

#### 8.4.1.1 Medication error

If a medication error is observed during the trial, the following information is required and a specific event form must be completed in the eCRF in addition to the AE form (see Section 8.4.1.2, 12.1.5 and appendix B):

- Trial product(s) involved
- Classification of medication error
- Whether the subject experienced any hypoglycaemic episode and/or adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see Section 12.1.4 and appendix B.

#### 8.4.1.2 Adverse events requiring additional data collection

For the following AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form:

- Acute coronary syndrome (MI or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or transient ischaemic attack)
- Heart failure
- Pancreatitis
- Neoplasm (excluding thyroid neoplasm)
- Thyroid disease (including thyroid neoplasm)
- Renal event
- Hypersensitivity reaction
- Acute gallstone disease
- Medication error
- Lactic acidosis
- Creatine kinase (CK) > 10x UNL
- Hepatic event defined as:
  - ALT or aspartate aminotransferase (AST) > 5x UNL and total bilirubin ≤ 2x UNL
  - ALT or AST > 3x UNL and total bilirubin > 2x UNL*
  - Hepatic event leading to trial product discontinuation.

*Please note that in case of a hepatic event defined as ALT or AST > 3 x UNL and total bilirubin > 2 x UNL, where no alternative aetiology exists (Hy's law), this must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable.

See Section 12 and appendix B for details about the additional information to report.

Note that additional assessments will be required according to appendix B in case of:

- suspicion of acute pancreatitis
- suspicion of hypersensitivity reaction
- increased levels of creatine kinase
- increased levels of aminotransferases

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see Section 12

### 8.4.2 Physical examination

A physical examination will be performed by the investigator according to local procedure (see Section 2 and Section 8.1.7).

A physical examination must include:

- General appearance
- Head, ears, eyes, nose, throat, neck
- Thyroid gland
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- Lymph node palpation

### 8.4.3 Vital signs

**Systolic and diastolic blood pressure**

Systolic and diastolic blood pressure should be measured in a sitting position after the subject has been resting for at least 5 minutes and by using the standard clinical practice at the site. The data must be recorded in the eCRF. The actual value of the blood pressure measurement should be recorded in the eCRF (without rounding). The same equipment should be used throughout the trial.

**Pulse**

Pulse (beats per minute) must be recorded in the eCRF at site visits after resting for 5 minutes in a sitting position.

### 8.4.4 Eye examination

Fundus photography or dilated fundoscopy will be performed as per the flow chart (see Section 2) by the investigator or according to local practice. Results of the fundus photography or dilated fundoscopy will be interpreted by the investigator (see Section 8.1.7).

If fundus photography or dilated fundoscopy has been performed within 90 days prior to randomisation, the procedure does not need to be repeated, unless worsening of visual function since the last examination. The results must be available prior to randomisation.

If the fundus photography or dilated fundoscopy is performed before the subject has signed the informed consent form, it must be documented in the medical records that the reason for performing the procedure was not related to this trial.

### 8.4.5 Electrocardiogram (12–lead)

12-lead ECG will be performed as per the flowchart (see Section 2) and the assessment must be reviewed as described in Section 8.1.7 by the investigator. The ECGs will also undergo central

assessment and the investigator must forward the ECGs to the central ECG reader as soon as possible.

If the central ECG evaluation of a baseline ECG is suggestive of a prior MI, the investigator will be notified. The investigator should consider if an update of the history of cardiovascular disease form is required.

If the central ECG evaluation of a post-baseline ECG is suggestive of new MI, the investigator will be notified and a confirmatory ECG should be performed. Unless already done, the investigator should report this as AE or SAE at investigator's discretion and according to Section 12.

Additional ECG recordings can be performed at the investigator's site at investigator's discretion at other visits than the planned ECG visits. All these ECGs will undergo central assessment. The reason for additional ECG assessments should be documented and an AE should be reported if applicable.

All findings suggestive of new MI detected by the central ECG reading will be adjudicated by the event adjudication committee (EAC) (see Section 12.7.2).

### 8.4.6 Laboratory assessments for safety

For overall description of laboratory assessments see Section 8.5.

Blood samples will be drawn according to the flow chart (see Section 2) and will be analysed at the central laboratory to determine levels of the following safety laboratory parameters:

**Haematology:**

- Haemoglobin
- Haematocrit
- Leucocytes
- Thrombocytes
- Differential count (eosinophils, neutrophils, basophils, lymphocytes and monocytes)

**Biochemistry:**

- Alanine aminotransferase (ALT)
- Albumin
- Alkaline phosphatase (ALP)
- Amylase
- Aspartate aminotransferase (AST)
- Bilirubin, total
- Calcium, total
- Creatinine
- eGFR per CKD-EPI[37]
- Creatine kinase (CK)
- Lipase
- Potassium
- Sodium
- Urea

**Hormones:**

- Calcitonin

In case any calcitonin value at any time during the trial is ≥ 10 ng/L, the algorithm in appendix A must be followed.

### 8.4.7 Pregnancy testing

Females of childbearing potential will have a urine dip-stick pregnancy test performed at site as specified in Section 2 or as required by local law. For definition of female of non-childbearing potential and contraceptive methods, see Section 8.2.6.

In case a menstrual period is missed or if pregnancy is suspected between the scheduled visits, a urine pregnancy test should be performed. Investigator should instruct the subject to contact the site in case the pregnancy test is positive. At V2, females of childbearing potential will be provided with a urine dip-stick pregnancy test.

### 8.4.8 Hypoglycaemic episodes

Plasma glucose (PG) should always be measured and recorded when a hypoglycaemic episode is suspected.

All PG values:

- ≤ 3.9 mmol/L (70 mg/dL) or
- > 3.9 mmol/L (70 mg/dL) occurring in conjunction with hypoglycaemic symptoms

should be reported in the diary according to the instructions below throughout the trial from V1 to end of trial.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the SMPG value is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines[38].

A SMPG value ≤ 3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms must trigger a hypoglycaemic episode form to be completed by the subject. Repeated SMPG measurements and/or symptoms will per default be considered as one hypoglycaemic episode until a succeeding SMPG value is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved. One hypoglycaemic episode form is to cover these measurements and/or symptoms.

In case of several low SMPG values within the hypoglycaemic episode, the lowest value is the one that will be reported as the SMPG value for the hypoglycaemic episode but the start time of the episode will remain as the time for the first SMPG value and/or symptom.

The record should include the following information:

- Start date and time of the hypoglycaemic episode.
- Stop date and time of the hypoglycaemic episode (stop time is the first time the PG value is > 3.9 mmol/L (70 mg/dL and/or symptoms have been resolved).
  If a stop date and time is not reported, a hypoglycaemic episode will cover a period of 60 minutes.
- The PG level before treating the episode (if available) and any follow up measurements.
  The lowest value measured during the hypoglycaemic episode will be reported as the PG value for the episode, the remaining values will be kept as source data in the diary.
- Whether the episode was symptomatic (Yes/No).
  A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode.
- Whether the subject was able to treat him/herself.
  If the severity of a hypoglycaemic episode aggravates, only one hypoglycaemic episode should be reported, reflecting the most severe degree of hypoglycaemia.

- Date and time of last trial product administration, and for selected anti-diabetic medications administered prior to the episode, date and time as well as dose must be collected.
- Date and time of last main meal (not including snacks) prior to the episode.
- Whether the episode occurred in relation to physical activity.
- Change in any concomitant illness.
- Any sign of fever and/or other acute disease.
- Whether the subject was asleep when the episode occurred.
  - If yes, whether the symptoms of the episode woke up the subject.

The answer to the question: "Was the subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration[38].

Oral carbohydrates must not be given if the subject is unconscious.

If the question "Was the subject able to treat him/herself?" is answered "No", the following information should be recorded by the subject:

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)?
- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by another person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet change, medication error (i.e. overdose, mix-up between products, incorrect use of device), other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[39] (layman term used in the diary is specified in brackets if different from the protocol term)?
  - Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
  - General malaise: headache or malaise (feeling discomfort/unease)
- Other symptoms

## 8.5 Laboratory assessments

The laboratory analyses will mainly be performed by a central laboratory. In case of suspicion of hypersensitivity reaction, anti-semaglutide antibodies and IgE anti-semaglutide antibodies samples will be analysed by Novo Nordisk A/S (see appendix B). For some of the analyses related to suspicion of pancreatitis and hypersensitivity reaction, a local laboratory must be used (see appendix B).

The handling, transportation and storage of biological samples are described in the laboratory manual (for central laboratory details see Attachment I).

Samples will be coded in order to keep subject identity anonymous.

Laboratory samples not drawn on the day of the actual visit should preferably be drawn on another day within the visit window stated in the flow chart (see Section 2). Please note that a laboratory sample pertaining to a specific visit must always be reported to that visit.

For some of the samples drawn during the trial, subjects will be asked to attend the site visits fasting (fasting for blood sampling is defined in Section 8.1.2).

The central laboratory will provide laboratory results to the investigator on an on-going basis. However, results obtained in case of suspicion of hypersensitivity reaction will be provided to the investigator upon request.

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to Section 8.2.5 and Section 12.

*For Brazil only: All laboratory results will be communicated to the investigators.*

Laboratory samples will be destroyed at the latest at the completion of the clinical trial report, or according to local regulations, except antibody samples collected in relation to suspicion of hypersensitivity reaction that will be stored as described in Section 24.2.

## 8.6 Other assessments

### 8.6.1 Subject diary

The diaries should be handed out at the visits described in the flow chart Section 2. The recordings must be reviewed as described in Section 8.1.7 and transcribed to the eCRF at the following visit.

Entries in the diaries are only to be made by the subject, unless otherwise specified.

The investigator should instruct the subject in recording the following data in the diary:

- date of first trial product administration
- hypoglycaemic episodes
- changes in concomitant medication
- AEs

## 8.7 Subject compliance

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

**Treatment compliance:** Will be assessed by monitoring of drug accountability. Prior to visits where drug accountability is performed, the subject will be asked to return all used, partly used and unused trial products. The investigator must assess the amount of trial products returned compared to what was dispensed at the last dispensing visit and, in case of discrepancies, question the subject.

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

# 9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the Trial Materials Manual (TMM).

Trial products must not be dispensed to any person not included in the trial.

## 9.1 Trial products

The following trial products are considered as investigational medicinal products and will be provided by Novo Nordisk A/S, Denmark Table 9–1:

**Table 9–1 Investigational medicinal products**

| Trial product | Strength | Dosage form | Route of administration | Container/ delivery device |
|---|---|---|---|---|
| Semaglutide 3 mg tablet | 3 mg | Tablet | Oral | Dosepack[a] |
| Semaglutide 7 mg tablet | 7 mg | | | |
| Semaglutide 14 mg tablet | 14 mg | | | |
| Sitagliptin film-coated tablet | 100 mg | Tablet | Oral | Dosepack[b] |

[a] One dosepack contains one blister card with 7 tablets.
[b] One dosepack contains one blister card with 14 tablets.

Metformin, SU, TZD, SGLT-2 inhibitors and rescue medication are considered NIMPs and will not be supplied by Novo Nordisk. However, metformin, SU, TZD, SGLT-2 inhibitors will be reimbursed if required by the country's regulatory authority or institutional review board (IRB)/independent ethics committee (IEC).

[redacted]

## 9.2 Labelling

The trial products will be labelled in accordance with Annex 13[40], local regulations and trial requirements.

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

## 9.3 Storage

Storage conditions of the trial products are outlined in Table 9–2.

**Table 9–2 Storage conditions**

| Trial product | Storage conditions (not-in-use) | In-use conditions |
|---|---|---|
| Semaglutide 3 mg tablet | Do not store above 30ºC (86ºF)<br><br>Do not freeze<br><br>Do not refrigerate<br><br>Store in the original package | Take the tablet immediately after dispensation from blister card<br><br>Take the tablets whole: Do not break or chew |
| Semaglutide 7 mg tablet | | |
| Semaglutide 14 mg tablet | | |
| Sitagliptin 100 mg tablet | No special storage conditions | N/A |

The investigator must ensure that trial product is kept under proper storage conditions and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range). Additional details regarding handling of temperature deviations can be found in the TMM.

Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

## 9.4 Drug accountability and destruction

Drug accountability of all trial products received at site is the responsibility of the investigator.

Subjects must be instructed to return all used, partly used and unused trial products including empty packaging material at each dispensing visit.

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product. Non-allocated trial products including expired or damaged products must be accounted as unused at the latest at closure of the trial site.

Drug accountability is performed by using the IWRS. Drug accountability must be done on tablet level.

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

## 9.5 Auxiliary supplies

The following will be provided by Novo Nordisk in accordance with the TMM:

- BG meter and BG meter auxiliaries

# 10 Interactive voice/web response system

A trial-specific IWRS will be set up which can be accessed at any time via the internet or telephone. Access to the IWRS must be restricted to and controlled by authorised persons.

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site. DUNs will be allocated using the IWRS. It is important to dispense the exact allocated DUNs to a subject.

# 11 Randomisation procedure

The trial is an open-label trial. A randomisation session will be made for all eligible subjects using IWRS.

At V2, eligible subjects will be randomised to one of the two parallel treatment arms as described in Section 5.1 and Section 5.2.

# 12 Adverse events, technical complaints and pregnancies

## 12.1 Definitions

### 12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A CLAE: a clinical laboratory abnormality which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see Section 8.4.8.

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild** - no or transient symptoms, no interference with the subject's daily activities.
  - **Moderate** - marked symptoms, moderate interference with the subject's daily activities.
  - **Severe** - considerable interference with the subject's daily activities; unacceptable.

- **Causality**
  Relationship between an AE and the relevant trial product(s):
  - **Probable** - Good reason and sufficient documentation to assume a causal relationship.
  - **Possible** - A causal relationship is conceivable and cannot be dismissed.
  - **Unlikely** - The event is most likely related to aetiology other than the trial product.

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

### 12.1.2 Serious adverse event

An SAE is an experience that at any dose results in any of the following:

- Death.
- A life-threatening[a] experience.
- In-patient hospitalisation[b] or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity[c].
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening[a] or require hospitalisation[b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE[d].

[a] The term "life threatening" in the definition of SAE 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 was more severe.

[b] The term "hospitalisation" is used when a subject:
  - Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
  - Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised and, when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial-related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

[c] A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

[d] For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

The following AEs must always be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:

- suspicion of transmission of infectious agents via the trial product
- risk of liver injury defined as ALT or AST > 3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

Additional assessments should be made for events meeting the criterion of Hy's law as stated above (see appendix B).

### 12.1.3 Non-serious adverse event

A non-serious AE is any AE which does not fulfil the definition of an SAE.

### 12.1.4 Medication errors

A medication error concerning trial products is defined 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
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product
- Accidental administration of a higher dose than intended. A higher dose is a dose of at least one tablet more than the intended dose; however, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

Medication errors must be reported on an AE form and a specific event form, see Section 8.4.1.1, 12.1.5 and appendix B.

### 12.1.5 Adverse events requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the product safety. A number of adverse events that always require additional data collection have been pre-specified. See appendix B for details about these events and the additional information to report.

Some events in this trial will be adjudicated by an independent external committee as described in Section 12.7.2.

Table 12–1 lists AEs that require completion of specific event forms in the eCRFs and/or are subject to event adjudication.

**Table 12–1 Adverse events requiring completion of specific event forms and/or are subject to event adjudication**

| Event | Specific event form | Event adjudication |
|---|---|---|
| Death | No | Yes |
| Acute coronary syndrome (MI or hospitalisation for unstable angina) | Yes | Yes |
| Cerebrovascular event (stroke or transient ischaemic attack [TIA]) | Yes | Yes |
| Heart failure | Yes | Yes (only if requiring hospitalisation) |
| Pancreatitis | Yes | Yes (only if acute pancreatitis) |
| Neoplasm (excluding thyroid neoplasm) | Yes | Yes (only if malignant) |
| Thyroid disease (including thyroid neoplasm) | Yes | Yes (only if malignant thyroid neoplasm or C-cell hyperplasia) |
| Renal event | Yes | Yes (only if acute kidney injury) |
| Hypersensitivity reaction | Yes | No |
| Acute gallstone disease | Yes | No |
| Medication error | Yes | No |
| Lactic acidosis | Yes | Yes |
| CK > 10 x UNL | Yes | No |
| Hepatic event defined as:<br>ALT or AST > 5x UNL and total bilirubin ≤ 2x UNL<br>ALT or AST > 3x UNL and total bilirubin > 2x UNL*<br>Hepatic event leading to trial product discontinuation. | Yes | No |

* Please note that in case of a hepatic event defined as ALT or AST > 3 x UNL and total bilirubin > 2 x UNL, where no alternative aetiology exists (Hy's law), this must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable.

For details about specific event forms, see appendix B.

### 12.1.6 Technical complaints

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:

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

Only technical complaints related to adverse events will be reported in the clinical trial report.

## 12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events occurring from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (V11) for subjects on trial product or until the end of trial (V10 or V11A, whichever comes last) for the subjects who have discontinued trial product prematurely. Events for withdrawn subjects will be collected and reported until last trial-related contact with the subject. The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the subject must be asked about AEs and technical complaints, for example by asking: “Have you experienced any problems since the last contact?”

All AEs, either observed by the investigator or subject, must be reported by the investigator and evaluated.

All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a safety information form must be completed in addition to the AE form. A safety information form is a form to collect supplementary clinical information. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

AEs requiring additional data collection must be reported using both the AE form and the specific event form. A specific event form is a form tailored to collect specific information related to the individual event. See appendix B for details about the events and the additional information to report.

In case any of the above events fulfil the criteria for seriousness in Section 12.1, then the event should be reported as serious.

Some events will undergo event adjudication by the EAC, please refer to Section 12.7.2. For AEs qualifying for event adjudication, the adjudication form will also have to be completed in the eCRF. The adjudication form is a checklist of clinical data to be provided from the site.

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.

**Timelines for initial reporting of AEs:**
The investigator must complete the following forms in the eCRF within the specified timelines:

- **SAEs**: The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.

  Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

  **For SAEs requiring reporting on a specific event form:** In addition to the above, the specific event form **within 14 calendar days** from the investigator's first knowledge of the AE.

- **Events for adjudication**: The adjudication form should be completed **within 14 calendar days** of investigator's first knowledge of the AE, see Section 12.7.2. The investigator should preferably provide the medical documentation within 4 weeks of event identification according to instructions in the event adjudication site manual.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the form into the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.

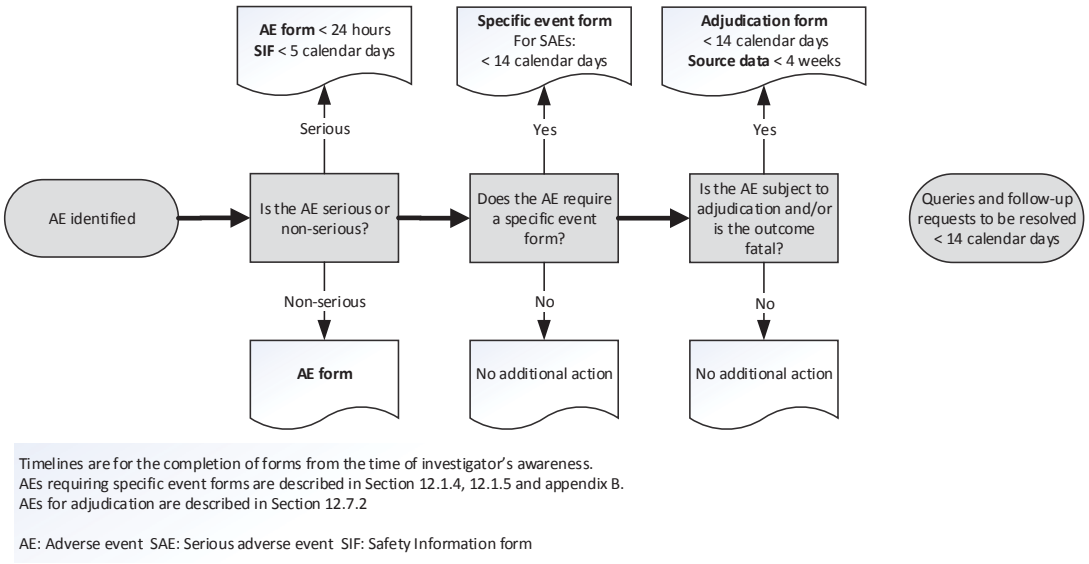



**Figure 12–1 Reporting of AEs**

**Novo Nordisk assessment of AE expectedness:**

Novo Nordisk assessment of expectedness is performed according to the following reference documents: IB for oral semaglutide (NN9924), edition 6[24] and Summary of Product Characteristics (SmPC) for Januvia® (sitagliptin)[41]; current version and any updates thereto.

**Reporting of trial product-related SUSARs by Novo Nordisk:**

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP[1]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including European Medicines Agency, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP[1], unless locally this is an obligation of the investigator.

**Novo Nordisk products used as concomitant medication or non-investigational medicinal product:**

If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as NIMP or concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this AE to relevant regulatory authorities.

### 12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the medical records and the forms in the eCRF.

Follow up information must be reported to Novo Nordisk according to the following:

- **SAEs**: All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

  The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

The investigator must ensure that the recording of the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

**SAEs after end of trial:** If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product occurring to a subject after the subject has ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

## 12.4 Technical complaints and technical complaint samples

### 12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- semaglutide 3 mg tablets
- semaglutide 7 mg tablets
- semaglutide 14 mg tablets
- sitagliptin 100 mg tablets

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

The investigator must assess whether the technical complaint is related to any AEs and/or SAEs.

Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each batch number must be completed

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints within **5 calendar days**

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

### 12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included

in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the batch number and, if available, the DUN. All parts of the DUN should be returned.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

### 12.5 Pregnancies in female subjects

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the trial. The investigator must report any pregnancy in subjects who have received trial product(s).

The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant is one month of age.

The investigator must report information about the pregnancy, pregnancy outcome and health of the newborn infant(s), as well as AEs in connection with the pregnancy and AEs in the foetus and newborn infant.

The following must be collected and reported by the investigator to Novo Nordisk - electronically (e.g. in PDF format), or by fax or courier:

1. **Reporting of pregnancy information**
   Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on Maternal Form 1A and 1B, respectively.

   When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy) and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

   Initial reporting and follow-up information must be reported **within 14 calendar days** of the investigator's first knowledge of initial or follow-up information.

**2. Reporting of AE information**

The investigator has to report AEs in connection with the pregnancy as well as in the foetus and newborn infant(s). The SAEs that must be reported include abnormal outcome, such as foetal death (including spontaneous abortion), congenital anomalies (including those observed at gross examination or during autopsy of the foetus), as well as other pregnancy complications fulfilling the criteria of an SAE.

Forms and timelines for reporting AEs:

Non-serious AEs:

- AE form[a] **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

SAEs:

- AE form[a] **within 24 hours** of the investigator's first knowledge of the SAE.
- Safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE.
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information.

[a] It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or newborn infant. If the AE occurred in the foetus or newborn infant, the AE can only be reported on paper AE and safety information form.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

### 12.6 Precautions and/or overdose

There are no specific antidotes to semaglutide. Treatment of an overdose should be symptomatic.

There is a potential risk of hypoglycaemia during dosing with semaglutide. The typical signs and symptoms of a non-severe hypoglycaemia include: hunger, slight headache, nausea, light-headedness, palpitations and sweating. Symptoms of non-severe hypoglycaemia should be treated by ingestion of carbohydrates.

Severe hypoglycaemia resulting in loss of consciousness should be treated according to best available medical practice.

One case of accidental overdose of oral semaglutide was reported in the NN9924-3692 trial. The subject accidentally took the trial product [redacted] day and was thus treated with 20 mg of

oral semaglutide. The subject did not report any symptoms and treatment was continued without any change.

One case of accidental overdose has been reported in subjects treated with s.c. semaglutide once weekly. The subject inadvertently injected [redacted] mg of semaglutide instead of 0.4 mg, which corresponds to a [redacted]-fold higher dose than the maximum dose included in that trial. After [redacted] hours the subject felt nauseated, vomited and had a headache. The subject was instructed to drink sufficient amounts of fluids. [redacted] and the subject wished to continue in the trial. No symptoms of hypoglycaemia or any other symptoms or signs were noted.

For further details please see the current edition of the IB for oral administration of semaglutide (NN9924), edition 6[24], and any updates hereof.

## 12.7 Committees related to safety

### 12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal oral semaglutide safety committee to perform ongoing safety surveillance.

### 12.7.2 Event adjudication committee

An independent external event adjudication committee (EAC) is established to perform validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical data related to the specific AE. Pre-defined clinical data consist of copies of source documents collected and delivered by the investigational sites.

The EAC is composed of permanent members covering required medical specialities. EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk.

The events are reviewed by the EAC in a blinded manner. The EAC will have no authorisations to impact on trial conduct, trial protocol or amendments.

The EAC works in accordance with written guidelines included in the EAC Charter describing in details the composition, tasks, responsibilities and work processes of the committee.

The events outlined in Table 12–2 have been selected for adjudication in order to obtain an external independent validation of the diagnosis. In addition, cardiovascular events are being adjudicated according to U.S. Food and Drug Administration (FDA) requirements[42].

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication packages (e.g. x-ray, ECGs, ultrasound images, discharge summaries, pathology reports and death certificates). The investigator must provide medical documentation as soon as possible, when they receive the request from Novo Nordisk or the event adjudication vendor.

The AEs for adjudication are listed in Table 12–2:

**Table 12–2 Adverse events for adjudication**

| Events | Description | Adjudication outcome |
|---|---|---|
| Death* | • All-cause death | • Cardiovascular death (including undetermined cause of death)<br>• Non-Cardiovascular death |
| Acute Coronary Syndrome | Acute Coronary Syndrome conditions include:<br>• ST-elevation acute myocardial infarction (STEMI)<br>• Non-ST elevation acute myocardial infarction (NSTEMI)<br>• Silent MI<br>• Unstable angina pectoris | • Acute MI (STEMI or NSTEMI), silent MI<br>• Unstable angina pectoris requiring hospitalisation |
| Cerebrovascular event | • Episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction<br>• TIA is defined as a transient episode (< 24 hours) of focal neurological dysfunction caused by brain, spinal cord, or retinal ischaemia, without acute infarction | • Ischaemic stroke<br>• Haemorrhagic stroke<br>• Undetermined stroke<br>• TIA |
| Heart failure requiring hospitalisation | • Hospitalisation with a primary diagnosis of heart failure (new episode or worsening of existing heart failure) | • Heart failure requiring hospitalisation |
| Acute pancreatitis | The diagnosis of acute pancreatitis requires two of the following three features:<br>• Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)<br>• Serum lipase activity (and/or amylase activity) at least three times greater than the UNL<br>• Characteristic findings of acute pancreatitis on imaging | Acute pancreatitis<br>• Mild<br>• Moderately severe<br>• Severe |

| | | |
|---|---|---|
| Malignant neoplasm | Malignant neoplasms are defined as<br>• neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body through the blood and lymph systems<br><br>Thyroid neoplasms are excluded in this event category | • Malignant neoplasm |
| Thyroid disease, if malignant thyroid neoplasm or C-cell hyperplasia | Malignant thyroid neoplasms are defined as<br>• thyroid neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body through the blood and lymph systems<br>• C-cell hyperplasia, defined as hyperplasia of the parafollicular C-cells of the thyroid gland | • Malignant thyroid neoplasm<br>• C-cell hyperplasia |
| Acute kidney injury | Acute kidney injury[43] is defined as any of the following (not graded):<br>• Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours, or<br>• Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, or<br>• Urine volume < 0.5 mL/kg/h for 6 hours | • Acute kidney injury |
| Lactic acidosis | • Lactic acidosis is characterized by increased blood lactate level in association with metabolic acidosis | • Lactic acidosis |

* Death is not a separate event, but an outcome

There are different processes for capturing events for adjudication:

- Direct reporting by investigator:
  - All AEs need to be assessed by the investigator if any AE category is applicable. If the AE category selected is in scope for adjudication, the event specific adjudication form will be populated for sites to complete.
  - AEs with fatal outcome.
- Screening:
  - All AEs will be screened by Novo Nordisk for potential missed events for adjudication and if needed, the investigator will be asked to provide additional information such as an alternative aetiology, underlying cause(s) and/or clinical details.
  - All ECGs will be centrally read. If the central reading conclusion is suggestive of new MI, the ECG adjudication form will be populated for sites to complete for all post-baseline ECGs.

- EAC identified events:
  - The EAC can decide to have an AE adjudicated even if not initially reported as an event for adjudication by the investigator.

Event adjudication will be performed for AEs in randomised subjects including AEs with an onset date during the screening period. Event adjudication will not be performed for AEs in screening failures.

AEs for adjudication must be reported according to Section 12.2. In addition, the specific adjudication form should be completed within 14 calendar days of the investigator's first knowledge of the AE and all relevant predefined documents provided within 4 weeks according to instructions in the event adjudication site manual.

The assessment made by the EAC will be included in the clinical trial report as well as assessments made by the investigator. However, the adjudication made by an EAC, given its independent analysis of each event, will be attributed with greater importance of the two.

# 13 Case report forms

Novo Nordisk will provide a system for the eCRF. This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms

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

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

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing “ND” (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing “NA” (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

## 13.1 Corrections to case report forms

Corrections to the eCRF data may be made by the investigator or the investigator’s delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction.

If corrections are made by the investigator’s delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

## 13.2 Case report form flow

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

At the end of the trial the investigator must ensure that all remaining data have been entered into the eCRF no later than 3 days after LSLV at the site in order to ensure the planned lock of the database.

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site. When the final clinical trial report is available, the data will be archived by Novo Nordisk.

# 14 Monitoring procedures

Monitoring will be conducted under a risk based approach.

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LSLV at the trial site (for trial sites with active subjects (defined as subjects in screening, treatment or follow-up)).

The monitor must be given direct access to all source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

All data must be verifiable in source documentation other than the eCRF.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The original diaries and/or PROs must not be removed from the trial site, unless they form part of the CRF and a copy is kept at the site.

The monitor will ensure that the eCRFs are completed and that paper CRFs are collected.

The following data will be source data verified for screening failures:

- Date for obtaining informed consent.
- Reason for screening failure.

Monitors will review the subject's medical records and other source data (e.g. the diaries and PROs) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

# 15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a Contract Research Organisation.

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The subject and any biological material obtained from the subject will be identified by subject number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

# 16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

# 17 Statistical considerations

**General considerations**

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock.

Data from all sites will be analysed and reported together.

In statistical analyses where stratification is included, the two levels of anti-diabetic background medication at screening (with and without SU) will be included based on the actual information collected through the eCRF. In case of missing eCRF information the information collected from the IWRS system will be used.

The latest available measurement, at or prior to the randomisation visit, will be used as the baseline measurement. If no measurement(s) have been obtained, at or prior to randomisation, the baseline value will be left missing.

Laboratory values below the lower limit of quantification (LLoQ) will be set to ½ LLoQ. Number of values below LLoQ by treatment and visit will be summarised if deemed relevant.

Results from a statistical analysis will as a minimum be presented by the estimated treatment contrasts for oral semaglutide versus sitagliptin comparisons with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference.

If no statistical analysis is specified, data will be presented using relevant summary statistics.

**Primary and secondary estimands**

Two estimands addressing different aspects of the trial objective will be defined; a primary de-facto (effectiveness) estimand and a secondary de-jure (efficacy) estimand:

- Primary estimand
  - de-facto treatment difference (oral semaglutide versus sitagliptin) at week 52 for all randomised subjects regardless of adherence to randomised treatment and initiation of rescue medication

The primary de-facto estimand assesses the expected glycaemic benefit in a future population that results from subjects initiating treatment with oral semaglutide including potential rescue medication(s) as compared to initiating treatment with sitagliptin including potential rescue medication(s). Generalisation of this estimand depends among other things on the extent to which

the use of rescue medication in this trial reflects clinical practice and the adherence to trial product administration in this trial reflects the behaviour of the target population. Accordingly, data collected regardless of discontinuation of trial product or initiation of rescue medication(s) will be used to draw inference.

- Secondary estimand
  - de-jure treatment difference (oral semaglutide versus sitagliptin) at week 52 for all randomised subjects if all subjects adhered to treatment and did not initiate rescue medication

The secondary de-jure estimand assesses the glycaemic benefit a future subject is expected to achieve if initiating and continuing treatment with oral semaglutide as compared to sitagliptin. It is considered a clinically relevant estimand as it provides information to treating clinicians about the expected glycaemic efficacy of oral semaglutide compared to sitagliptin for purposes of treating individual subjects. Generalisation of this estimand depends among other things on the extent to which the adherence to trial product administration in this trial reflects the behaviour of the target population. Accordingly, only data collected prior to discontinuation of trial product or initiation of rescue medication will be used to draw inference. This will avoid confounding from rescue medication.

**Missing data considerations at week 52**

When estimating the primary estimand, the proportion of missing data, i.e., data that do not exist even though subjects are intended to stay in the trial regardless of treatment status and initiation of rescue medication(s), is expected to be maximum 15% . Missing data will mainly be due to withdrawal from trial or lost to follow-up.

When estimating the secondary estimand, the proportion of missing data is expected to be higher (20-30%) since data collected after discontinuation of trial product or initiation of rescue medication(s) will be set to missing. The 20-30% of missing data is based on the sitagliptin phase 3 trials[41], the oral semaglutide phase 2 trial (NN9924-3790), that indicates that a low starting dose with gradual dose-escalation diminishes gastrointestinal AEs compared with more aggressive dosing regimens. The possibility to reduce the dose due to issues with tolerability is also expected to reduce the number of subjects withdrawing from the oral semaglutide arm. Across treatment arms the main reasons for missing data are expected to be early treatment discontinuation due to gastrointestinal AEs and eventually initiation of rescue medication. Initiation of rescue medication is expected to be more frequent in the sitagliptin than in the oral semaglutide arm. A higher proportion of subjects are expected to discontinue treatment due to AEs in the oral semaglutide arm, compared to the sitagliptin treatment arm. So overall the frequency of missing data is expected to be similar across treatment arms.

Descriptive summaries and graphical representation of extent, reason(s) for and pattern of missing data will be presented by treatment arm.

## 17.1 Sample size calculation

The primary endpoint, if a subject after week 52 achieves (yes/no) $HbA_{1c} < 7\%$ (53 mmol/mol) and the confirmatory secondary endpoint, change from baseline to week 52 in body weight (kg) are planned to be tested for superiority of oral semaglutide versus sitagliptin.

The sample size calculation is made to ensure at least 90% to confirm superiority of oral semaglutide vs. sitagliptin on the primary endpoint, if a subject after week 52 achieves $HbA_{1c} < 7\%$ (yes/no). Two pre-specified confirmatory hypotheses are shown in Figure 17–1. The hierarchal testing strategy is used to control the overall type-1 error at a nominal two-sided 5% level. The statistical testing strategy is built on the principle that glycaemic effect will have to be established in terms of $HbA_{1c}$ superiority before testing for added benefits in terms of body weight superiority.

The sample size calculation is based on a 5% (two-sided) significance level and Fishers exact test. The sample size depends on the proportion of responders and the absolute difference in proportions between semaglutide and sitagliptin. Assuming an absolute difference in proportions of 15 percentage-points (taking the retrieved and imputed data into account) and that the proportion of sitagliptin responders are distributed around 20 to 50%, the power for confirming superiority on the primary endpoint, if a subject after week 52 achieves (yes/no) $HbA_{1c} < 7\%$ (53 mmol/mol) will be at least 90% with 250 subjects per arm. In total 500 subjects are planned to be randomised.

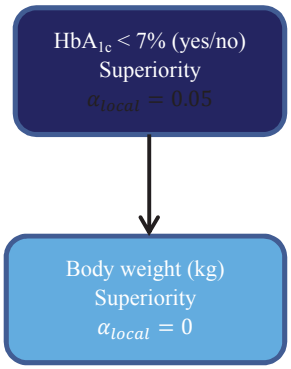



**Figure 17–1 Graphical illustration of the closed testing procedure**

The overall significance level of $\alpha = 0.05$ (two-sided) is initially allocated to the $HbA_{1c}$ superiority test. The local significance level (α-local) will be reallocated to the body weight hypothesis if the first hypothesis is confirmed. The sample size is based on the $HbA_{1c}$ hypothesis.

## 17.2 Definition of analysis sets

The following analysis sets will be defined:

**Full analysis set (FAS):** Includes all randomised subjects. Subjects in the FAS will contribute to the evaluation "as randomised".

**Safety analysis set (SAS):** Includes all subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation "as treated".

**Data selections and observation periods**

Unless subjects withdraw their informed consent, data collection will continue for the full duration of the trial. The full duration of the trial is defined as up to and including:

- the follow-up visit (V11) for subjects on trial product
- the latest occurring visit of the end-of-treatment visit (V10) or the follow-up premature discontinuation visit (V11A), for subjects who have discontinued trial product prematurely

Subjects and data to be used in an analysis will be selected in a two-step manner:

- Firstly, subjects will be selected based on the specified analysis set
- Secondly, data points on the selected subjects from the first step will be selected based on the specified observation period

Definition of the observation periods:

**In-trial:** This observation period represents the time period where subjects are considered to be in the trial, regardless of discontinuation of trial product or initiation of rescue medication. The in-trial observation period starts at randomisation (as registered in the IWRS) and ends at the date of:

- the last direct subject-site contact, which is scheduled to take place 5 weeks after planned last dose of trial product at the follow-up visit (V11)
- withdrawal for subjects who withdraw their informed consent
- the last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up
- death for subjects who dies before any of the above

**On-treatment:** This observation period represents the time period where subjects are considered treated with the trial product. The observation period is a subset of the in-trial observation period. It starts at the date of first dose of trial product. Two slightly different end dates will be needed to cover all assessments appropriately.

For adjudicated events, ECGs and AEs including hypoglycaemic episodes, the observation period ends at the first date of any of the following:

- the follow-up visit (V11)
- the follow-up prematurely discontinuation visit (V11A)
- the last date on trial product +38 days
- the end-date for the in-trial observation period

The follow-up visit (V11/V11A) is scheduled to take place 5 weeks after the last date on trial product corresponding to approximately five half-lives of oral semaglutide. The visit window for the follow-up visit is +3 days.

For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) the observation period ends at the last date on trial product +3 days. This will be used in order to ensure specificity to reversible effects of treatment.

**On-treatment without rescue medication:** This observation period is a subset of the on-treatment observation period, where subjects are considered treated with trial product, but have not initiated any rescue medications. Specifically it starts at date of first dose of trial product and the observation period ends at the first date of any of the following:

- the last dose of trial product +3 days
- initiation of rescue medication

The in-trial observation period will be the primary observation period when estimating the primary estimand. The on-treatment without rescue medication observation period will be the primary observation period when estimating the secondary estimand. The on-treatment observation period will be considered supportive for evaluating efficacy. Safety will be evaluated based on the in-trial and the on-treatment observation periods.

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period. For adjudicated events, the onset date will be the EAC adjudicated onset date.

Before data are locked for statistical analysis and the randomisation code is broken, a review of all data will take place. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group.

Exclusion of data from analyses should be used restrictively, and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The subjects

and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

**Confirmatory hypotheses**

For the primary $HbA_{1c}$ endpoint the following confirmatory one-sided hypothesis are planned to be tested for oral semaglutide versus sitagliptin.

- $H_0$: OR $\leq 1$ against $H_a$: OR $>1$

For the confirmatory secondary body weight endpoint the following confirmatory one-sided hypothesis are planned to be tested for oral semaglutide versus sitagliptin.

- $H_0$: $\mu \geq 0.0$kg against $H_a$: $\mu < 0.0$ kg, where $\mu$ = (oral semaglutide minus sitagliptin)

Operationally both confirmatory hypotheses will be evaluated by two-sided tests at the 5% significance level.

**Multiplicity and criteria for confirming hypotheses**

The type I error for testing the two confirmatory hypotheses related to the $HbA_{1c}$ and body weight endpoints will be preserved in the strong sense at 5 % (two-sided) using an hierarchical testing strategy as outlined in Figure 17–1.

Superiority of the primary hypotheses will be considered confirmed if the odds ratio is supporting the corresponding alternative hypothesis and the two-sided p-value from the primary analysis of the primary estimand is strictly below the 5% two-sided significance level. This is equivalent to using a one-sided p-value (nominal $\alpha = 0.025$) and a one-sided 2.5 % overall significance level. If the primary hypothesis is confirmed, the testing strategy will continue testing the confirmatory secondary hypothesis at a 5% two-sided significance level. Superiority of the secondary confirmatory hypotheses will then be considered confirmed if the treatment difference is supporting the corresponding alternative hypothesis and the two-sided p-value from the primary analysis of the primary estimand is strictly below the 5% two-sided significance level.

## 17.3 Primary endpoint

The primary endpoint is if a subject after week 52 achieves (yes/no) $HbA_{1c} < 7\%$ (53 mmol/mol) ADA target.

### 17.3.1 Primary analysis for the primary estimand

The primary estimand will be estimated based on the FAS using week 52 measurements from the in-trial observation period. The primary statistical analysis will be a logistic regression model with

treatment, region, and stratification factor as fixed effects and baseline $HbA_{1c}$ measurement as a covariate. Firstly, a pattern mixture model using multiple imputation is used to impute missing values for continuous $HbA_{1c}$ assessments assuming that the missing data mechanism is missing at random (MAR) within the groups used for imputation. Imputation of missing data at week 52 will be done within 4 groups of subjects defined by randomised treatment arm, and whether subjects at week 52; (i) have discontinued treatment or initiated rescue medication or (ii) are still on treatment and have not initiated rescue medication. It is hereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who at week 52 are similar in terms of randomised treatment arm and treatment adherence/rescue status.

Missing values for each group will be imputed as follows:

- An analysis of covariance (ANCOVA) with region and stratification factor as categorical fixed effects and baseline $HbA_{1c}$ measurement as a covariate will be fitted to observed values of the change from baseline to week 52 in $HbA_{1c}$.
- The estimated parameters for location and dispersion will be used to impute 100 values for each subject with missing week 52 data based on region and stratification factor as categorical fixed effects and baseline $HbA_{1c}$ measurement as a covariate. Thus, 100 complete data sets will be generated including observed and imputed values.
- The binary endpoint will be created for each of the 100 complete data sets.
- A logistic regression model with treatment, region, and stratification factor as fixed effects and baseline $HbA_{1c}$ measurement as a covariate is fitted for each of the imputed datasets.
- The resulting 100 estimates and variances will be combined using Rubin's rule[44], and the estimated odds ratio between oral semaglutide and sitagliptin together with two-sided 95 % CI and two-sided p-value for testing no difference from one will be presented.

### 17.3.2 Primary analysis for the secondary estimand

The secondary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 52 from the on-treatment without rescue medication observation period. Handling of missing data will be determined from the imputed continuous responses. A total of 100 imputed data sets will be created using a mixed model for repeated measurements (MMRM) based analysis. The binary endpoint will be created for each of the 100 complete data sets. The imputed complete data sets will be analysed using a logistic regression model with treatment, region, and stratification factor as fixed effects, and baseline $HbA_{1c}$ measurement as a covariate. The resulting 100 estimates and variances will be combined using Rubin's rule[44]. The MMRM based analysis will use a restricted maximum likelihood (REML) and include all post-baseline $HbA_{1c}$ measurements collected at scheduled visits up to and including week 52 as dependent variables. The independent effects included in the model will be treatment, region, and stratification factor as categorical fixed effects and baseline $HbA_{1c}$ as a covariate, all nested within visit. An unstructured covariance matrix

for $HbA_{1c}$ measurements within the same subject will be employed, assuming measurements from different subjects are independent.

The MMRM is a well-established method that accounts for the uncertainty pertaining to missing data. This analysis assumes that the missing data mechanism is MAR. Under this assumption the statistical behaviour of the missing data (given the observed responses and model fixed effects and covariates) is assumed to be same as the observed data.

### 17.3.3 Sensitivity analyses

To investigate the sensitivity of the primary analysis results, complementary and separate analyses will be performed for the primary and secondary estimand. In line with European Medicines Agency recommendations (CHMP 2010)[45] and with a report from the US National Research Council (NAS 2010)[46], these analyses will primarily evaluate the sensitivity of the results due to the impact of missing data.

The evaluation of the robustness of the primary analysis will in all cases be a logistics regression model with treatment, region, and stratification factor as fixed effects and baseline $HbA_{1c}$ measurement as a covariate. However missing data will be based on different pattern mixture model approaches using multiple imputation. The binary endpoint will be created using the imputed continuous data. An overview of the sensitivity analyses for each of the estimands are specified below followed by a more detailed description of the two different pattern mixture models used. Finally, an additional sensitivity analyses for the primary analysis will be described that is not based on the pattern mixture model approach.

**Sensitivity analyses for the primary estimand**

The estimation of the primary estimand will be repeated using the following sensitivity analyses for imputing missing continuous $HbA_{1c}$ assessments before testing the binary primary endpoint using logistic regression:

- A comparator multiple imputation analysis based on FAS using the in-trial observation period
- A tipping-point multiple imputation analysis based on FAS using the in-trial observation period.
- A MMRM based analysis implemented in a multiple imputation setting (the primary analysis for the secondary estimand) based on FAS using the in-trial observation period

**Sensitivity analyses for the secondary estimand**

The estimation of the secondary estimand will be repeated using the following sensitivity analyses:

- A comparator multiple imputation analysis based on FAS using the on-treatment without rescue medication observation period.
- A comparator multiple imputation analysis based on FAS using the on-treatment observation period. This sensitivity analysis aims to compare oral semaglutide versus sitagliptin for subjects who adhere to treatment regardless of whether or not rescue medication has been initiated.
- A tipping-point multiple imputation analysis based on FAS using the on-treatment without rescue medication observation period.

#### 17.3.3.1 Pattern mixture models

Common for the two pattern mixture model sensitivity analyses is that they all aim to stress-test the primary $HbA_{1c}$ results by changing the assumptions for missing data in the oral semaglutide treatment arms, while maintaining the missing at random data assumption for the sitagliptin arm:

- *Comparator multiple imputation analysis:* In this sensitivity analysis missing data at week 52 for all subjects will be imputed to resemble the distribution of the week 52 values observed in the sitagliptin treatment arm. In effect, this imputation approach removes the treatment difference between oral semaglutide and sitagliptin for all subjects randomised to oral semaglutide, given that oral semaglutide is better than sitagliptin.
- *Tipping-point multiple imputation analysis:* In this sensitivity analysis, missing data will first be imputed according to the primary analysis. Secondly, for the oral semaglutide treatment arm a penalty will be added to the imputed values at week 52. The approach is to gradually increase this penalty until a confirmed $HbA_{1c}$ conclusion from the primary analysis is changed. The specific value of the penalty that changes the conclusion will be used to evaluate the robustness of the primary analysis result.

#### 17.3.3.2 Other sensitivity analysis

The following additional sensitivity analysis will be specified:

- *Last observation carried forward (LOCF) analysis:* This sensitivity analysis will be based on the FAS using the on-treatment without rescue medication observation period. The statistical analysis will be a logistic regression model with treatment, region, and stratification factor as fixed effects and baseline $HbA_{1c}$ as a covariate

**Assessment of sensitivity analyses**

The results from the sensitivity analyses will be collectively used to interpret the robustness of the trial results for $HbA_{1c}$. Due to the sensitivity analyses inherent conservative nature, it will not be a requirement that all confirmatory hypotheses are consistently confirmed across the sensitivity

analyses. Thus, no absolute success criteria will be pre-defined for each sensitivity analysis. The sensitivity results in totality will be used to substantiate the credibility of the trial results.

## 17.4 Secondary endpoints

### 17.4.1 Confirmatory secondary endpoints

Change from baseline to week 52 in body weight (kg) will be a confirmatory secondary endpoint.

The primary and secondary estimands will be estimated using the same approaches as described for the primary $HbA_{1c}$ endpoint without dichotomizing the endpoint and with a linear normal regression model instead of the logistic regression model. Baseline body weight will be used as a covariate instead of baseline $HbA_{1c}$ in both the multiple imputation and analysis models.

Superiority will be considered confirmed if the mean treatment difference is supporting the corresponding hypothesis and the two-sided p-value from the analysis of the primary estimand is strictly below its local two-sided significance level resulting from the closed testing procedure in Figure 17–1. Sensitivity analyses similar to the ones pre-specified for testing superiority for the primary $HbA_{1c}$ endpoint will be made to evaluate the robustness of the body weight results.

### 17.4.2 Supportive secondary endpoints

#### 17.4.2.1 Efficacy endpoints

The below supportive secondary efficacy endpoints will be evaluated for:

- the primary estimand based on FAS using the in-trial observation period
- the secondary estimand based on FAS using the on-treatment without rescue medication observation period

No sensitivity analyses are planned for these.

**Continuous efficacy endpoints**

Change from baseline to week 52 in:

- $HbA_{1c}$
- FPG
- Body weight (%)
- BMI
- Waist circumference
- Fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)

BMI will be calculated based on body weight and height based on the formulae:
BMI $kg/m^2$ = body weight (kg)/(height [m] × height [m]) or ($kg/m^2$ = [$lb/in^2$ × 703])

The above continuous endpoints will be analysed separately using similar model approaches as for the secondary endpoint with the associated baseline response as a covariate. Fasting lipid profile endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate

**Binary efficacy endpoints**

If a subject after 52 weeks achieves (yes/no):

- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) AACE target
- $HbA_{1c}$ reduction ≥ 1%-point (10.9 mmol/mol)
- Weight loss ≥ 3%
- Weight loss ≥ 5%
- Weight loss ≥ 10%
- $HbA_{1c} < 7.0\%$ (53 mmol/mol) without hypoglycaemia (treatment-emergent severe or BG-confirmed symptomatic hypoglycaemia) and no weight gain
- $HbA_{1c}$ reduction ≥ 1%-point (10.9 mmol/mol) and weight loss ≥ 3%

The above binary endpoints will be analysed separately using similar model approaches as for the primary endpoint with the associated baseline response as a covariate.

**Time to event endpoint**

- Time to rescue medication

The endpoint will be analysed based on FAS using both the on-treatment observation period and the in-trial observation period. For the analysis based on the on-treatment observation period, subject without need for rescue medication during the on-treatment observation period will be censored at the time point of the date of last trial product. For the in-trial period subject without need for addition of glucose-lowering medication during the in-trial observation period, will be censored at the time point of the date of end of the in-trial observation period. For this analysis, the follow-up period will be excluded from the in-trial observation period, since subjects will have to stop treatment at the end-of-treatment visit and therefore might need addition of glucose-lowering medication during the follow-up period.

The endpoint will be described and compared for oral semaglutide versus sitagliptin using likelihood ratio tests obtained from a Cox proportional hazards model with treatment, stratification factors, the interaction between the two stratification factors and region as categorical fixed effects

and baseline $HbA_{1c}$ as a covariate. From this analysis the estimated Hazard ratios between oral semaglutide versus sitagliptin will be presented together with 95% confidence intervals and two sided p values for test of no difference.

#### 17.4.2.2 Safety endpoints

The safety endpoints will be evaluated based on SAS using the on-treatment observation period and based on SAS using the in-trial observation period unless otherwise stated. The following endpoints are used to support the safety objectives.

**Adverse events**

- Number of TEAEs during exposure to trial product, assessed up to approximately 57 weeks

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding.

A treatment-emergent AE is defined as an AE with onset in the on-treatment observation period (see definition of observation periods in Section 17.2).

TEAEs will be summarised in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 patient years of observation time (R) for the on-treatment observation period. Supportive summaries of AEs will be made for the in-trial observation period. The development over time in gastrointestinal AEs will be presented graphically.

**Other safety endpoints**

Change from baseline to week 52 in:

- Amylase (part of biochemistry)
- Lipase (part of biochemistry)
- Pulse
- Systolic blood pressure
- Diastolic blood pressure

The above safety endpoints will be evaluated using the primary analysis for the primary estimand based on SAS using the in-trial observation period and using the primary analysis for the secondary estimand based on SAS using the on-treatment observation period. Endpoints will be analysed as described above for continuous efficacy endpoints. Results will be presented at week 52. Amylase and lipase endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

Change from baseline to week 52 in:

- Haematology
- Biochemistry (except for amylase and lipase)
- Calcitonin
- ECG category
- Physical examination

The above safety endpoints will be summarised descriptively by treatment arm and visit. Categorical safety endpoints will be summarised as counts and relative frequencies. Calcitonin will also be presented by gender.

**Hypoglycaemia**

- Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks
- Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks (yes/no)

**Classification of hypoglycaemia:**

Hypoglycaemic episodes will be summarised for the SAS and the on-treatment observation period only.

Treatment-emergent: hypoglycaemic episodes will be defined as treatment-emergent if the onset of the episode occurs within the on-treatment observation period (see definition of observation periods in Section 17.2).

Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05.59 both inclusive.

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia and the ADA classification of hypoglycaemia (see Figure 17–2).

**Novo Nordisk classification of hypoglycaemia**

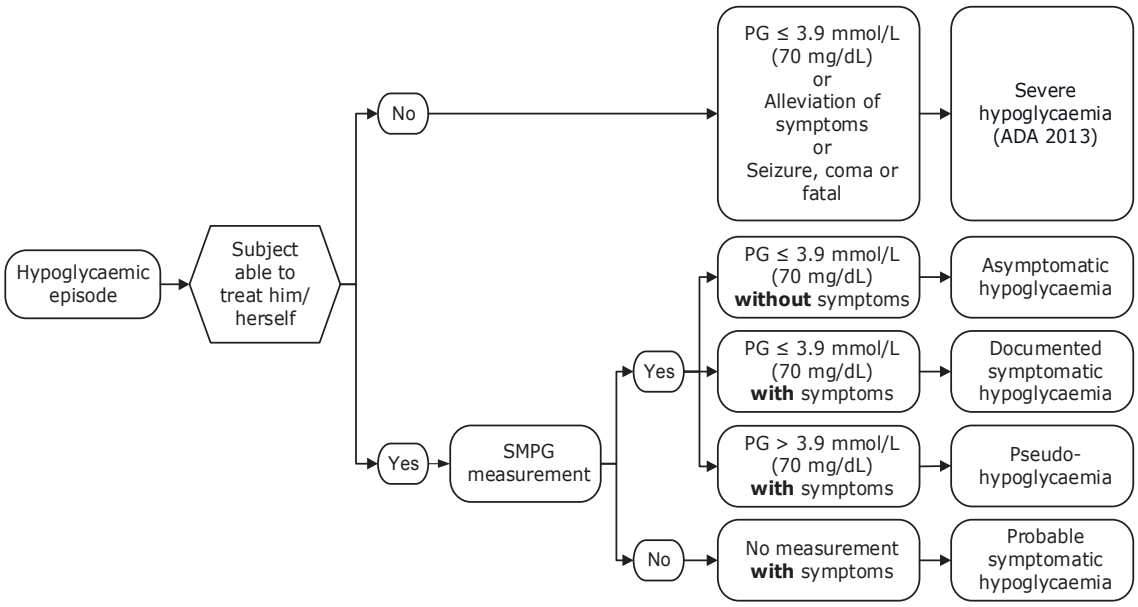
In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L (56 mg/dL)[47]. Therefore, Novo Nordisk has included hypoglycaemia with PG levels below this cut-off point in the definition of BG-confirmed hypoglycaemia.

Novo Nordisk uses the following classification in addition to the ADA classification:

- Severe or BG-confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[38] or BG-confirmed by a PG value < 3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.

**ADA classification[38] of hypoglycaemia**

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured PG concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a PG determination but that was presumably caused by a PG concentration ≤ 3.9 mmol/L (70 mg/dL).




Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

PG: plasma glucose SMPG: Self-measured plasma glucose

**Figure 17–2 ADA classification of hypoglycaemia**

Data on treatment-emergent hypoglycaemic episodes will be presented in terms of the number of subjects with at least one episode, the percentage of subjects with at least one episode (%), the total number of episodes and the episode rate per 100 patient years of observation time.

**Analysis of severe or BG-confirmed symptomatic hypoglycaemic endpoints**

The number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during the on-treatment period will be analysed using a negative binomial regression model with a log-link function and the logarithm of the duration of the subject's on-treatment observation period as offset. The model will include treatment, stratification factor and region as fixed factors and baseline $HbA_{1c}$ as covariate.

The binary endpoint showing whether a subject has at least one treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episode will be analysed using a logistic regression model with treatment, stratification factor and region as fixed factors and baseline $HbA_{1c}$ as covariate.

## 17.5 Interim analysis

No interim analyses or other analyses of unblinded data will be performed before the database is locked.

## 17.6 Patient reported outcomes

Change from baseline to week 52:

- SF-36v2™ (acute version) health survey: Scores from the 8 domains and the physical component score and mental component score summary scores
- DTSQ: individual items and treatment satisfaction score (6 of the 8 items summed)

The PRO endpoints will be evaluated using the primary analysis for the primary estimand and using the primary analysis for the secondary estimand based on FAS using the on-treatment without rescue medication period. All of the above individual items and scores will be analysed separately as the other continuous efficacy endpoints with the associated baseline response as a covariate.

# 18 Ethics

## 18.1 Benefit-risk assessment of the trial

### 18.1.1 Risks and precautions

The nonclinical safety programme of oral semaglutide has not revealed any safety issues precluding use in humans.

The sections below describe the important identified and potential risks and precautions associated with oral semaglutide treatment. These are based on findings in nonclinical studies and clinical trials with oral semaglutide as well as other GLP-1 RAs. For each of these risks and precautions, mitigating actions have been implemented to minimise the risks for subjects enrolled in this trial.

**Identified risks**

**Gastrointestinal adverse events**

Consistent with findings with other GLP-1 RAs, the most frequently reported AEs in clinical trials with oral semaglutide have been gastrointestinal disorders (nausea, vomiting, diarrhoea, dyspepsia and constipation). Clinical trials have indicated that a low starting dose and gradual dose-escalation mitigates the risk of gastrointestinal AEs. Consequently, a low starting dose and dose-adjustment every 8 weeks according to $HbA_{1c}$ and tolerability (nausea/vomiting) have been implemented in this trial.

**Potential risks**

**Medullary thyroid cancer**

The human relevance of the proliferative C-cell changes found in rodents treated with GLP-1 RAs is unknown, but data suggest that rodents are more sensitive to the mode of action of GLP-1 RAs for induction of C-cell tumours. However, as a precaution, subjects with a family or personal history of MEN 2 or MTC will not be enrolled in the trial. During the trial, calcitonin will be measured on a regular basis, and the guidance for investigators on further evaluation and action on elevated calcitonin concentrations is included in appendix A.

**Acute pancreatitis**

Acute pancreatitis has been reported in subjects treated with GLP-1 RAs including oral semaglutide. As a precaution, subjects with a history of acute or chronic pancreatitis will not be enrolled in the trial. Also, subjects will be informed about the symptoms of acute pancreatitis and serum levels of lipase and amylase will be monitored throughout the trial.

**Pancreatic cancer**

Patients with T2DM have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from nonclinical studies or clinical trials or post marketing data that GLP-1-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been included as a separate potential risk due to the scientific debate surrounding a potential association to GLP-1-based therapies and the unknown long-term effects of stimulation of β-cells and suppression of α-cells. Pancreatic cancer has been classified as a potential class risk of GLP-1 RAs by European Medicines Agency.

**Allergic reactions**

As in the case with all protein-based pharmaceuticals, treatment with oral semaglutide may evoke allergic reactions. These may include urticaria, rash, pruritus as well as anaphylactic reactions. As a precaution, subjects with known or suspected hypersensitivity to trial product(s) or related products will not be enrolled in the 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.

**Hypoglycaemia**

Based on current knowledge about the GLP-1 RA drug class, there is a risk of hypoglycaemic episodes. Hypoglycaemic episodes have mainly been observed when a GLP-1 RA is combined with sulphonylurea or insulin. The risk for development of hypoglycaemia with oral semaglutide in combination with sulphonylurea and insulin is currently unknown.

**Acute renal impairment**

In subjects treated with GLP-1 RAs, including oral semaglutide, gastrointestinal AEs such as nausea, vomiting and diarrhoea may lead to significant dehydration and secondary acute renal impairment. Subjects with gastrointestinal AEs are recommended to drink plenty of fluids to avoid volume depletion. Also, serum creatinine and other markers of kidney function will be monitored throughout the trial.

SGLT-2 inhibitors, an allowed background medication, have also been associated with volume depletion. It is recommended to monitor for signs and symptoms of fluid loss during therapy. Severe dehydration may be a risk factor for ketoacidosis.

Impaired renal function may increase the risk of metformin associated lactic acidosis when GLP-1 RAs are co-administered with metformin. As a precaution serum creatinine will be measured regularly. In subjects treated with metformin who experience prolonged or severe nausea and vomiting, the investigator should monitor serum creatinine, and if clinically indicated, withhold metformin until resolution of renal dysfunction.

The use of the background medication should be in accordance with the current approved labels.

**Other safety considerations**

**Teratogenicity (embryo-foetal development toxicity)**

Semaglutide caused embryo-foetal malformations in the rat through a GLP-1 receptor mediated effect on the inverted yolk sac placenta leading to impaired nutrient supply to the developing embryo. Primates do not have an inverted yolk sac placenta which makes this mechanism unlikely to be of relevance to humans. However, as a precaution, females who are pregnant, breast-feeding or intend to become pregnant or are of childbearing potential and not using an adequate contraceptive method will not be enrolled in the trial. In addition, pregnancy tests will be performed at all visits, including screening and follow-up and at any time during the trial if a menstrual period is missed, or as required by local law.

**General precautions**

All subjects will be included after a thorough evaluation with regards to in- and exclusion criteria defined in order to ensure that subjects are eligible for trial treatment.

There are also strict glyacemic rescue criteria in place to ensure acceptable glycaemic control during the trial. If rescue medication is required, it should be in accordance with ADA/European Association for the Study of Diabetes[25, 26] (excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues).

It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2016 Standards of Medical Care in Diabetes[48].

Further details with regards to safety of trial product are described in the current edition of the IB for oral semaglutide (NN9924) edition 6[24], or any updates thereto.

#### 18.1.1.1 Sitagliptin

The most commonly reported side effects associated with sitagliptin are upper respiratory tract infection, nasopharyngitis and headache. Also acute pancreatitis, acute renal failure, hypersensitivity reaction, severe and disabling arthralgia and hypoglycaemia have been reported[41, 49].

### 18.1.2 Benefits

In this trial, subjects will be randomised to one of two treatment arms involving a treatment regimen anticipated to be more efficacious than the treatment they receive at the time of entry into the trial. Based on the results of the phase 2 dose finding trial oral semaglutide is expected to provide clinically relevant improvements in glycaemic control and body weight in subjects with T2DM.

Similarly treatment with sitagliptin is expected to provide clinically relevant improvements in glycaemic control[41]. In addition, it is expected that all subjects will benefit from participation through close contact with the study site, with close follow-up of their T2DM and a careful medical examination; all of which will most likely result in an intensified management of their T2DM.

All subjects in this trial will receive trial products and auxiliary supplies free of charge.

### 18.1.3 Risk and benefit conclusion

The safety profile for oral semaglutide generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of oral semaglutide in accordance with the planned clinical trial.

Sitagliptin is already a marketed drug approved for the use in subjects with T2DM.

Safety and efficacy will be monitored regularly and acceptable glycaemic control will be reinforced at all times during the trial.

In conclusion, the potential risk to the subjects in this trial is considered low and acceptable in view of the anticipated benefits oral semaglutide/sitagliptin will provide to subjects with T2DM.

## 18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[1] and the requirements in the Declaration of Helsinki[2].

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand.

The subjects must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

The responsibility for 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. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the investigator must inform the subject in a timely manner and a revised written subject information must be provided and a new informed consent must be obtained.

In order to avoid missing data, the subjects will be informed about the importance of completing the trial also if the subjects discontinue from trial product.

### 18.3 Data handling

If the subject withdraws from the trial or is lost to follow up, then the subject's data will be handled as follows:

- Data already collected and any data collected at the end-of-trial visit including follow-up visit will be retained by Novo Nordisk, entered into the database and used for the clinical trial report.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used, it will always be in accordance with local regulations and IRBs/IECs.

### 18.4 Information to subjects during 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.

### 18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If the trial is suspended or prematurely 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.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of subjects who have participated in the trial. If it has an impact, the actions needed to inform and protect the subjects should be described.

# 19 Protocol compliance

## 19.1 Protocol deviations

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

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

Documentation on protocol deviations must be kept in the investigator's trial master file and sponsor trial master file.

## 19.2 Prevention of missing data

The importance of subject retention will be addressed by Novo Nordisk in the training and communication with the trial sites.

The subjects will be carefully informed about the trial procedures before signing informed consent, so that they know the implications of participating in the trial.

Close surveillance of subject retention will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial product or withdrawal of consent to secure early mitigations in collaboration with the trial sites.

The investigator will make every effort to ensure that all assessments are performed and data is collected. If missing data does occur the reason will be collected via the protocol deviation process, see Section 19.1. Novo Nordisk will monitor protocol deviations on an on-going basis throughout the trial followed by appropriate actions (e.g. re-training of site staff).

# 20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

# 21 Critical documents

Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received and the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of IB for oral semaglutide and SmPC or similar product information for Januvia® (sitagliptin)
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

*Only applicable for US trial sites:*

- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

**FDA form 1572:**

For US sites:

- Intended for US sites
- Conducted under the IND
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP[1], applicable regulatory requirements and the Declaration of Helsinki[2].

By signing the protocol agreement, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

# 22 Responsibilities

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

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

The investigator will follow instructions from Novo Nordisk when processing data.

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 no unauthorized persons can get access to the data.

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

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

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

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

# 23 Reports and publications

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

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

One or two investigators will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator(s) will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[50].

## 23.1 Communication of results

Novo Nordisk commits to communicating and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a 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, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[27].

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim 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. All authors will be given the relevant statistical tables, figures and reports needed to evaluate the planned publication. 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.

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

Novo Nordisk maintains the right to be informed of plans by any investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to Novo Nordisk before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

### 23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[50] (sometimes referred to as the Vancouver Criteria). Novo Nordisk will appoint investigator(s) to prepare publications in collaboration with Novo Nordisk.

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

For a multi-centre 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. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

## 23.2 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.

# 24 Retention of clinical trial documentation and human biosamples

## 24.1 Retention of clinical trial documentation

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

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project, whichever is longest.

The files from the trial site/institution must be retained for 15 years after end of trial as defined in Section 7, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

## 24.2 Retention of human biosamples

Antibody samples collected in relation to suspicion of hypersensitivity reaction during the trial may be retained at Novo Nordisk until market authorisation in case Health Authorities request further characterisation of the antibody response (maximum up to 15 years from end of trial).

*For Brazil only: Biological samples from Brazil will be destroyed at the end of the trial.*

The subject's identity will remain confidential and the antibody 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. Only Novo Nordisk staff will have access to the stored antibody samples. Subjects can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

# 25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

**IRB/IEC:**

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to IB, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the subjects.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

**Regulatory Authorities:**

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs and the clinical trial report according to national requirements.

# 26 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with:

*For Austria only: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBl Nr. 63/2009.*

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

*For Switzerland only: Therapeutic Products Act of 15 December 2000 (Status as of 1 January 2014) (TPA/HMG) and Ordinance on Clinical Trials in Human Research (ClinO/KlinV) of 20 September 2013.*

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## Global and country key Novo Nordisk staff

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff

## Appendix A

# Monitoring of Calcitonin

# 1 Background

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

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

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

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

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

# 2 Calcitonin monitoring

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

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

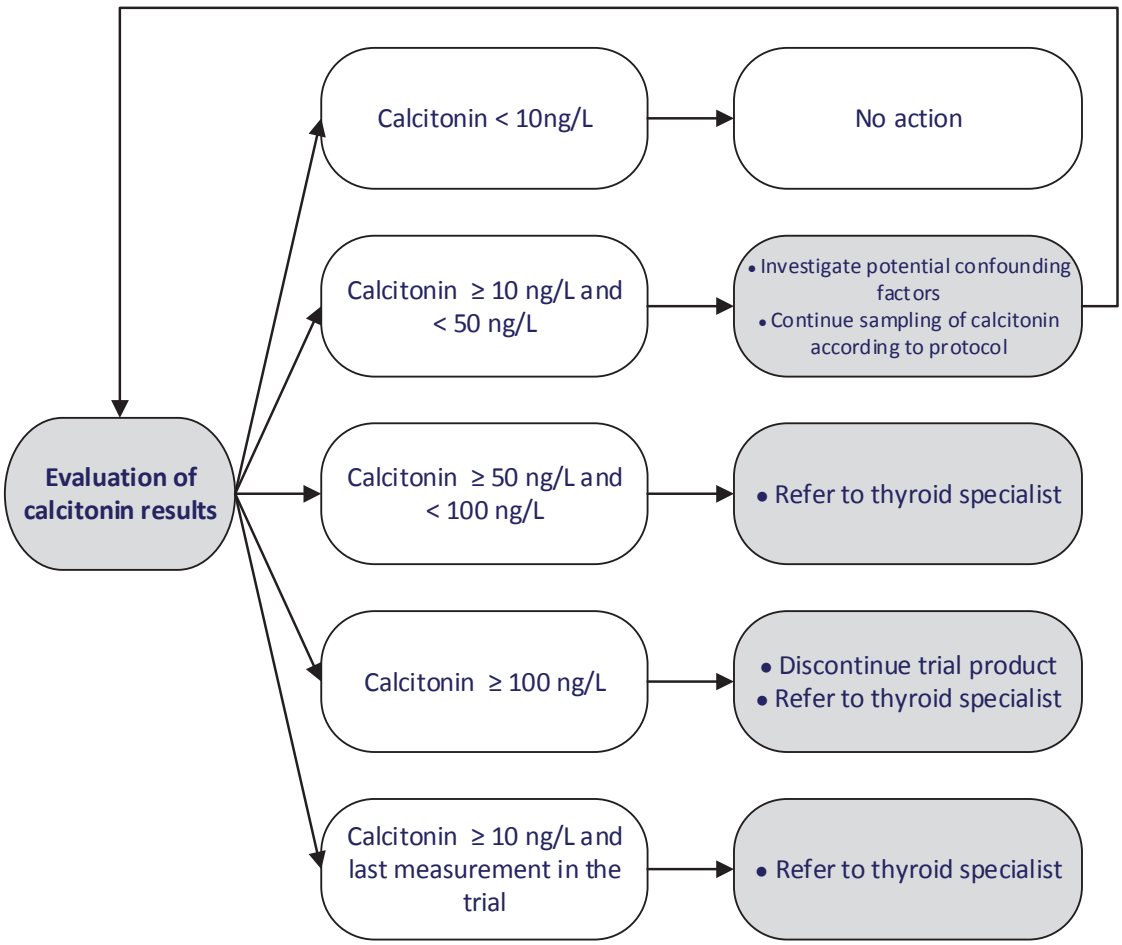


**Figure 1 Flow of calcitonin monitoring**

## 2.1 Calcitonin ≥ 100 ng/L

**Action:** The subject must immediately be referred to a thyroid specialist for further evaluation and the trial product must be discontinued (see protocol Section 6.5 premature discontinuation of trial

product). The subject should remain in the trial, however, all medications suspected to relate to this condition must be discontinued until diagnosis has been established.

**Background:** These values were found in 9 (0.15%) of a population of 5817 patients with thyroid nodular disease.[1] All of these patients were diagnosed with MTC resulting in a positive predictive value of 100 %.

Diagnostic evaluation should include:

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

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

### 2.2 Calcitonin ≥ 50 and < 100 ng/L

**Action:** The subject should be referred to a thyroid specialist for further evaluation. The subject should remain in the trial and continuation on trial product should be based on the evaluation done by the thyroid specialist.

**Background:** These values were found in 8 (0.14%) of the population of 5817 patients with thyroid nodular disease.[1] Two of these subjects were diagnosed with MTC and two were diagnosed with C-cell hyperplasia, resulting in a positive predictive value of a C-cell anomaly of 50%.

Diagnostic evaluation should include:

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

### 2.3 Calcitonin ≥ 10 and < 50 ng/L

**Action:** The subject can continue in the trial on trial product. Continue sampling of calcitonin according to the protocol.

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

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

For calcitonin values between 10-20 ng/L Costante et al[1] identified 216 (3.7%) patients. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin of 33 ng/L, and had C-cell hyperplasia at surgery. Two other studies used a cut-off of calcitonin > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal calcitonin > 10 and < 20 ng/L to allow conclusions.[2,3]

# 3 References

1 Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab 2007; 92(2):450-455.

2 Scheuba C, Kaserer K, moritz A, drosten R. Sporadic hypercalcitoninemia: clinica and therapeutic consequences. Endocrine Related Cancer 2009; 16(1):243-253.

3 Verga U, Ferrero S, Vicentini L, Brambilla T, Cirello V, Muzza M et al. Histopathological and molecular studies in patients with goiter and hypercalcitoninemia: reactive or neoplastic C-cell hyperplasia? Endocr Relat Cancer 2007; 14(2):393-403.

# Appendix B

# Adverse events requiring additional data collection

# 1 Adverse events requiring additional data collection

For the following AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form:

- Acute coronary syndrome (myocardial infarction [MI] or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or transient ischaemic attack [TIA])
- Heart failure
- Pancreatitis
- Neoplasm (excluding thyroid neoplasm)
- Thyroid disease (including thyroid neoplasm)
- Renal event
- Hypersensitivity reaction
- Acute gallstone disease
- Medication error (concerning trial products):
  - 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.
  - Administration of an overdose with the intention to cause harm (e.g. suicide attempt) misuse or abuse of trial product.
  - Accidental administration of a higher dose than intended. A higher dose is a dose of at least one tablet more than the intended dose; however the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.
- Lactic acidosis
- Creatine kinase (CK) > 10 x upper normal limit (UNL)
- Hepatic event:
  - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 x UNL and total bilirubin ≤ 2 x UNL
  - ALT or AST > 3 x UNL and total bilirubin > 2 x UNL*
  - Hepatic event leading to trial product discontinuation

*Please note that in case of a hepatic event defined as ALT or AST > 3 x UNL and total bilirubin > 2 x UNL, where no alternative aetiology exists (Hy's law), this must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable.

In case any of these events fulfil the criteria for an SAE, please report accordingly, see protocol Section 12.1.2.

Some of these events will undergo event adjudication by the event adjudication committee (EAC), please see protocol Section 12.7.2 and protocol Table 12-1.

### 1.1 Acute coronary syndrome

If an event of acute coronary syndrome (ranging from unstable angina pectoris to MI) is observed during the trial, the following additional information must be reported if available:

- Duration of symptoms
- Changes in ECG
- Collection of cardiac biomarkers
- Cardiac imaging
- Cardiac stress testing
- Angiography
- Use of thrombolytic drugs
- Revascularisation procedures

### 1.2 Cerebrovascular event

If a cerebrovascular event (e.g. TIA, stroke) is observed during the trial, the following additional information must be reported if available:

- Type of event (e.g. TIA, Stroke)
- Contributing condition
- Neurologic signs and symptoms
- History of neurologic disease
- Imaging supporting the condition
- Treatment given for the condition

### 1.3 Heart failure

If an event of heart failure is observed during the trial, the following additional information must be reported if available:

- Signs and symptoms of heart failure
- New York Heart Association (NYHA) Class
- Supportive imaging
- Supportive laboratory measurements
- Initiation or intensification of treatment for this condition

## 1.4 Pancreatitis

For all confirmed events of pancreatitis the following additional information must be reported if available:

- Signs and symptoms of pancreatitis
- Specific laboratory test supporting a diagnosis of pancreatitis
- Imaging performed and consistency with pancreatic disease
- Treatment for and complications of the event
- Relevant risk factors for pancreatic disease
- Family history of pancreatic disease

### 1.4.1 Assessments in case of suspicion of acute pancreatitis

Most patients with acute pancreatitis experience severe abdominal pain that is located generally in the epigastrium and radiates to the back. The onset of the pain may be swift reaching maximum intensity within 30 min, it is frequently unbearable and characteristically persists for more than 24 hours without relief[1]. The pain is often associated with nausea and vomiting. Physical examination usually reveals severe upper abdominal tenderness at times associated with guarding.

In general, both amylase and lipase are elevated during the course of acute pancreatitis. The serum lipase may remain elevated slightly longer than amylase. The level of the serum amylase and/or lipase does not correlate with the severity of acute pancreatitis[1]. In general, serum lipase is thought to be more sensitive and specific than serum amylase in the diagnosis of acute pancreatitis.

In case of suspicion of acute pancreatitis, the trial product should promptly be interrupted (no treatment discontinuation call should be made in IWRS before diagnosis of acute pancreatitis is confirmed). Appropriate additional examinations must be performed, including local measurement of amylase and lipase.

The diagnosis of acute pancreatitis requires two of the following three features[2]:

- abdominal pain **consistent** with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
- serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal
- **characteristic** findings of acute pancreatitis on imaging.

If acute pancreatitis is ruled out, trial product should be re-initiated.

If acute pancreatitis is confirmed, appropriate treatment and careful monitoring of the subject should be initiated. The subject must be discontinued from trial product (treatment discontinuation call), but should remain in the trial (see protocol Section 6.5 and 8.1.5).

### 1.5 Neoplasm

All events of neoplasms (excluding thyroid neoplasm, which will be reported under thyroid disease) must be reported during the trial and the following additional information must be reported if available:

- Type of neoplasm
- Symptoms leading to identification of event
- Diagnostic imaging
- Pathological examination results
- Treatment for the event
- Participation in screening programs
- Risk factors associated to the event

### 1.6 Thyroid disease

If an event of thyroid disease, including any thyroid neoplasms, is observed during the trial, the following additional information must be reported if available:

- History of thyroid disease
- Signs and symptoms leading to investigations of thyroid disease
- Specific laboratory tests describing thyroid function
- Diagnostic imaging performed and any prior imaging supporting the disease history
- Pathologic examinations
- Treatment given for the condition
- Risk factors identified
- Family history of thyroid disease

### 1.7 Renal event

If a renal event is observed during the trial, the following additional information must be reported if available:

- Signs and symptoms of renal failure
- Specific laboratory tests supporting the diagnosis
- Imaging performed supporting the diagnosis
- Kidney biopsy results
- Risk or confounding factors identified including exposure to nephrotoxic agents

## 1.8 Hypersensitivity reaction

All events of hypersensitivity reactions must be reported and the following additional information must be reported if available:

- Signs and symptoms associated to the event
- Time of appearance after administration of trial drug
- Relevant immunological tests performed
- Treatment given for the reaction
- Previous history of similar reaction
- Risk or confounding factors identified

### 1.8.1 Assessments in case of suspicion of hypersensitivity reaction

In case of suspicion of a severe immediate systemic hypersensitivity reaction[3] to the trial product, the subject must be discontinued from trial product but should remain in the trial (see protocol Section 6.5 and 8.1.5).

If suspicion of a hypersensitivity reaction occurs, the subjects should be instructed to contact the site staff as soon as possible for further guidance.

To assist in the diagnostic evaluation it is recommended to draw a blood sample for measurement of tryptase (total and/or mature tryptase, local assessment) within 3 hours of onset of the hypersensitivity reaction, and if this is achieved, a tryptase sample should also be drawn at V11A. Furthermore, a blood sample for assessment of IgE anti-semaglutide antibodies and anti-semaglutide antibodies should be drawn as soon as possible after the event and at V11A and sent to central laboratory. Tryptase concentrations, if available, should be included in the specific event form when reporting the AE.

In case of suspicion of immune complex disease[3], the subject must be discontinued from trial product but should remain in the trial (see protocol Section 6.5 and 8.1.5). It is recommended to draw a blood sample for local assessment of complement levels (C3 and C4) to assist in the diagnostic evaluation. Complement level results should be included in the specific event form when reporting the AE.

### 1.9 Acute gallstone disease

If an event of acute gallstone disease or clinical suspicion of this is observed during the trial, the following additional information must be reported if available:

- Signs and symptoms of acute gallstone disease
- Specific laboratory tests supporting a diagnosis of gallstone
- Imaging performed and consistency with gallstone disease
- Treatment given for the condition
- Relevant risk factors for acute gallstone disease
- Family history of gallstones

### 1.10 Medication error

If a medication error is observed during the trial, the following additional information is required and must be reported:

- Trial product(s) involved
- Classification of medication error
  - Wrong drug(s) administered
  - Administration of an overdose
- Whether the subject experienced any hypoglycaemic episode and/or AE(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication error, see protocol Section 12.1.4.

### 1.11 Lactic acidosis

If an event of lactic acidosis is observed during the trial, the following additional information must be reported if available:

- Signs and symptoms of lactic acidosis
- Specific laboratory tests describing the event
- Possible cause(s) of the event

### 1.12 Creatine kinase > 10 x UNL

If an event of CK > 10 x UNL is observed during the trial the following additional information must be reported if available:

- Signs and symptoms associated to the event
- Recent physical activity
- Possible cause(s) of the event

### 1.12.1 Assessments in case of increased levels of creatine kinase

In case of CK > 10 x UNL prompt repeat testing (at central laboratory) of CK should be done. Repeat testing (at central laboratory) should be done regularly until CK levels return to normal or baseline state. Additional clinical information should be gathered to seek possible cause of the observed CK elevation.

## 1.13 Hepatic events

- ALT or AST > 5 x UNL and total bilirubin ≤ 2 x UNL
- ALT or AST > 3 x UNL and total bilirubin > 2 x UNL*
- Hepatic events leading to trial product discontinuation

*Please note that risk of liver injury defined as ALT or AST > 3 x UNL and total bilirubin > 2 x UNL, where no alternative aetiology exits (Hy's law), should also be reported as a SAE (important medical event, according to protocol Section 12.1.2).

If one of the above events is observed during the trial, the following additional information must be reported if available:

- Signs and symptoms associated to the event
- Risk factors
- Relevant laboratory test results
- Diagnostic imaging performed
- Possible cause(s) of the event

### 1.13.1 Assessments in case of increased levels of aminotransferases

Both events should prompt repeat testing (at central laboratory) including ALT, AST, alkaline phosphatase (ALP) and total bilirubin and discontinuation of trial product should be considered. Thereafter, repeat testing (at central laboratory) of ALT, AST, ALP and total bilirubin should be done regularly until the abnormalities return to normal or baseline state. Additional clinical information such as related symptoms, risk factors and contributing conditions (e.g. viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, hepatobiliary or pancreatic disorders) should be gathered to seek a possible cause of the observed laboratory test abnormalities.

# 2 References

1. Banks PA, Freeman ML, Practice Parameters Committee of the American College of G. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101(10):2379-400.
2. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11.
3. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products. August 2015.

# Protocol Amendment

## no 1
## to Protocol, final version 1.0
## dated 06 April 2016

# Trial ID: NN9924-4257

## Efficacy and Safety of Oral Semaglutide Using a Flexible Dose Adjustment Based on Clinical Evaluation versus Sitagliptin in Subjects with Type 2 Diabetes Mellitus

*A 52-week Randomised, Open-label, Active-controlled Trial*

**Trial phase: 3a**

**Applicable to all countries**

Amendment originator:

[redacted]

# Table of Contents

**Page**

# 1 Introduction including rationale for the protocol amendment

This protocol amendment introduces:

1. Additional eye examinations and additional data collection on diabetic retinopathy
2. Addition of bicarbonate as a part of the biochemistry laboratory assessment
3. Investigator's responsibility in ensuring evaluation and management of certain risk factors and complications
4. Clarification of the criteria for completion, withdrawal and lost to follow-up
5. Other minor adjustments, clarifications and correction of typographical errors

## 1.1 Additional eye examinations and additional data collection on diabetic retinopathy

Updated protocol Sections: 2, 4.2.2.2, 8.4.1.2, 8.4.4, 12.1.5, 17.4.2.2, 18.1 and Appendix B.

Transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive antidiabetic treatment[1,2,3]. Risk factors for these events include long-standing poor glycaemic control and presence of proliferative retinopathy, and initial large improvements in blood glucose may be an additional aggravating factor. In a recently completed cardiovascular outcomes trial with s.c. semaglutide, results indicate an increased risk of events related to diabetic retinopathy in subjects treated with semaglutide compared to placebo[4]. The majority of the related adverse events were moderate in severity and did not lead to premature discontinuation of trial product. [redacted] additional eye examinations have been implemented in all trials in the PIONEER programme. Also, to further understand this safety signal, additional information will be collected for all diabetic retinopathy events reported during the trial. The information will be collected not only from new subjects enrolled by the time of this amendment, but also from already enrolled subjects to the extent that the information is available. Furthermore, information to the investigators and subjects related to diabetic retinopathy has been added to the protocol (see Section 18) and the subject information.

[1] Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. Br Med J (Clin Res Ed). 1985;290(6471):811-5.
[2] The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol. 1998;116(7):874-86.
[3] Varadhan L, Humphreys T, Walker AB, Varughese GI. The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. Diabetes Res Clin Pract. 2014;103(3):37-9.
[4] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016.

### 1.2 Addition of bicarbonate as a part of the biochemistry laboratory assessment

Updated protocol Section: 8.4.6

[redacted] that bicarbonate is added as a routine laboratory test in trials where SGLT2-inhibitors are used as background medication, because SGLT2-inhibitors have been associated with a risk for metabolic acidosis.

### 1.3 Investigator's responsibility in ensuring evaluation and management of certain risk factors and complications

Updated protocol Section: 8.4.2, 8.4.4 and18.1

[redacted] text is added to highlight the investigator's responsibility in relation to further evaluation of potential incidental thyroid nodules discovered at the physical examination.

In addition, text is added to highlight the investigator's responsibility in ensuring evaluation and management of cardiovascular risk factors and microvascular complications such as diabetic kidney disease and diabetic retinopathy.

### 1.4 Clarification of the criteria for completion, withdrawal and lost to follow-up

Updated protocol Sections: 6.6, 8.1.4, 8.1.5 and 8.1.6.1

The criteria for subject completion, -withdrawal and -lost to follow-up respectively are clarified and have been made consistent across sections. Lost to follow-up is considered a subcategory to withdrawal from trial. In addition, it is emphasised that as soon as contact to a subject is lost, efforts must be made to regain contact and the efforts must continue until the subjects last planned visit. Only if contact is not regained at that time point can the subject be considered lost to follow up. Because this trial is not an outcome trial the terminology 'health status' is replaced with "relevant safety information" - the purpose of which is to follow up on any adverse events or pregnancy, and not to determine if a subject completes the trial or not.

### 1.5 Other minor adjustments, clarifications and correction of typographical errors

#### 1.5.1 Statistical considerations

Updated protocol Sections: 17.3.1 and 17.3.2

For the pattern mixture model using multiple imputation, the number of imputations will be increased from 100 to 1000 data sets, to ensure a greater precision of the estimates.

### 1.5.2 Adverse events for Adjudication

Updated protocol Section: 12.7.2 and Appendix B

Table 12-2 has been aligned with Table 12-1 reflecting that unstable angina pectoris requires hospitalisation to qualify for Event Adjudication.

### 1.5.3 Pregnancies in female partners of male subjects (only applicable for Brazil)

Updated protocol Section: 12.5

Brazilian National Ethical Committee (CONEP) has requested the use of a local subject information/informed consent form for a female partner of male subject. The protocol is updated accordingly.

# 2 Changes

In this protocol amendment:

- Any new text is written *in italics*.
- Any text deleted from the protocol is written using ~~strike through~~.

## 2.1 Section 2 Flow chart

| **Trial Periods** | Screening [a] | Randomisation | Treatment | | | | | | | End-of-treatment (EoT) | Follow-up [b] | EoT premature discontinuation [c] | Follow-up premature discontinuation [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit (V), Phone contact (P)** | V1 | V2 | P3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V10A | V11A |
| **Timing of visit (weeks)** | Up to -2 wks | 0 | 4 | 8 | 16 | 24 | 32 | 40 | 48 | 52 | 57 | Day of discontinuation of trial product | 5 weeks after discontinuation of trial product |
| **Visit window (days)** | | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | +3 | +3 | +3 |
| **SAFETY** | | | | | | | | | | | | | |
| Eye examination[g] | x | | | | | | | | | *x* | | *x* | |

| Footer | Description |
|---|---|
| x[g] | Fundus photography or dilated fundoscopy performed within 90 days before randomisation is acceptable if results are available for evaluation at visit 2 and no deterioration in visual function since last examination.<br><br>*Fundus photography or dilated fundoscopy must be performed again:*<br>• *at V10 or within 5 weeks thereafter for subjects completing treatment*<br>• *at V10A or within 5 weeks thereafter, and again within 5 weeks prior to V10, for subjects who have prematurely discontinued trial product* |

## 2.2 Section 4.2.2.2 Supportive secondary endpoints

**Supportive secondary safety endpoints**

Change from baseline to week 52 in:

- Haematology
- Biochemistry
- Calcitonin
- Pulse
- Systolic blood pressure
- Diastolic blood pressure
- Electrocardiogram (ECG) category
- Physical examination
- *Eye examination category*

## 2.3 Section 6.6 Withdrawal from trial

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected. ~~Only subjects who withdraw consent should be considered as withdrawn from trial.~~ *A subject who does not complete the trial is also considered withdrawn from the trial. Hence a subject is considered withdrawn if the following applies:*

- *Subject withdrew consent*
- *Subject is lost to follow-up (only to be used if there is no contact with the subject by the time of the subject's last scheduled visit, see Sections 8.1.4, 8.1.5, 8.1.6 and 8.1.6.1)*
- *Other (subject deceased or closure of trial site)*

## 2.4 Section 8.1.4 End-of-treatment (visit 10) and Follow-up (visit 11)

*At V10 the subject should be reminded about the importance of attending the follow-up visit (V11). If the subject, nonetheless, dose not attend V11, the site should make efforts to obtain contact with the subject within the visit window.*

*A trial completer is defined as a subject who attends, or is in contact with the site, at the subject's last scheduled visit. For subjects who complete treatment, the last scheduled visit is V11. (For subjects who discontinue trial product, see Section 8.1.5)*

~~In case the subject cannot be reached (by clinic visit or phone contact) at the scheduled visit 11, the site should consult the contacts provided by the subject (e.g. close relatives), relevant physicians, medical records and locator agencies (if allowed according to local law) to collect health status. If no health status can be collected, the subject should be considered lost to follow up and this should be specified in the end-of-trial form.~~

## 2.5 Section 8.1.5 Premature discontinuation of trial product and follow-up (visits 10A and 11A)

~~Subjects, who only agree to attend or provide health status at the planned V10, should not be considered withdrawn from the trial. In case the subject cannot be reached (by clinic visit or phone contact) at the scheduled V10, the site should consult the contacts provided by the subject (e.g. close relatives), relevant physicians, medical records and locator agencies (if allowed according to local law) to collect health status. If no health status can be collected, the subject should be considered lost to follow-up and this should be specified in the end-of-trial form~~.

*A subject who prematurely discontinued trial product is still considered a trial completer if the subject attends or is in contact with the site, at the subject's last scheduled visit. For subjects who prematurely discontinue trial product, the last scheduled visit is V10 (or V11A if it is scheduled after V10). For subjects who complete treatment, see Section 8.1.4.The site should prepare in due time to establish contact with the subject within the visit window of the scheduled V10 if the subject has agreed to attend this visit.*

In summary, subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule, missing assessments or trial product discontinuation for any reason. Only subjects who decline any further contact with the site in relation to the trial should be considered as *having* withdrawn ~~from the trial~~ *consent* (see Section 8.1.6).

## *2.6 Section 8.1.6.1 Lost to follow-up*

*In case contact to the subject is lost during the trial, the site should immediately undertake efforts to re-establish contact. If the subject cannot be reached (by clinic visit or phone contact) and the subject has consented to it, the site should consult the contacts provided by the subject (e.g. close relatives), relevant physicians, medical records and locator agencies (if allowed according to local law) in an attempt to regain contact with the subject or to obtain relevant safety information from other sources. Efforts to regain contact should continue until the end of the subject's last scheduled visit: V11 for subjects who have completed treatment, whereas for subjects who have discontinued trial product prematurely the last visit is V10 (or V11A if it is scheduled after V10). Only if contact with the subject is not regained by the end of the visit window of the last scheduled visit can the subject be considered lost to follow-up (see Section 6.6).*

## 2.7 Section 8.4.1.2 Adverse events requiring additional data collection

For the following AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form:

- Acute coronary syndrome (MI or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or transient ischaemic attack)
- Heart failure

- Pancreatitis
- Neoplasm (excluding thyroid neoplasm)
- Thyroid disease (including thyroid neoplasm)
- Renal event
- Hypersensitivity reaction
- Acute gallstone disease
- Medication error
- Lactic acidosis
- Creatine kinase (CK) > 10x UNL
- Hepatic event defined as:
  - ALT or aspartate aminotransferase (AST) > 5x UNL and total bilirubin ≤ 2x UNL
  - ALT or AST > 3x UNL and total bilirubin > 2x UNL*
  - Hepatic event leading to trial product discontinuation.
- *Diabetic retinopathy and related complications*

*Please note that in case of a hepatic event defined as ALT or AST >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law), this must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable.

### 2.8 Section 8.4.2 Physical examination

A physical examination will be performed by the investigator according to local procedure (see Section 2 and 8.1.7).

A physical examination must include:

- General appearance
- Head, ears, eyes, nose, throat, neck
- Thyroid gland*
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- Lymph node palpation

**Please note that the diagnostic evaluation of thyroid nodules should be in accordance with the American Thyroid Association Management Guidelines or any updates hereof[37], and adapted to local treatment guidelines if applicable.*

## 2.9 Section 8.4.4 Eye examination

Fundus photography or dilated fundoscopy will be performed as per the flow chart (see Section 2) by the investigator or according to local practice. *Fundoscopy requires pharmacological dilation of both pupils.* Results of the fundus photography or dilated fundoscopy will be interpreted by the investigator (see Section 8.1.7).

## 2.10 Section 8.4.6 Laboratory assessments for safety

Biochemistry:

- Alanine aminotransferase (ALT)
- Albumin
- Alkaline phosphatase (ALP)
- Amylase
- Aspartate aminotransferase (AST)
- Bilirubin, total
- Calcium, total
- Creatinine
- eGFR per CKD-EPI~~[37]~~ *[38]*
- Creatine kinase (CK)
- Lipase
- Potassium
- Sodium
- Urea
- *Bicarbonate*

## 2.11 Section 12.1.5 Adverse events requiring additional data collection

**Table 12-1 Adverse events requiring completion of specific event forms and/or are subject to event adjudication** [Note: In this document only the additional event is shown, all other events are unchanged]

| Event | Specific event form | Event adjudication |
|---|---|---|
| *Diabetic retinopathy and related complications* | *Yes* | *No* |

## 2.12 Section 12.5 *Pregnancies*

*12.5.1* Pregnancies in female subjects

[Note: This section is not changed.]

*12.5.2 Pregnancies in female partners of male subjects (only applicable for Brazil)*

*Male subjects must be instructed to notify the investigator if their female partner becomes pregnant during the trial, except in the screening period. At the last scheduled visit, male subjects must be asked if their female partner has become pregnant.*

*If a female partner has become pregnant during the trial, the investigator must follow-up on the pregnancy outcome and until the newborn infant is one month of age, irrespective of whether the trial is completed or not. The investigator must ask the male subject and assess, if the pregnancy outcome is normal or abnormal.*

*When the pregnancy outcome is **normal** this information is recorded in the subject's medical record only, no further information is collected and reported to Novo Nordisk. When the pregnancy outcome is **abnormal** (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), the following must be reported by the investigator to Novo Nordisk electronically (e.g. in PDF format) or by fax:*

***1. Reporting of pregnancy information***

*Information from the male subject has to be reported on the Paternal Form. Furthermore, information from the female partner (including information about the pregnancy outcome and health status of the infant until the age of one month) has to be reported on the Maternal Forms 1A, 1B and 2, after an informed consent has been obtained from the female partner.*

*Initial reporting and follow-up information must be reported **within 14 calendar days** of the investigator's first knowledge of initial or follow-up information.*

***2. Reporting of AE information***

*The following AEs in the foetus and newborn infant have to be reported:*

- *Non-serious AEs evaluated as possible/probably related to the father's treatment with the trial product(s).*
- *SAEs in the foetus and newborn infant - whether or not related to the father's treatment with the trial product(s). This includes an abnormal outcome - such as foetal death (including spontaneous abortion) and congenital anomalies (including those observed at gross examination or during autopsy of the foetus).*

*Forms and timelines for reporting AEs:*

*See Section 12.5.1, point 2, "Forms and timelines for reporting AEs".*

*Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator* ***within 14 calendar days*** *from the date of receipt of the request, unless otherwise specified in the follow-up request.*

### 2.13 Section 12.7.2 Event adjudication committee

**Table 12-2 Adverse events for adjudication** [Note: Only shown is the event with updated event description, all other events are unchanged]

| Events | Description | Adjudication outcome |
|---|---|---|
| Acute Coronary Syndrome | Acute Coronary Syndrome conditions include:<br>• ST-elevation acute myocardial infarction (STEMI)<br>• Non-ST elevation acute myocardial infarction (NSTEMI)<br>• Silent MI<br>• Unstable angina pectoris *requiring hospitalisation* | • Acute MI (STEMI or NSTEMI), silent MI<br>• Unstable angina pectoris requiring hospitalisation |

### 2.14 Section 17.3.1 Primary analysis for the primary estimand

Missing values for each group will be imputed as follows:

- An analysis of covariance (ANCOVA) with region and stratification factor as categorical fixed effects and baseline $HbA_{1c}$ measurement as a covariate will be fitted to observed values of the change from baseline to week 52 in $HbA_{1c}$.
- The estimated parameters for location and dispersion will be used to impute ~~100~~ *1000* values for each subject with missing week 52 data based on region and stratification factor as categorical fixed effects and baseline $HbA_{1c}$ measurement as a covariate. Thus, ~~100~~ *1000* complete data sets will be generated including observed and imputed values.
- The binary endpoint will be created for each of the ~~100~~ *1000* complete data sets.
- A logistic regression model with treatment, region, and stratification factor as fixed effects and baseline $HbA_{1c}$ measurement as a covariate is fitted for each of the imputed datasets.
- The resulting ~~100~~ *1000* estimates and variances will be combined using Rubin's rule[~~44~~ *45*], and the estimated odds ratio between oral semaglutide and sitagliptin together with two-sided 95 % CI and two-sided p-value for testing no difference from one will be presented.

### 2.15 Section 17.3.2 Primary analysis for the secondary estimand

The secondary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 52 from the on-treatment without rescue medication observation

period. Handling of missing data will be determined from the imputed continuous responses. A total of ~~100~~ *1000* imputed data sets will be created using a mixed model for repeated measurements (MMRM) based analysis. The binary endpoint will be created for each of the ~~100~~ *1000* complete data sets. The imputed complete data sets will be analysed using a logistic regression model with treatment, region, and stratification factor as fixed effects, and baseline $HbA_{1c}$ measurement as a covariate. The resulting ~~100~~ *1000* estimates and variances will be combined using Rubin's rule[~~44~~*45*]. The MMRM based analysis will use a restricted maximum likelihood (REML) and include all post-baseline $HbA_{1c}$ measurements collected at scheduled visits up to and including week 52 as dependent variables. The independent effects included in the model will be treatment, region, and stratification factor as categorical fixed effects and baseline $HbA_{1c}$ as a covariate, all nested within visit. An unstructured covariance matrix for HbA1c measurements within the same subject will be employed, assuming measurements from different subjects are independent.

## 2.16 Section 17.4.2.2 Safety endpoints

**Other safety endpoints**

Change from baseline to week 52 in:

- Haematology
- Biochemistry (except for amylase and lipase)
- Calcitonin
- ECG category
- Physical examination
- *Eye examination category*

## 2.17 Section 18.1 Benefit-risk assessment of the trial

**Other safety considerations**

***Diabetic retinopathy complications***

*A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive antidiabetic treatment[49,50,51]. Risk factors for these events include long-standing poor glycaemic control and presence of proliferative retinopathy, and initial large improvements in blood glucose may be an additional aggravating factor. Several studies have, however, documented long-term beneficial effects of intensive glycaemic treatment in reducing retinopathy progression[52,53] even in intensively treated patients who experienced early worsening[50]. In a cardiovascular outcomes trial with s.c. semaglutide, results indicate an increased risk of events related to diabetic retinopathy in subjects treated with semaglutide compared to placebo[54]. As a precaution in this trial, all subjects are required to have a fundus photography or dilated fundoscopy performed before enrolment into the trial; moreover, subjects with proliferative*

*retinopathy or maculopathy requiring acute treatment will be excluded. As part of good diabetes management the investigator is encouraged to ensure adequate monitoring and treatment of diabetic retinopathy in subjects enrolled into the trial*[55].

**General precautions**

It is the responsibility of the investigator to ensure the best possible care *of the subject. This includes adequate glycaemic control, appropriate risk factor modification such as optimal treatment of hypertension, dyslipidaemia and other cardiovascular risk factors, as well as regular monitoring and treatment of diabetic kidney disease and diabetic retinopathy* ~~according to the principles outlined in Diabetes Care 2016 Standards of Medical Care in Diabetes~~[48~~55~~].

## 2.18 Section 27 References

*37. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.*

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*50. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol. 1998;116(7):874-86.*

*51. Varadhan L, Humphreys T, Walker AB, Varughese GI. The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. Diabetes Res Clin Pract. 2014;103(3):37-9.*

*52. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837-53, Erratum 1999; 354: 602.*

*53. The Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Eye Study Group and the Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study Group. Persistent Effects of Intensive Glycemic Control on*

*Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study. Diabetes Care. 2016;39(7):1089-100.*

*54. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016.*

*55. American Diabetes Association. Standards of medical care in diabetes - 2016. Diabetes Care. 2016;39 (Suppl. 1):S1-S109.*

~~48. American Diabetes Association. Standards of medical care in diabetes - 2016. Diabetes Care. 2016;39 (Suppl. 1):S13-S22.~~

### 2.19 Appendix B Section 1 Adverse events requiring additional data collection

For the following AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form:

- Acute coronary syndrome (myocardial infarction [MI] or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or transient ischaemic attack [TIA])
- Heart failure
- Pancreatitis
- Neoplasm (excluding thyroid neoplasm)
- Thyroid disease (including thyroid neoplasm)
- Renal event
- Hypersensitivity reaction
- Acute gallstone disease
- Medication error (concerning trial products):
  - 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.
  - Administration of an overdose with the intention to cause harm (e.g. suicide attempt) misuse or abuse of trial product.
  - Accidental administration of a higher dose than intended. A higher dose is a dose of at least one tablet more than the intended dose; however the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.
- Lactic acidosis
- Creatine kinase (CK) > 10 x upper normal limit (UNL)

- Hepatic event:
  - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 x UNL and total bilirubin ≤ 2 x UNL
  - ALT or AST > 3 x UNL and total bilirubin > 2 x UNL*
  - Hepatic event leading to trial product discontinuation
- *Diabetic retinopathy and related complications*

## 2.20 Appendix B, new section

### *1.14 Diabetic retinopathy and related complications*

*If an event of diabetic retinopathy or related complications is observed during the trial the following additional information must be reported, if available:*

- *Signs and symptoms associated with the event*
- *Results of the eye examination*
- *Treatment for and complications of the event*
- *Contributing conditions*

# Protocol Amendment

**no 2**
**to Protocol, final version 2.0**
**dated 11 November 2016**

# Trial ID: NN9924-4257

## PIONEER 7 – Flexible dose adjustment

## Efficacy and Safety of Oral Semaglutide Using a Flexible Dose Adjustment Based on Clinical Evaluation versus Sitagliptin in Subjects with Type 2 Diabetes Mellitus

*A 52-week Randomised, Open-label, Active-controlled Trial*

**Trial phase: 3a**

**Applicable to all countries**

Amendment originator:

[redacted]

# Table of Contents

**Page**

# 1 Introduction including rationale for the protocol amendment

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through~~.

## 1.1 Rationale for the amendment

This protocol amendment introduces a 52-week extension period to the trial in order to assess:

a) Sustainability of glycaemic control and long-term safety in subjects exposed to oral semaglutide using flexible dose adjustment in combination with 1-2 oral antidiabetics for a period of up to 104 weeks
b) Effect of switching from sitagliptin to oral semaglutide on glycaemic control and safety for a period of up to 52 weeks

The protocol sections 1-8, 11-12, 14, 17, 18, 27 (see Section 2 of this amendment) and Appendix B, Section 1.8.1 (see Section 3.1 of this amendment) have been updated due to the inclusion of the 52-week extension phase.

In addition, minor clarifications and corrections are included in this amendment and Attachment I (see Section 4.1 of this amendment) has been updated.

## 1.2 Design of the extension period

After 52 weeks of participation in the main phase of the trial, subjects who are on randomised treatment will be offered to enter the additional 52-week extension phase.

The extension phase will consist of two parts (three treatment arms):

a) **Extension phase (sustainability):**
   - Subjects randomised to oral semaglutide in the main phase of the trial will continue to receive oral semaglutide at unchanged conditions (flexible dose adjustment) throughout the extension phase
b) **Extension phase (switch):** Subjects randomised to sitagliptin in the main phase of the trial will be re-randomised to receive either oral semaglutide or sitagliptin in the extension phase.
   - Subjects re-randomised to oral semaglutide will initiate treatment with the 3 mg dose for the first 8 weeks, followed by a flexible dose adjustment every 8 weeks throughout the extension phase.
   - Subjects re-randomised to sitagliptin will continue unchanged on the 100 mg dose throughout the extension phase

For subjects continuing in the extension phase, additional 52 weeks treatment will be added and the total trial duration will be approximately 111 weeks (2 weeks screening, 104 weeks treatment and 5 weeks follow-up).

No new parameters will be introduced to be measured or evaluated during the extension phase.

### 1.3 Subject Information and Informed Consent form

An addendum to the master Subject Information and Informed Consent form has been prepared for those subjects who are eligible and wish to continue in the extension phase of the trial.

# 2 Changes

## 2.1 Protocol sub-title

A 52-week Randomised, Open-label, Active-controlled Trial *with a 52-week Extension Phase*

## 2.2 Section 1 Summary

**Primary objective**

***Main phase***

To compare the effect of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once daily, both in combination with 1-2 oral anti-diabetic drugs (OADs) on glycaemic control in subjects with Type 2 diabetes mellitus (T2DM).

**Secondary objectives**

***Main phase***

- To compare the effect of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once daily, both in combination with 1-2 OADs on body weight in subjects with T2DM.
- To compare the safety and tolerability of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once daily, both in combination with 1-2 OADs in subjects with T2DM.

***Extension phase (sustainability)***

- *To evaluate the sustainability of glycaemic control and body weight reduction of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation in subjects with T2DM.*
- *To evaluate the long term safety of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation in subjects with T2DM.*

***Extension phase (switch)***

- *To compare the effect on glycaemic control of switching to once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus staying on once-daily sitagliptin in subjects with T2DM.*
- *To compare the effect on body weight of switching to once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus staying on once-daily sitagliptin in subjects with T2DM.*
- *To compare the safety and tolerability of switching to once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus staying on once-daily sitagliptin in subjects with T2DM.*

**Primary endpoint**

***Main phase***

If a subject after week 52 achieves (yes/no) glycosylated haemoglobin ($HbA_{1c}$) < 7% (53 mmol/mol) American Diabetes Association target.

**Key secondary endpoints**

***Main phase***

.....
Number of treatment-emergent adverse events during exposure to trial product, assessed up to approximately ~~57~~ *52* weeks.

Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately ~~57~~ *52* weeks.

***Extension phase (sustainability)***

*If a subject after week 104 achieves (yes/no) $HbA_{1c}$ < 7% (53 mmol/mol) American Diabetes Association target.*

*Change from baseline to week 104 in:*
- *Body weight (kg)*
- *$HbA_{1c}$*
- *Fasting plasma glucose (FPG)*

*Number of treatment-emergent adverse events during exposure to trial product, assessed up to approximately 109 weeks.*

*Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 109 weeks.*

***Extension phase (switch)***

*If a subject after week 104 achieves (yes/no) $HbA_{1c}$ < 7% (53 mmol/mol) American Diabetes Association target.*

*Change from week 52 to week 104 in:*
- *Body weight (kg)*
- *$HbA_{1c}$*
- *Fasting plasma glucose (FPG)*

*Number of treatment-emergent adverse events during exposure to trial product, assessed from week 52 up to approximately 109 weeks.*

*Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed from week 52 up to approximately 109 weeks.*

**Trial design:**

*The trial consists of two 52-week treatment periods. The first 52-week treatment period is referred to as the main phase and the second 52-week treatment period as the extension phase. The extension phase consists of two parts; these are referred to as extension phase (switch) and extension phase (sustainability).*

***Main phase***

*The main phase* ~~This~~ is a 52-week randomised, open-label, active-controlled, parallel-group, multi-centre, multi-national *treatment phase* ~~trial~~ with two arms comparing the efficacy and safety of oral semaglutide using a flexible dose adjustment versus sitagliptin, in subjects with T2DM treated with 1-2 OADs.

Subjects will be randomised 1:1 to receive one of the following treatments as add-on to their anti-diabetic background medication:

- flexible dosing (3, 7 or 14 mg) of oral semaglutide once daily
- 100 mg sitagliptin once daily

***Extension phase***

*The extension phase is a 52-week open-label, 3-arm, parallel-group treatment period following the main phase. The extension phase (switch) is active-controlled.*

*Subjects randomised to oral semaglutide in the main phase and who are still on trial product will continue treatment with oral semaglutide using a flexible dose adjustment in the 52-week extension phase (sustainability).*

*Subjects randomised to sitagliptin in the main phase and who are still on trial product will be re-randomised 1:1 at week 52 to receive one of the following two treatments in the 52-week extension phase (switch) as add-on to their anti-diabetic background medication:*

- *flexible dosing (3, 7 or 14 mg) of oral semaglutide once daily*
- *100 mg sitagliptin once daily*

***Main and extension phase***

In this trial the dosing of oral semaglutide is flexible, following predefined dose adjustment criteria which are based on the subject's individual $HbA_{1c}$ and tolerability (nausea/vomiting). Sitagliptin should be taken once-daily ~~on~~ at a fixed dose of 100 mg throughout the trial.

The total trial duration *of the main phase* for the individual subject will be *either* approximately *54 weeks or* approximately 59 weeks *depending on whether or not the subject continues into the extension phase*. The trial includes a 2-week screening period, a 52-week treatment period and *for subjects not continuing in the extension phase,* a 5-week follow-up period. *For subjects continuing in the extension phase, 52 additional weeks will be added and the total trial duration will be approximately 111 weeks (2 week screening, 104 week treatment and 5 week follow up).* The trial is designed to have visits every 8 weeks~~, including~~ *and* a phone contact at week 4 *and week 56.*

**Trial population:**

***Main phase***: Number of subjects planned to be randomised: 500

***Extension phase****: Number of subjects planned to continue in the extension phase: 380*

***Key inclusion criteria***

***Main phase***

- 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.

  …..

***Extension phase***

- *Informed consent for the extension phase obtained before any trial-related activities for the extension phase.*
- *On randomised treatment with or without rescue medication at week 52.*

***Key exclusion criteria***

***Main phase***

- Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).

  …..

***Extension phase***

*There are no new exclusion criteria for the extension phase.*

## 2.3 Section 2 Flow Chart

| **Trial Periods** | Screening [a] | Randomisation | Treatment *(main phase)* | | | | | | | End-of-treatment ~~(EoT)~~/ *Start of extension phase* [k] | Follow-up [b] | EoT premature discontinuation [c] | Follow-up premature discontinuation [c] | *Treatment (extension phase)* | | | | | | | *End-of-treatment* | *Follow-up* [b] | *EoT premature discontinuation* [c] | *Follow-up premature discontinuation* [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit (V), Phone contact (P)** | V1 | V2 | P3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V10A | V11A | *P12* | *V13* | *V14* | *V15* | *V16* | *V17* | *V18* | *V19* | *V20* | *V19A* | *V20A* |
| **Timing of visit (weeks)** | Up to -2 weeks | 0 | 4 | 8 | 16 | 24 | 32 | 40 | 48 | 52 | 57 | Day of disc. of trial product | 5 weeks after disc. of trial product | *56* | *60* | *68* | *76* | *84* | *92* | *100* | *104* | *109* | *Day of disc. of trial product* | *5 weeks after disc. of trial product* |
| **Visit window (days)** | | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | +3 | +3 | +3 | *±3* | *±3* | *±3* | *±3* | *±3* | *±3* | *±3* | *±3* | *+3* | *+3* | *+3* |
| **SUBJECT RELATED INFO/ASSESSMENTS** | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent | x | | | | | | | | | ***x**** | | | | | | | | | | | | | | |
| In/exclusion criteria | x | x | | | | | | | | ***x**** | | | | | | | | | | | | | | |
| Concomitant medication | x | x | x | x | x | x | x | x | x | x | x | x | x | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* |
| Concomitant illness and medical history | x | | | | | | | | | | | | | | | | | | | | | | | |
| Demography | x | | | | | | | | | | | | | | | | | | | | | | | |
| Diagnosis of diabetes/diabetes complication | x | | | | | | | | | | | | | | | | | | | | | | | |
| Hypoglycaemia unawareness | x | | | | | | | | | | | | | | | | | | | | | | | |
| Tobacco use | x | | | | | | | | | | | | | | | | | | | | | | | |
| History of cardiovascular disease | x | | | | | | | | | | | | | | | | | | | | | | | |

| **Trial Periods** | Screening [a] | Randomisation | Treatment *(main phase)* | | | | | | | End-of-treatment ~~(EoT)~~/ *Start of extension phase* [k] | Follow-up [b] | EoT premature discontinuation [c] | Follow-up premature discontinuation [c] | *Treatment (extension phase)* | | | | | | | *End-of-treatment* | *Follow-up* [b] | *EoT premature discontinuation* [c] | *Follow-up premature discontinuation* [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit (V), Phone contact (P)** | V1 | V2 | P3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V10A | V11A | *P12* | *V13* | *V14* | *V15* | *V16* | *V17* | *V18* | *V19* | *V20* | *V19A* | *V20A* |
| **Timing of visit (weeks)** | Up to -2 weeks | 0 | 4 | 8 | 16 | 24 | 32 | 40 | 48 | 52 | 57 | Day of disc. of trial product | 5 weeks after disc. of trial product | *56* | *60* | *68* | *76* | *84* | *92* | *100* | *104* | *109* | *Day of disc. of trial product* | *5 weeks after disc. of trial product* |
| **Visit window (days)** | | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | +3 | +3 | +3 | *±3* | *±3* | *±3* | *±3* | *±3* | *±3* | *±3* | *±3* | +3 | +3 | +3 |
| History of gallbladder disease | x | | | | | | | | | | | | | | | | | | | | | | | |
| History of gastrointestinal disease | x | | | | | | | | | | | | | | | | | | | | | | | |
| Randomisation | | x | | | | | | | | ***x**** | | | | | | | | | | | | | | |
| Criteria for premature discontinuation of trial product | | | x | x | x | x | x | x | x | ***x**** | | | | *x* | *x* | *x* | *x* | *x* | *x* | *x* | | | | |
| **EFFICACY** | | | | | | | | | | | | | | | | | | | | | | | | |
| Height | | x | | | | | | | | | | | | | | | | | | | | | | |
| Body weight | | x | | x | x | x | x | x | x | x | | x | | | *x* | *x* | *x* | *x* | *x* | *x* | *x* | | *x* | |
| Waist circumference | | x | | | x | | x | | | x | | x | | | *x* | | *x* | | *x* | | *x* | | *x* | |
| PRO questionnaires | | x | | x | x | | x | | | x | | x | | | *x* | *x* | | *x* | | | *x* | | *x* | |
| Dose adjustment criteria[d] | | | | x | x | x | x | x | x | ***x**** | | | | | *x* | *x* | *x* | *x* | *x* | *x* | | | | |
| Fasting plasma glucose | | x | | | | x | | | | x | | x | | | *x* | | | *x* | | | *x* | | *x* | |
| $HbA_{1c}$ [e] | x | x | | x | x | x | x | x | x | x | | x | | | *x* | *x* | *x* | *x* | *x* | *x* | *x* | | *x* | |

| **Trial Periods** | Screening [a] | Randomisation | Treatment *(main phase)* | | | | | | | End-of-treatment ~~(EoT)~~/ *Start of extension phase* [k] | Follow-up [b] | EoT premature discontinuation [c] | Follow-up premature discontinuation [c] | *Treatment (extension phase)* | | | | | | | *End-of-treatment* | *Follow-up* [b] | *EoT premature discontinuation* [c] | *Follow-up premature discontinuation* [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit (V), Phone contact (P)** | V1 | V2 | P3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V10A | V11A | *P12* | *V13* | *V14* | *V15* | *V16* | *V17* | *V18* | *V19* | *V20* | *V19A* | *V20A* |
| **Timing of visit (weeks)** | Up to -2 weeks | 0 | 4 | 8 | 16 | 24 | 32 | 40 | 48 | 52 | 57 | Day of disc. of trial product | 5 weeks after disc. of trial product | *56* | *60* | *68* | *76* | *84* | *92* | *100* | *104* | *109* | *Day of disc. of trial product* | *5 weeks after disc. of trial product* |
| **Visit window (days)** | | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | +3 | +3 | +3 | *±3* | *±3* | *±3* | *±3* | *±3* | *±3* | *±3* | *±3* | *+3* | *+3* | *+3* |
| Lipids | | x | | | | x | | | | x | | x | | | | | | | | | *x* | | *x* | |
| **SAFETY** | | | | | | | | | | | | | | | | | | | | | | | | |
| Adverse events[f] | | x | x | x | x | x | x | x | x | x | x | x | x | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* |
| ECG | | x | | | | x | | | | x | x | x | x | | | | *x* | | | | *x* | *x* | *x* | *x* |
| Eye examination[g] | x | | | | | | | | | x | | x | | | | | | | | | *x* | | *x* | |
| Physical examination | x | | | | | | | | | x | | x | | | | | | | | | *x* | | *x* | |
| Vital signs | | x | | x | x | x | x | x | x | x | x | x | x | | *x* | | *x* | | *x* | | *x* | *x* | *x* | *x* |
| Biochemistry[h] | x | x | | x | x | x | x | x | | x | x | x | x | | *x* | | *x* | | *x* | | *x* | *x* | *x* | *x* |
| Haematology | | x | | x | x | x | x | x | | x | x | x | x | | *x* | | *x* | | *x* | | *x* | *x* | *x* | *x* |
| Calcitonin | | x | | | | x | | | | x | x | x | x | | | | *x* | | | | *x* | *x* | *x* | *x* |
| Pregnancy test[i] | x | x | | x | x | x | x | x | x | x | x | x | x | | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* |
| Technical complaints | | | x | x | x | x | x | x | x | x | | x | | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | | *x* | |
| Hypoglycaemic episodes | | x | x | x | x | x | x | x | x | x | x | x | x | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* |
| **TRIAL MATERIAL** | | | | | | | | | | | | | | | | | | | | | | | | |
| Dispensing visit | | x | | x | x | x | x | x | x | ***x**** | | | | | *x* | *x* | *x* | *x* | *x* | *x* | | | | |

| **Trial Periods** | Screening [a] | Randomisation | Treatment *(main phase)* | | | | | | | End-of-treatment ~~(EoT)~~/ *Start of extension phase* [k] | Follow-up [b] | EoT premature discontinuation [c] | Follow-up premature discontinuation [c] | *Treatment (extension phase)* | | | | | | | *End-of-treatment* | *Follow-up* [b] | *EoT premature discontinuation* [c] | *Follow-up premature discontinuation* [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit (V), Phone contact (P)** | V1 | V2 | P3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V10A | V11A | *P12* | *V13* | *V14* | *V15* | *V16* | *V17* | *V18* | *V19* | *V20* | *V19A* | *V20A* |
| **Timing of visit (weeks)** | Up to -2 weeks | 0 | 4 | 8 | 16 | 24 | 32 | 40 | 48 | 52 | 57 | Day of disc. of trial product | 5 weeks after disc. of trial product | *56* | *60* | *68* | *76* | *84* | *92* | *100* | *104* | *109* | *Day of disc. of trial product* | *5 weeks after disc. of trial product* |
| **Visit window (days)** | | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | +3 | +3 | +3 | *±3* | *±3* | *±3* | *±3* | *±3* | *±3* | *±3* | ±3 | +3 | +3 | +3 |
| Drug accountability | | x | | x | x | x | x | x | x | x | | x | | | *x* | *x* | *x* | *x* | *x* | *x* | *x* | | *x* | |
| IWRS call | x | x | | x | x | x | x | x | x | x | | x | | | *x* | *x* | *x* | *x* | *x* | *x* | *x* | | *x* | |
| **REMINDERS** | | | | | | | | | | | | | | | | | | | | | | | | |
| Attend visit fasting[j] | | x | | | | x | | | | x | | x | | | *x* | | | *x* | | | *x* | | *x* | |
| Handout and instruct in BG meter use | | x | | | | | | | | | | | | | | | | | | | | | | |
| Handout ID card | x | | | | | | | | | | | | | | | | | | | | | | | |
| Training in dosing instructions | x | x | x | x | x | x | x | x | x | ***x**** | | | | *x* | *x* | *x* | *x* | *x* | *x* | *x* | | | | |
| Dispense and/or collect diary | x | x | | x | x | x | x | x | x | x | x | x | x | | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* | *x* |

| Footer | Description |
|---|---|
| x[a] | Subject can be randomised as soon as all inclusion and exclusion criteria are confirmed. The screening assessments must not exceed 2 weeks prior to randomisation (V2). |
| x[b] | *Only subjects who have completed treatment in the main phase and are not continuing in the extension phase are required to attend V11.*<br>Subjects who have discontinued trial product prematurely are not required to attend V11 (Follow-up) *in the main phase or V20 (Follow-up) in the extension phase.* |
| x[c] | V10A and V11A *in the main phase and V19A and V20A in the extension phase* are only applicable for subjects who have discontinued trial product prematurely. |
| x[d] | Dose adjustment criteria are subject's $HbA_{1c}$ (measured by point-of-care device) and tolerability (nausea/vomiting).<br>• *at V10 the dose adjustment criteria are only relevant for subjects on oral semaglutide in the main phase and are continuing on oral semaglutide in the extension phase. In addition, for stratification purpose at V10, $HbA_{1c}$ (measured by point-of-care device) is also applicable for subjects on sitagliptin in the main phase continuing in the extension phase (see Section 8.3.5 and 11)*<br>• *at V4-V9 and V13-V18, $HbA_{1c}$ (measured by point-of-care device) is only applicable for subjects on oral semaglutide* |
| x[e] | Assessed at central laboratory. |
| x[f] | Adverse events reporting includes adverse events from the first trial-related activity after the subject has signed the informed consent at V1. Pre-existing conditions identified as a result of the screening procedures should be reported as medical history. |
| x[g] | Fundus photography or dilated fundoscopy performed within 90 days before randomisation is acceptable if results are available for evaluation at visit 2 and no deterioration in visual function since last examination.<br>Fundus photography or dilated fundoscopy must be performed *for all subjects* again:<br>• at V10 or within 5 weeks thereafter for subjects completing treatment<br>• at V10A or within 5 weeks thereafter, and again within 5 weeks prior to V10, for subjects who have prematurely discontinued trial product<br>*In the extension phase:*<br>• *at V19 or within 5 weeks thereafter for subjects completing treatment*<br>• *at V19A or within 5 weeks thereafter, and again within 5 weeks prior to V19, for subjects who have prematurely discontinued trial product* |
| x[h] | At V1, only ALT, creatinine and eGFR will be assessed as part of Biochemistry. |
| x[i] | For women of child-bearing potential: Urine pregnancy test should also be performed at any time during the trial if menstrual period is missed, and/or according to local regulations/law. For details regarding local regulations/law see Section 6.3. |

| | |
|---|---|
| x[j] | Fasting for blood sampling is defined as no food or liquid within the last 8 hours prior to blood sampling, however water is allowed up until 2 hours prior to blood sampling. Trial product must be taken after blood sampling. Other oral medication can be taken 30 minutes after trial product (for subjects randomised to oral semaglutide only). Injectable medications can be administered after blood sampling. |
| x[k] | ***For subjects not continuing in the extension phase****: V10 is the end-of-treatment (EoT) visit.*<br><br>***For subjects continuing in the extension phase:***<br>• *subjects on semaglutide in the main phase: V10 is a treatment visit*<br>• *subjects on sitagliptin in the main phase: V10 is a combined re-randomisation and treatment visit* |
| ***x**** | *Activities at V10 marked with **x*** are NOT applicable for patients who will not continue in the extension phase.*<br><br>***Additional activities at V10 applicable for patients who have signed the addendum to the informed consent and are continuing in the extension phase (see Section 8.1.3):***<br>• *inclusion criteria for the extension phase must be assessed*<br>• *$HbA_{1c}$ (measured by point-of-care device) is applicable for all subjects at V10 continuing in the extension phase. The dose adjustment criteria are only relevant for subjects randomised to oral semaglutide in the main phase and are continuing in the extension phase (see Section 5.3.1). For subjects on sitagliptin in the main phase, the $HbA_{1c}$ value will be used for stratification of the re-randomisation (see Section 5.2 and 11)*<br>• *subjects randomised to sitagliptin in the main phase, will at V10 be re-randomised in IWRS to one of the two parallel treatment arms as described in Section 5.1 and 5.2*<br>• *dispense diary (for extension phase) and trial product. All V10 assessments must be performed before administration of trial product in the extension phase* |

## 2.4 Section 3.2 Rationale for trial

***Rationale for the 52-week extension phase***

1. ***Extension phase (sustainability):*** *Evaluate the sustainability of glycaemic control and long-term safety of once-daily oral semaglutide using flexible dose adjustment based on clinical evaluation over a period of 104 weeks (in subjects randomised to oral semaglutide flexible dosing in the main phase and continuing on oral semaglutide flexible dosing in the extension phase).*
2. ***Extension phase (switch):*** *Evaluate the switch from sitagliptin to oral semaglutide in subjects randomised to sitagliptin in the main phase and re-randomised at week 52 to either switch to once-daily oral semaglutide flexible dosing or continue on once-daily sitagliptin in the extension phase.*

## 2.5 Section 4.1 Objectives

### 2.5.1 Section 4.1.1 Primary objective

***Main phase***

To compare the effect of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once daily, both in combination with 1-2 OADs on glycaemic control in subjects with T2DM.

### 2.5.2 Section 4.1.2 Secondary objectives

***Main phase***

- To compare the effect of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once daily, both in combination with 1-2 OADs on body weight in subjects with T2DM.
- To compare the safety and tolerability of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once daily, both in combination with 1-2 OADs in subjects with T2DM.

***Extension phase (sustainability)***

- *To evaluate the sustainability on glycaemic control and body weight reduction of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation in subjects with T2DM.*
- *To evaluate the long term safety of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation in subjects with T2DM.*

***Extension phase (switch)***

- *To compare the effect on glycaemic control of switching to once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus staying on once-daily sitagliptin in subjects with T2DM.*
- *To compare the effect on body weight of switching to once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus staying on once-daily sitagliptin in subjects with T2DM.*
- *To compare the safety and tolerability of switching to once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus staying on once-daily sitagliptin in subjects with T2DM.*

## 2.6 Section 4.2 Endpoints

Baseline refers to randomisation *at V2 (in the main phase)*, ~~and~~ week 52 refers to 52 weeks after randomisation *at V2, and week 104 refers to 104 weeks after randomisation at V2.*

*The endpoints will be evaluated based on the following time periods and treatment arms, see more details in Section 17.*

***Main phase, baseline to week 52:***

- *Oral semaglutide (3, 7 or 14 mg)*
- *Sitagliptin (100 mg)*

***Extension phase (sustainability), baseline to week 104:***

- *Oral semaglutide (3, 7 or 14 mg) during 104 weeks*

***Extension phase (switch), week 52 to week 104:***

- *Oral semaglutide (3, 7 or 14 mg) switching from sitagliptin (100 mg) at week 52*
- *Sitagliptin (100 mg) continuing on sitagliptin (100 mg) after week 52*

### 2.6.1 Section 4.2.1 Primary endpoint

***Main phase***

If a subject after week 52 achieves (yes/no) $HbA_{1c}$ < 7% (53 mmol/mol) American Diabetes Association (ADA) target.

### 2.6.2 Section 4.2.2.1 Confirmatory secondary endpoints

***Main phase***

Change from baseline to week 52 in body weight (kg)

***Extension phase (switch)***

*Change from week 52 to week 104 in $HbA_{1c}$*

*Change from week 52 to week 104 in body weight (kg)*

### 2.6.3 Section 4.2.2.2 Supportive secondary endpoints

~~Key supportive secondary endpoints prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT) are marked with an asterisk (*).~~

**Supportive secondary efficacy endpoints**

***Main phase***

Change from baseline to week 52 in:

- $HbA_{1c}$~~*~~
- Fasting plasma glucose (FPG)~~*~~

.....

***Extension phase (sustainability)***

*Change from baseline to week 104 in:*

- *$HbA_{1c}$*
- *Fasting plasma glucose (FPG)*
- *Body weight (kg)*
- *Body weight (%)*
- *Body mass index (BMI)*
- *Waist circumference*
- *Patient-reported outcomes (PROs):*
    - *Short Form (SF-36v2$^{TM}$) (acute version) health survey*
    - *Diabetes Treatment Satisfaction Questionnaire (DTSQs)*

*If a subject after week 104 achieves (yes/no):*

- *$HbA_{1c}$ < 7% (53 mmol/mol) American Diabetes Association (ADA) target*
- *$HbA_{1c}$ ≤ 6.5% (48 mmol/mol) American Association of Clinical Endocrinologists (AACE) target*
- *$HbA_{1c}$ reduction ≥ 1%-point (10.9 mmol/mol)*
- *$HbA_{1c}$ < 7% (53 mmol/mol) or $HbA_{1c}$ reduction ≥ 1%-point (10.9 mmol/mol)*
- *Weight loss ≥ 5%*
- *$HbA_{1c}$ < 7.0% (53 mmol/mol) without hypoglycaemia (treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes) and no weight gain*

***Extension phase (switch)***

*Change from week 52 to week 104 in:*

- *Fasting plasma glucose (FPG)*
- *Body weight (%)*
- *Body mass index (BMI)*
- *Waist circumference*
- *Patient-reported outcomes (PROs):*
  - *Short Form (SF-36v2™) (acute version) health survey*
  - *Diabetes Treatment Satisfaction Questionnaire (DTSQs)*

*If a subject after week 104 achieves (yes/no):*

- *$HbA_{1c}$ < 7% (53 mmol/mol) American Diabetes Association (ADA) target*
- *$HbA_{1c}$ ≤ 6.5% (48 mmol/mol) American Association of Clinical Endocrinologists (AACE) target*
- *$HbA_{1c}$ reduction ≥ 1%-point (10.9 mmol/mol) compared to week 52*
- *Weight loss ≥ 5% compared to week 52*
- *$HbA_{1c}$ < 7.0% (53 mmol/mol) without hypoglycaemia (treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes) after week 52 and no weight gain compared to week 52*
- *$HbA_{1c}$ < 7% (53 mmol/mol) and no need for rescue medication after week 52*
- *No need for rescue medication after week 52*

*Time to event:*

- *Time to rescue medication after week 52*

***Supportive secondary safety endpoints***

***Main phase***

- Number of treatment-emergent adverse events (TEAEs) during exposure to trial product, assessed up to approximately ~~57~~ *52* weeks
- Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately ~~57~~ *52* weeks
- Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up approximately ~~57~~ *52* weeks (yes/no)

***Extension phase (sustainability)***

- *Number of treatment-emergent adverse events (TEAEs) during exposure to trial product, assessed up to approximately 109 weeks*
- *Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 109 weeks*

- *Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 109 weeks (yes/no)*

***Extension phase (switch)***

- *Number of treatment-emergent adverse events (TEAEs) during exposure to trial product, assessed from week 52 up to approximately 109 weeks*
- *Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed from week 52 up to approximately 109 weeks*
- *Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed from week 52 up to approximately 109 weeks (yes/no)*

***Main phase***

Change from baseline to week 52 in:

…..

***Extension phase (sustainability)***

*Change from baseline to week 104 in:*

- *Haematology*
- *Biochemistry*
- *Calcitonin*
- *Pulse*
- *Systolic blood pressure*
- *Diastolic blood pressure*
- *Eye examination category*

***Extension phase (switch)***

*Change from week 52 to week 104 in:*

- *Haematology*
- *Biochemistry*
- *Calcitonin*
- *Pulse*
- *Systolic blood pressure*
- *Diastolic blood pressure*
- *Eye examination category*

## 2.7 Section 5.1 Type of trial

*The trial consists of two 52-week treatment periods. The first 52-week treatment period is referred to as the main phase and the second 52-week treatment period as the extension phase. The*

*extension phase consists of two parts; these are referred to as the extension phase (sustainability) and the extension phase (switch).*

***Main phase***

*The main phase*~~This~~ is a 52-week randomised, open-label, active-controlled, parallel-group, multi-centre, multi-national *treatment phase* ~~trial~~ with two arms comparing the efficacy and safety of oral semaglutide using a flexible dose adjustment versus sitagliptin 100 mg once-daily, in subjects with T2DM treated with 1-2 OADs (metformin, sulfonylureas [SU], thiazolidinediones [TZD], sodium glucose co-transporter 2 [SGLT-2] inhibitors).

Subjects will be randomised 1:1 to receive one of the following treatments as add-on to their anti-diabetic background medication:

- flexible dosing (3, 7 or 14 mg) of oral semaglutide once daily
- 100 mg sitagliptin once daily

***Extension phase***

*The extension phase is a 52-week open-label, 3-arm, parallel-group treatment period following the main phase. The extension phase (switch) is active-controlled.*

***Extension phase (sustainability)***

*Subjects randomised to oral semaglutide in the main phase and still on trial product will continue treatment with oral semaglutide using a flexible dose adjustment in the 52-week extension phase.*

***Extension phase (switch)***

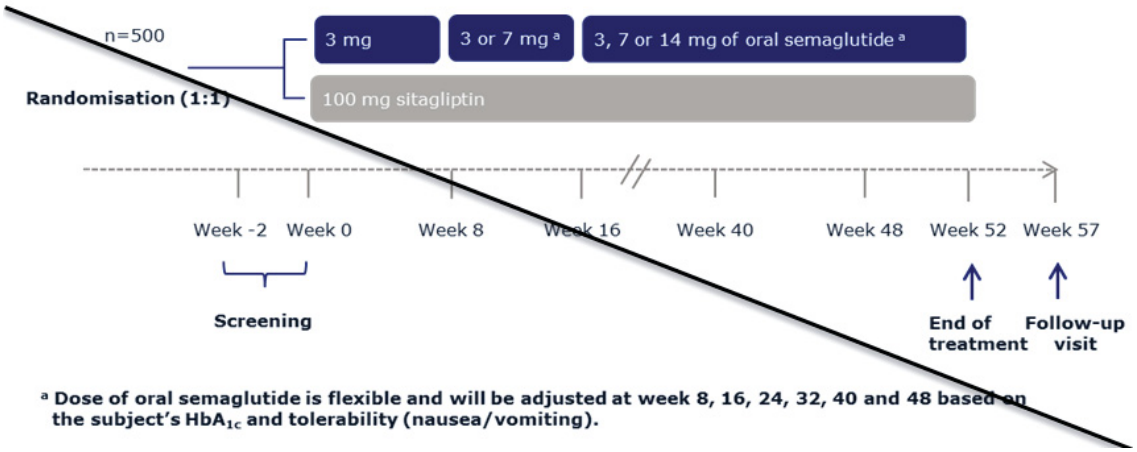
*Subjects randomised to sitagliptin in the main phase and still on trial product will be re-randomised 1:1 at week 52 to receive one of the following treatments in the 52-week extension phase as add-on to their anti-diabetic background medication:*

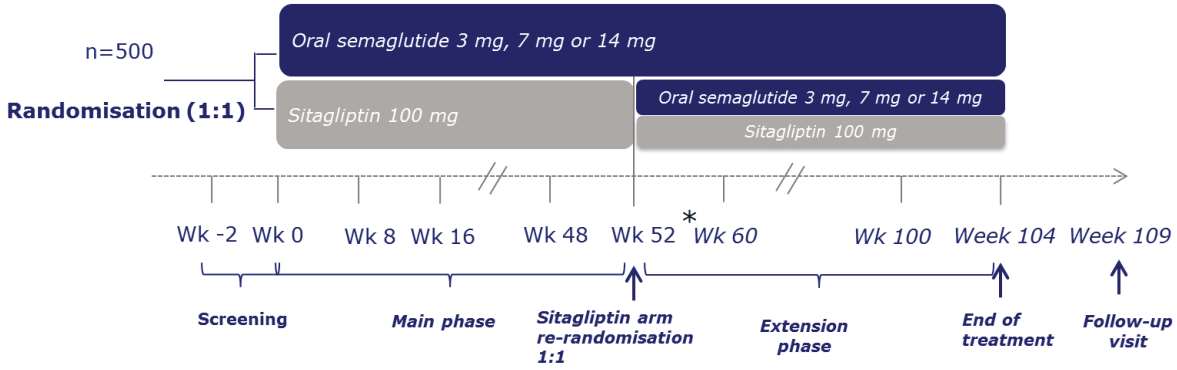
- *flexible dosing (3, 7 or 14 mg) of oral semaglutide once daily*
- *100 mg sitagliptin once daily*

***Trial duration***

The total trial duration *of the main phase* for the individual subject will be *either* approximately *54 weeks or* approximately 59 weeks *depending on whether or not the subject continues into the extension phase*. The trial includes a 2-week screening period, a 52-week treatment period and, *for subjects not continuing in the extension phase,* a 5-week follow-up period. *For subjects continuing in the extension phase, additional 52 weeks will be included and the total trial duration will be approximately 111 weeks (2 weeks screening, 104 weeks treatment and 5 weeks follow-up).* The trial is designed to have visits every 8 weeks~~, including~~ *and* a phone contact at week 4 *and week 56.*

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




** Subjects who have completed treatment in the main phase and are not continuing in the extension phase must attend the Follow-up visit (Week 57) 5 week after the last date on trial product.*

***Figure 5–1 Trial design***

## 2.8 Section 5.2 Rationale for trial design

***Main phase***

The *main phase of the* trial has been designed as an open-label, parallel-group, 2-arm superiority trial, where oral semaglutide will be compared with the DPP-4 inhibitor sitagliptin.

…..

***Extension phase***

*The extension phase of this trial has been designed as an additional 52-week open-label extension phase after completion of 52 weeks of treatment in the main phase. Subjects randomised to oral semaglutide in the main phase and still on trial product at week 52 will continue on oral semaglutide in the extension phase. Subjects randomised to sitagliptin in the main phase and still on trial product at week 52 will be re-randomised in a 1:1 manner to either switch to oral semaglutide or continue on sitagliptin.*

*Overall, the extension phase consists of 3 treatment arms:*

1. *subjects continuing on oral semaglutide*
2. *subjects randomised to sitagliptin in the main phase and re-randomised to oral semaglutide*
3. *subjects randomised to sitagliptin in the main phase and re-randomised to sitagliptin*

*The trial design will allow for the evaluation of the sustainability of the effect and safety of the flexible dosing of once-daily oral semaglutide during a 104-week period as well as of the switch from once-daily sitagliptin to once-daily oral semaglutide. Subjects are only eligible to continue in the extension phase if they are still on the randomised treatment at week 52, regardless of use of rescue medication. The re-randomisation in the sitagliptin arm will be stratified according to $HbA_{1c}$ below 7% (yes/no) and if the subject is currently on prescribed rescue medication and continuing on the same medication in the extension phase (yes/no). This is to ensure an even distribution in the two treatment arms in the extension phase (switch).*

## 2.9 Section 5.3 Treatment of subjects

### Table 5-1 Treatment of subjects

***Treatment of subjects in the main phase:***

| **Trial periods** | | **Screening** | **Treatment *main phase (52 weeks)*** ~~**period 1 Treatment period 2 Treatment period 3**~~ | | | **Follow-up*** ***(V11)*** |
|---|---|---|---|---|---|---|
| **First visit in each period** | | V1 | V2 | V4 | V5 | ~~V11~~ |
| **Duration of each period** | | 2 weeks | 8 weeks | 8 weeks | 36 weeks | 5 weeks |
| **Treatment arm** | **N** | | | | | |
| Oral semaglutide | 250 | Screening | 3 mg | flexible dosing (3 or 7 mg) | flexible dosing (3, 7 or 14 mg) | Follow-up |
| Sitagliptin | 250 | Screening | 100 mg ~~100 mg100 mg~~ | | | Follow-up |

** Only applicable for subjects not continuing in the extension phase*

***Treatment of subjects continuing in the extension phase:***

| ***Trial periods*** | | ***Treatment extension phase (52 weeks)*** | | | ***Follow-up (V20)*** |
|---|---|---|---|---|---|
| ***First visit in each period*** | | *V10* | *V13* | *V14* | |
| ***Duration of each period*** | | *8 weeks* | *8 weeks* | *36 weeks* | *5 weeks* |
| ***Treatment arm*** | ***N****** | | | | |
| *Oral semaglutide (sustainability)* | *190* | *flexible dosing (3, 7 or 14 mg)* | | | *Follow-up* |
| *Sitagliptin (switch)**** | *95* | *100 mg* | | | *Follow-up* |
| *Oral semaglutide (switch)**** | *95* | *3 mg* | *flexible dosing (3 or 7 mg)* | *flexible dosing (3, 7 or 14 mg)* | *Follow-up* |

*** Only estimated numbers*

**** Subjects on sitagliptin in the main phase continuing in the extension phase will be re-randomised (1:1) at V10 to sitagliptin or oral semaglutide*

### 2.9.1 Section 5.3.1 Oral semaglutide treatment

***Extension phase (sustainability)***

*Subjects randomised to oral semaglutide in the main phase will continue to receive oral semaglutide in the extension phase using the same clinical criteria as applied in the main phase for oral semaglutide. Starting from V10, the point-of-care device must be used to measure the subject's $HbA_{1c}$ level prior to evaluation of the dose-adjustment criteria (see Section 2 and 8.1.3).*

***Extension phase (switch)***

*Subjects randomised to sitagliptin in the main phase and re-randomised at week 52 to oral semaglutide in the extension phase will initiate treatment with 3 mg of oral semaglutide without any wash-out of sitagliptin, and the dose of oral semaglutide will starting from V13 be adjusted using the same clinical criteria as applied in the main phase.*

### 2.9.2 Section 5.3.2 Sitagliptin treatment

***Main phase***
The selected active comparator
....

***Extension phase (switch)***
*Subjects randomised to sitagliptin in the main phase and re-randomised at week 52 to sitagliptin in the extension phase will continue with once-daily sitagliptin 100 mg.*

### 2.9.3 Section 5.3.4 Background medication

After signing the informed consent, subjects must continue using their anti-diabetic background medication throughout the entire trial. The background medication must be maintained at the same dose level as given at trial entrance *(V1)* and with the same frequency during the entire treatment period unless rescue medication is needed (see Section 6.4), any safety concerns related to the background medication arise~~s~~ or if the subject has unacceptable hypoglycaemia on a background of SU in which case the dose of SU can be reduced.

*For the two treatment arms in the extension phase (switch), the current prescribed rescue medication (at V10) in the main phase will be treated as background medication in the extension phase. During the extension phase the anti-diabetic background medication must be maintained at the same dose level as given at V10 and with the same frequency during the entire treatment period unless rescue medication is needed (see Section 6.4), any safety concerns related to the background medication arise or if the subject has unacceptable hypoglycaemia on a background of SU or insulin in which case the dose of SU or insulin can be reduced.*

### 2.10 Section 6.1 Number of subjects

***Main phase***
…..

Number of subjects expected to complete *the first 52 weeks of* the trial on or off trial product: 425

***Extension phase***
*Planned number of subjects to continue into the extension phase:* *380*

*Number of subjects expected to complete the trial (including the extension phase) on or off trial product:* *323*

### 2.11 Section 6.2 Inclusion criteria

***Inclusion criteria for the main phase:***
For an eligible subject, all inclusion criteria must be answered "yes". *The inclusion criteria for the main phase are not re-assessed for the extension phase.*

***Inclusion criteria for the extension phase:***

*7. Informed consent for the extension phase obtained before any trial-related activities for the extension phase.*

*8. On randomised treatment with or without rescue medication at week 52.*

## 2.12 Section 6.3 Exclusion criteria

***Exclusion criteria for the main phase:***

For an eligible subject, all exclusion criteria must be answered "no". *The exclusion criteria for the main phase are not re-assessed for the extension phase.*

***Exclusion criteria for extension phase:***

*There are no new exclusion criteria for the extension phase.*

## 2.13 Section 6.4 Rescue criteria

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification with rescue medication. It is important for trial integrity that only subjects actually needing treatment intensification (i.e. intensification of existing anti-diabetic medication and/or initiation of new anti-diabetic medication) are started on rescue medication. *For subjects who are re-randomised at week 52 to switch from sitagliptin to oral semaglutide in the extension phase, the dose of oral semaglutide should be increased to the maximal tolerated dose before initiation of rescue medication.*

## 2.14 Section 6.8 Rationale for trial population

***Main phase***

Subjects with T2DM inadequately controlled on 1-2 OADs (metformin, SU, TZD, SGLT-2 inhibitors) will be included in the trial.

…..

***Extension phase (sustainability)***

*To investigate the sustainability of glycaemic effect and safety of oral semaglutide flexible dosing, all subjects treated with oral semaglutide at week 52 in the main phase are invited to continue treatment with oral semaglutide flexible dosing in the extension phase independent of their level of glycaemic control and whether or not rescue medication has been initiated.*

***Extension phase (switch)***

*To investigate the effect and safety of switching from sitagliptin to oral semaglutide flexible dosing, all subjects treated with sitagliptin at week 52 in the main phase are invited to be re-randomised to either switch to oral semaglutide flexible dosing or continue sitagliptin in the extension phase*

*independent of glycaemic control and whether rescue medication has been initiated. No wash-out period will be included.*

### 2.15 Section 7 Milestones

Planned LSLV *for the main phase*: ~~19-Mar-~~*Apr*-2018

*Planned LSLV for the complete trial (including the extension phase):* *Apr-2019*

*Primary Completion Date for the main phase of the trial is 52 weeks (visit 10) after the date of randomisation of the last randomised subject in the main phase.*

End of trial is defined as~~:~~ LSLV *for the complete trial.*

*The results from the trial will be reported in two clinical trial reports; the first clinical trial report will report the results from the main phase and the second clinical trial report will report the results of the entire trial period, including the extension phase.*

### 2.16 Section 8.1 Visit procedures

Each subject will have 10 site visits and 1 phone contact *if only completing the main phase of the trial*. *Eligible subjects who accept to continue in extension phase will not attend follow-up V11 but will continue with 8 additional visits and 1 phone contact.*

### 2.16.1 Section 8.1.3 Randomisation and trial products administration

***Main phase***

…..

The investigator must document that subjects are trained in the dosing instructions at every dispensing visit, see Section 5.3.*3*~~1~~.

***Extension phase (visit 10)***

*Subjects are considered eligible to continue in the extension phase if they are still on the randomised treatment at V10 (regardless of use of rescue medication) and have consented to continue in the extension phase. Subjects who have prematurely discontinued trial product are not eligible for the extension phase. The inclusion and exclusion criteria for the main phase are not re-assessed at week 52 before entering the extension phase.*

*Eligible subjects, who have signed the addendum to the informed consent, will continue in the extension phase at V10. The first trial-related activity only for subjects continuing in the extension phase is the measurement of $HbA_{1c}$ at V10 using the point-of-care device (see Section 2 and 8.3.5).*

*Subjects randomised to oral semaglutide in the main phase will continue to receive oral semaglutide in the extension phase using the same clinical criteria as applied in the main phase (See Section 5.1). The point-of-care device must be used to measure the subject's $HbA_{1c}$ prior to evaluation of the dose-adjustment criteria at V10 (see Section 5.3.1 and 8.3.5).*

*Subjects randomised to sitagliptin in the main phase will be re-randomised at week 52 to either oral semaglutide or sitagliptin in the extension phase (see Section 5.1, 5.2 and 11). The re-randomisation will be stratified according to $HbA_{1c}$ below 7% (yes/no) measured by a point-of-care device, and if the subject is currently on prescribed rescue medication and continuing on the same medication in the extension phase (yes/no). Rescue medication is defined as intensification of existing background anti-diabetic medication compared to V1 and/or initiation of new anti-diabetic medication. A dispensing session and re-randomisation must be made in the IWRS which will allocate the DUN of trial product to be dispensed to the subject.*

*All V10 assessments must be performed before administration of first dose of trial product in the extension phase.*

*Trial products (see Section 9) will be dispensed to the subject in the extension phase by the site, hospital pharmacy or equivalent at each site visit during the trial from V10 to last visit before the end-of-treatment visit (see Section 2). The investigator must document that subjects are trained in the dosing instructions at every dispensing visit, see Section 5.3.3.*

*For the subjects in the sitagliptin arm re-randomised to oral semaglutide, the date of first semaglutide administration will be captured in the eCRF.*

### 2.16.2 Section 8.1.4 End-of-treatment ~~(visit 10)~~ and Follow-up ~~(visit 11)~~

***For subjects only completing the main phase***

Subjects~~,~~ who stay on trial product throughout the *main phase* ~~trial~~, must attend the end-of-treatment visit ~~(~~V10~~)~~ 52 weeks after randomisation and the follow-up visit ~~(~~V11~~)~~ 5 weeks after the last date on trial product (+3 days visit window). *The end-of-trial form in the eCRF must be completed if subjects are not continuing in the extension phase.* Throughout the protocol, last date on trial product is defined as date of the subject's last dosage of trial product. A completion call must be performed in the IWRS after completion of V10 (see Section 10).

At V10 the subject should be reminded about the importance of attending the follow-up visit ~~(~~V11~~)~~. If the subject, nonetheless, ~~dose~~ *does* not attend V11, the site should make efforts to obtain contact with the subject within the visit window.

A ~~trial~~ completer *of the main phase* is defined as a subject who attends, or is in contact with the site, at the subject's last scheduled visit. For subjects who complete treatment in the main phase and do

not continue in the extension phase, the last scheduled visit is V11. (For subjects who discontinue trial product, see Section 8.1.5).

***For subjects continuing in and completing the extension phase***

*Subjects who continue in the extension phase and stay on trial product throughout the trial must attend the end-of-treatment visit V19 and the follow-up visit V20 5 weeks after the last date on trial product (+3 days visit window). The end-of-trial form in the eCRF must be completed. A completion call must be performed in the IWRS after completion of V19 (see Section 10).*

*At V19, the subject should be reminded about the importance of attending the follow-up visit V20. If the subject, nonetheless, does not attend V20, the site should make efforts to obtain contact with the subject within the visit window.*

*A completer of the extension phase is defined as a subject who attends or is in contact with the site at the subject's last scheduled visit. For subjects who complete treatment in the extension phase, the last scheduled visit is V20 (for subjects who discontinue trial product prematurely, see Section 8.1.5).*

### 2.16.3 Section 8.1.5 Premature discontinuation of trial product and follow-up ~~(visits 10A and 11A)~~

*In general subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule, missing assessments or trial product discontinuation for any reason. Only subjects who decline any further contact with the site in relation to the trial should be considered as having withdrawn consent (see Section 8.1.6).*

***Subjects not continuing in the extension phase***

…..

A subject who prematurely discontinued trial product is still considered a ~~trial~~ completer *of the main phase* if the subject attends or is in contact with the site, at the subject's last scheduled visit. For subjects who prematurely discontinue trial product, the last scheduled visit is V10 (or V11A if it is scheduled after V10). For subjects who complete treatment *in the main phase*, see Section 8.1.4. The site should prepare in due time to establish contact with the subject within the visit window of the scheduled V10 if the subject has agreed to attend this visit.

***Subjects continuing in the extension phase***

*Subjects who discontinue trial product prematurely in the extension phase should attend V19A, which is scheduled to take place on the day of discontinuation of trial product (+3 days visit window). V20A should be scheduled 5 weeks (+3 days visit window) after the last date on trial product. The primary reason for premature discontinuation of trial product must be specified in the*

*end-of-trial form in the eCRF, and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS at V19A (see Section 10).*

*If premature discontinuation of trial product is decided during a scheduled visit, the visit will be converted into a V19A and trial procedures must be performed accordingly.*

*Subjects should continue with the originally scheduled site contacts after V20A, up to and including V19. If necessary, to retain the subject in the trial, site visits can be replaced by phone contacts after V20A. However, if a subject is unable or unwilling to attend all subsequent visit(s), the investigator should at least aim to have the subject attend V19 (end-of-treatment) at week 104, because this visit should be performed for all subjects if at all possible (except subjects who withdraw informed consent, see Section 8.1.6).*

*A subject who prematurely discontinued trial product is still considered a completer of the extension phase if the subject attends or is in contact with the site, at the subject's last scheduled visit. For subjects who prematurely discontinue trial product, the last scheduled visit is V19 (or V20A if it is scheduled after V19). For subjects who complete treatment, see Section 8.1.4. In due time, the site should prepare to establish contact with the subject within the visit window of the scheduled V19 if the subject has agreed to attend this visit.*

~~In summary, subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule, missing assessments or trial product discontinuation for any reason. Only subjects who decline any further contact with the site in relation to the trial should be considered as having withdrawn consent (see Section 8.1.6).~~

### 2.16.4 Section 8.1.6 Withdrawal from trial

If a subject considers withdrawing from the trial, the investigator must aim to undertake procedures for V10A *(main phase)/V19A (extension phase)* as soon as possible and V11A (*main phase)/V20A (extension phase)* should be scheduled 5 weeks (+3 days visit window) after the last date on trial product, if the subject agrees to it.

### 2.16.5 Section 8.1.6.1 Lost to follow-up

In case contact to the subject is lost during the trial, the site should immediately undertake efforts to re-establish contact. If the subject cannot be reached (by clinic visit or phone contact) and the subject has consented to it, the site should consult the contacts provided by the subject (e.g. close relatives), relevant physicians, medical records and locator agencies (if allowed according to local law) in an attempt to regain contact with the subject or to obtain relevant safety information from other sources.

Efforts to regain contact should continue until the end of the subject's last scheduled visit.~~:~~

***For subjects not continuing in the extension phase:***

- V11 for subjects who have completed treatment, whereas for subjects who have discontinued trial product prematurely the last visit is V10 (or V11A if it is scheduled after V10)~~.~~

***For subjects continuing in the extension phase:***

- *V20 for subjects who have completed treatment, whereas for subjects who have discontinued trial product prematurely the last visit is V19 (or V20A if it is scheduled after V19)*

Only if contact with the subject is not regained by the end of the visit window of the last scheduled visit can the subject be considered lost to follow-up (see Section 6.6).

### 2.17 Section 8.3.5 Point-of-care $HbA_{1c}$ measurement

*In addition, the point-of-care device should be used to assess the $HbA_{1c}$ at V10 for subjects randomised to sitagliptin in the main phase and continuing in the extension phase as this value will be used to stratify (according to whether or not the subject had an $HbA_{1c}$ < 7.0% at week 52) the re-randomisation of the subjects.*

### 2.18 Section 8.4.4 Eye examination

If fundus photography or dilated fundoscopy has been performed within 90 days prior to randomisation *at V2*, the procedure does not need to be repeated, unless worsening of visual function since the last examination. The results must be available prior to randomisation *at V2*.

### 2.19 Section 8.6.1 Subject diary

- *For subjects switching from sitagliptin to oral semaglutide at V10 in the extension phase: date of first semaglutide administration*

### 2.20 Section 11 Randomisation procedure

The trial is an open-label trial. A randomisation session will be made *at V2* for all eligible subjects using IWRS.

At V2, eligible subjects will be randomised to one of the two parallel treatment arms as described in Section 5.1 and Section 5.2. *Randomisation will be stratified (two strata) according to anti-diabetic background medication at screening (with and without SU).*

*Subjects randomised to sitagliptin at V2 who are still on trial product at V10 and decide to continue in the extension phase will be re-randomised to one of the two parallel treatment arms as described in Section 5.1 and Section 5.2. The re-randomisation in the sitagliptin arm will be stratified according to $HbA_{1c}$ below 7% (yes/no) and if the subject is currently on prescribed rescue medication and continuing on the same medication in the extension phase (yes/no). This is to ensure an even distribution in the two treatment arms in the extension phase (switch).*

### 2.21 Section 12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events occurring from the first trial-related activity after the subject has signed the informed consent until the *last planned visit.*

*Subjects not continuing in the extension phase:*

- *V11 for subjects completing treatment*
- *V10 (or V11A if it is scheduled after V10) for subjects who prematurely discontinue trial product*

*Subjects continuing in the extension phase:*

- *V20 for subjects completing treatment*
- *V19 (or V20A if it is scheduled after V19) for subjects who prematurely discontinue trial product*

~~end of the post-treatment follow-up period (V11) for subjects on trial product or until the end of trial (V10 or V11A, whichever comes last) for the subjects who have discontinued trial product prematurely.~~

### 2.22 Section 12.7.2 Event adjudication committee

Event adjudication will be performed for AEs in randomised subjects including AEs with an onset date during the screening period. Event adjudication will not be performed for AEs in screening failures. *The adjudication process will be the same throughout the trial, including the extension phase.*

### 2.23 Section 14 Monitoring procedures

Monitoring will be conducted under a risk based approach *including risk assessment, monitoring plans, centralised monitoring and visits to trial sites*. During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the *centralised* ~~remote~~ monitoring of the eCRFs *(remote assessment of data by Novo Nordisk)*, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LSLV at the trial site (for trial sites with active subjects (defined as subjects in screening, treatment or follow-up)).

## 2.24 Section 17 Statistical considerations

*The results from the trial will be reported in two clinical trial reports; the first clinical trial report will report the results from the main phase and the second clinical trial report will report the results of the entire trial period, including the extension phase.*

*A database lock for the main phase will be performed when all subjects have completed the main phase to be able to report the results in the first clinical trial report. After completion of the extension phase, there will be a second database lock followed by the reporting of the results of the entire trial in the second clinical trial report.*

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock *for the main phase*.

Data from all sites will be analysed and reported together. *The data from the different dose levels for each oral semaglutide arm will be pooled as one oral semaglutide arm and not analysed by dose level. However, the two oral semaglutide arms in the extension phase will not be pooled.*

In statistical analyses where stratification is included, the ~~two levels of anti-diabetic background medication at screening (with and without SU)~~ *stratification factors* will be included based on the actual information collected through the eCRF *via the concomitant medication form and the central laboratory results for $HbA_{1c}$ (extension phase only). The stratification factor in the main phase will be anti-diabetic background medication at screening (with and without SU)*. In case of missing eCRF information *for the anti-diabetic background medication* the information collected from the IWRS system will be used. *The stratification factors in the extension phase will be $HbA_{1c}$ below 7% (yes/no) and if the subject is currently on prescribed rescue medication and continuing on the same medication in the extension phase (yes/no). Rescue medication is defined as intensification of existing background anti-diabetic medication compared to V1 and/or initiation of new anti-diabetic medication.*

The latest available measurement, at or prior to the randomisation visit*, for the main phase and the extension phase (switch) respectively*, will be used as the baseline measurement. If no measurement(s) have been obtained, at or prior to randomisation, the baseline value will be left missing.

Laboratory values below the lower limit of quantification (LLoQ) will be set to ½ LLoQ. Number of values below LLoQ by treatment and visit will be summarised if deemed relevant.

*The results will be presented as follows.*

***Main phase***

Results from a statistical analysis will as a minimum be presented by the estimated treatment contrasts for oral semaglutide versus sitagliptin comparisons with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference.

- *Oral semaglutide (3, 7 or 14 mg)*
- *Sitagliptin (100 mg)*

If no statistical analysis is specified, data will be presented using relevant summary statistics.

***Extension phase (sustainability)***

*Relevant descriptive statistics will be presented, including graphical presentations, to evaluate the data from the below treatment arm for subjects randomised to oral semaglutide and continuing on oral semaglutide in the extension phase.*

- *Oral semaglutide (3, 7 or 14 mg) during 104 weeks*

***Extension phase (switch)***

*The results from the extension phase (switch) will be presented as for the main phase; however, the comparison will be between the below two treatment arms in which subjects were randomised to sitagliptin at trial entry and re-randomised at week 52 to either continue on sitagliptin or switch to oral semaglutide.*

- *Oral semaglutide (3, 7 or 14 mg), switching from sitagliptin at week 52*
- *Sitagliptin (100 mg), continuing on sitagliptin after week 52*

**Primary and secondary estimands**

Two estimands addressing different aspects of the trial objective will be defined; a primary de-facto (effectiveness) estimand and a secondary de-jure (efficacy) estimand:

- Primary estimand
  - de-facto treatment *effect* ~~difference (oral semaglutide versus sitagliptin) at week 52~~ for all randomised subjects regardless of adherence to randomised treatment and initiation of rescue medication

The primary de-facto estimand assesses the expected glycaemic benefit in a future population that results from subjects initiating treatment with oral semaglutide including potential rescue medication(s) as compared to initiating treatment with sitagliptin including potential rescue

medication(s). Generalisation of this estimand depends among other things on the extent to which the use of rescue medication in this trial reflects clinical practice and the adherence to trial product administration in this trial reflects the behaviour of the target population. Accordingly, data collected regardless of discontinuation of trial product or initiation of rescue medication(s) will be used to draw inference.

- Secondary estimand
  - de-jure treatment *effect*~~difference (oral semaglutide versus sitagliptin) at week 52~~ for all randomised subjects if all subjects adhered to treatment and did not initiate rescue medication

The secondary de-jure estimand assesses the glycaemic benefit a future subject is expected to achieve if initiating and continuing treatment with oral semaglutide as compared to sitagliptin. It is considered a clinically relevant estimand as it provides information to treating clinicians about the expected glycaemic efficacy of oral semaglutide compared to sitagliptin for purposes of treating individual subjects. Generalisation of this estimand depends among other things on the extent to which the adherence to trial product administration in this trial reflects the behaviour of the target population. Accordingly, only data collected prior to discontinuation of trial product or initiation of rescue medication will be used to draw inference. *For the two treatment arms in the extension phase (switch), the current prescribed rescue medication (at V10) in the main phase will be treated as background medication in the extension phase and only data collected after initiation of rescue medication in the extension phase will be excluded.* This will avoid confounding from rescue medication.

***Main phase***
*For both estimands, the treatment effect refers to an odds ratio (OR) for the primary endpoint of achieving $HbA_{1c}$ < 7.0% at week 52 (yes/no). The treatment effect refers to a treatment difference for the confirmatory secondary endpoint; change from baseline to week 52 in body weight.*

***Extension phase (switch)***
*For both estimands, the treatment effect refers to a treatment difference for both confirmatory secondary endpoints; change from week 52 to week 104 in $HbA_{1c}$ and in body weight.*

**Missing data considerations at week 52 *and at week 104***

When estimating the primary estimand, the proportion of missing data, i.e., data that do not exist even though subjects are intended to stay in the trial regardless of treatment status and initiation of rescue medication(s), is expected to be maximum 15%. Missing data will mainly be due to withdrawal from trial or lost to follow-up.

When estimating the secondary estimand, the proportion of missing data is expected to be higher (20-30%) since data collected after discontinuation of trial product or initiation of rescue

medication(s) will be set to missing. The 20-30% of missing data is based on the sitagliptin phase 3 trials[42], *and* the oral semaglutide phase 2 trial (NN9924-3790), that indicates that a low starting dose with gradual dose-escalation diminishes gastrointestinal AEs compared with more aggressive dosing regimens. The possibility to reduce the dose due to issues with tolerability is also expected to reduce the number of subjects withdrawing from the oral semaglutide arm. Across treatment arms the main reasons for missing data are expected to be early treatment discontinuation due to gastrointestinal AEs and ~~eventually~~ initiation of rescue medication. Initiation of rescue medication is expected to be more frequent in the sitagliptin than in the oral semaglutide arm. A higher proportion of subjects are expected to discontinue treatment due to AEs in the oral semaglutide arm, compared to the sitagliptin treatment arm. So overall the frequency of missing data is expected to be similar across treatment arms.

*The proportion of missing data from week 52 to week 104 is expected to be similar as for the first 52 weeks in the two treatment arms of re-randomised subjects. The rate of missing data is expected to decline over time in the oral semaglutide arm in which subjects were randomised to oral semaglutide at baseline due to decreased tolerability issues over time.*

*It is expected that 190 subjects will enter the extension phase (switch). This is based on the assumption that maximum 25% of the subjects do not continue in the extension phase (switch) due to withdrawal from trial or they are lost to follow up, off treatment or unwilling to continue.*

Descriptive summaries and graphical representation of extent, reason(s) for and pattern of missing data will be presented by treatment arm.

### 2.25 Section 17.1 Sample size calculation

~~The primary endpoint, if a subject after week 52 achieves (yes/no) $HbA_{1c}$ < 7% (53 mmol/mol) and the confirmatory secondary endpoint, change from baseline to week 52 in body weight (kg) are planned to be tested for superiority of oral semaglutide versus sitagliptin.~~

*The following four hypotheses are planned to be tested:*
*Main phase:*

- *Superiority of $HbA_{1c}$ < 7% (yes/no) at week 52*
- *Superiority of change from baseline to week 52 in body weight*

*Extension phase (switch):*

- *Superiority of change from week 52 to week 104 in $HbA_{1c}$*
- *Superiority of change from week 52 to week 104 in body weight*

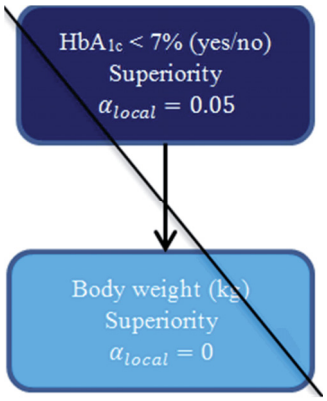
The sample size calculation is made to ensure at least 90% power to confirm superiority of $HbA_{1c}$ < 7% (yes/no) at week 52 of oral semaglutide versus sitagliptin. ~~The sample size calculation~~

~~is made to ensure at least 90% to confirm superiority of oral semaglutide vs. sitagliptin on the primary endpoint, if a subject after week 52 achieves $HbA_{1c}$ < 7% (yes/no). Two~~The four pre-specified confirmatory hypotheses are shown in Figure 17-1. The hierarchal testing strategy is used to control the overall type-1 error at a nominal two-sided 5% level for the four confirmatory tests.

The statistical testing strategy is built on the principle that glycaemic effect will have to be established in terms of $HbA_{1c}$ superiority before testing for added benefits in terms of body weight superiority. The hypotheses related to the main phase will be tested and reported in the first clinical trial report. If these confirmatory hypotheses are confirmed, the two confirmatory hypotheses related to the extension phase (switch) will be tested in the hierarchical order shown in Figure 17-1 and reported in the final clinical trial report.

*The assumptions used in the sample size calculation are based on the oral semaglutide phase 2 results (trial NN9924-3790)[24], sitagliptin phase 3a trial results[42], and supported by results from the s.c. semaglutide phase 3 trial, SUSTAIN 2[45].*

The sample size calculation is based on a 5% (two-sided) significance level and Fishers exact test. The sample size depends on the proportion of responders and the absolute difference in proportions between semaglutide and sitagliptin. Assuming an absolute difference in proportions of 15 percentage-points (taking the retrieved and imputed data into account) and that the proportion of sitagliptin responders are distributed around 20 to 50%, the power for confirming superiority on the primary endpoint, if a subject after week 52 achieves (yes/no) $HbA_{1c}$ < 7% (53 mmol/mol) will be at least 90% with 250 subjects per arm. In total 500 subjects are planned to be randomised.



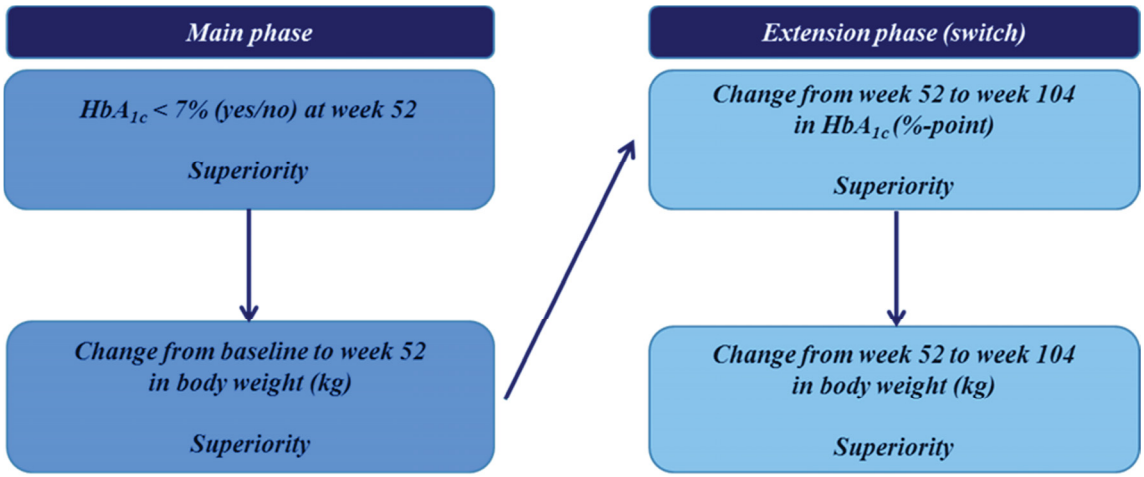



**Figure 17-1 Graphical illustration of the closed testing procedure**

The overall significance level of $\alpha = 0.05$ (two-sided) is initially allocated to the $HbA_{1c}$ superiority test *at week 52*. The local significance level ~~(α local)~~ will be reallocated to the ~~body weight~~ *second* hypothesis if the first hypothesis is confirmed *and so on*. The sample size is based on the *first* $HbA_{1c}$ hypothesis *(main phase)*.

*The sample size assumptions for treatment effects (TE), adjusted TE and the standard deviations (SD) used to calculate the power for the additional three confirmatory hypotheses are presented in Table 17-1.*

*Because the equalising effect of rescue medication will be included in the analyses and because a conservative approach for handling of missing data will be applied, an adjustment of the TE will be implemented for the 15% of subjects who are expected to either discontinue trial product prematurely or initiate rescue medication as well as for the 15% of subjects who are expected to have missing data. The TEs used in the sample size calculation will be adjusted according to a 75% smaller effect in these subjects. The adjusted TE is calculated as follows:*

$$0.7 \times TE + 0.3 \times TE \times 0.25$$

*The calculated marginal and conditional powers for each of the four tests are also presented in Table 17-1. All the confirmatory hypotheses are assumed to be independent. Because positive correlation amongst the test is expected, the assumption of independence is viewed as conservative.*

***Table 17-1 Assumptions used in sample size and power calculation***

| *Endpoint* | *Treatment effect (TE)* | *Adjusted TE* | *SD* | *Number of subjects* | *Marginal power* | *Conditional power* |
|---|---|---|---|---|---|---|
| ***Main phase:*** | | | | | | |
| *$HbA_{1c}$ < 7% (yes/no)* | *15%-point difference* | | | *500* | *90%* | *90%* |
| *Change in body weight (kg)* | *2.5* | *1.94* | *4.0* | *500* | *>99%* | *90%* |
| ***Extension phase (switch):*** | | | | | | |
| *Change in $HbA_{1c}$ (%-point)* | *0.4* | *0.31* | *1.1* | *190* | *49%* | *44%* |
| *Change in body weight (kg)* | *2.5* | *1.94* | *4.0* | *190* | *91%* | *40%* |

## 2.26 Section 17.2 Definition of analysis sets

The following analysis sets will be defined:

***Main phase***

**Full analysis set (FAS):** Includes all randomised subjects. Subjects in the FAS will contribute to the evaluation "as randomised".

**Safety analysis set (SAS):** Includes all subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation "as treated".

***Extension phase (sustainability)***

***Extension (sustainability) FAS:*** *Includes all subjects randomised to oral semaglutide in the main phase and continuing on oral semaglutide in the extension phase. Subjects in the extension (sustainability) FAS will contribute to the evaluation "as randomised".*

***Extension (sustainability) SAS:*** *Includes all subjects randomised to oral semaglutide in the main phase and exposed to at least one dose of oral semaglutide in the extension phase. Subjects in the extension (sustainability) SAS will contribute to the evaluation "as treated".*

***Extension phase (switch)***
***Extension (switch) FAS:*** *Includes all subjects randomised to sitagliptin in the main phase and re-randomised to either continue on sitagliptin or switch to oral semaglutide in the extension phase. Subjects in the extension (switch) FAS will contribute to the evaluation "as randomised".*

***Extension (switch) SAS:*** *Includes all subjects randomised to sitagliptin in the main phase and re-randomised and exposed with at least one dose of either sitagliptin or oral semaglutide in the extension phase. Subjects in the extension (switch) SAS will contribute to the evaluation "as treated".*

**Data selections and observation periods**

Unless subjects withdraw their informed consent, data collection will continue for the full duration of the trial. The full duration of the trial is defined as up to and including:

- ~~the follow-up visit (V11) for subjects on trial product~~
- ~~the latest occurring visit of the end-of-treatment visit (V10) or the follow-up premature discontinuation visit (V11A), for subjects who have discontinued trial product prematurely~~
- *the follow-up visit V11 for subjects who do not discontinue trial product in the main phase, but decide not to continue in the extension phase*
- *the latest occurring visit of the end-of-treatment visit V10 or the follow-up premature treatment discontinuation visit V11A for subjects who discontinue trial product prematurely in the main phase*
- *the follow-up visit V20 for subjects who continue in the extension phase and do not discontinue trial product in the extension phase*
- *the latest occurring visit of the end-of-treatment visit V19 or the follow-up premature treatment discontinuation visit V20A for subjects who discontinue trial product prematurely in the extension phase*

Subjects and data to be used in an analysis will be selected in a two-step manner:

- Firstly, subjects will be selected based on the specified analysis set
- Secondly, data points on the selected subjects from the first step will be selected based on the specified observation period

Definition of the observation periods:

**In-trial:** This observation period represents the time period where subjects are considered to be in the trial, regardless of discontinuation of trial product or initiation of rescue medication.

*Main phase*
The in-trial observation period starts at randomisation (as registered in the IWRS) and ends at the date of:

- the last direct subject-site contact, which is scheduled to take place 5 weeks after planned last dose of trial product at the follow-up visit V11 *for subjects who decide not to continue in the extension phase*
- *V10 for subjects who continue in the extension phase*
- withdrawal for subjects who withdraw their informed consent
- the last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up
- death for subjects who dies before any of the above

*Extension phase (sustainability)*

*The in-trial observation period starts at randomisation in main phase (as registered in the IWRS) and ends at the date of:*

- *the last direct subject-site contact, which is scheduled to take place 5 weeks after planned last dose of trial product at the follow-up visit V20 for subjects who continue in the extension phase*
- *withdrawal for subjects who withdraw their informed consent*
- *the last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up*
- *death for subjects who dies before any of the above*

*Extension phase (switch)*
*The in-trial observation period starts at re-randomisation (as registered in the IWRS) planned at V10 and ends at the date of:*

- *the last direct subject-site contact, which is scheduled to take place 5 weeks after planned last dose of trial product at the follow-up visit V20 for subjects who continue in the extension phase*
- *withdrawal for subjects who withdraw their informed consent*
- *the last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up*
- *death for subjects who dies before any of the above*

**On-treatment:** This observation period represents the time period where subjects are considered treated with the trial product. The observation period is a subset of the in-trial observation period.

*Main phase*
*The on-treatment observation period ~~It~~* starts at the date of first dose of trial product. Two slightly different end dates will be needed to cover all assessments appropriately.

For adjudicated events, ECGs, *eye examination category* and AEs including hypoglycaemic episodes, the observation period ends at the first date of any of the following:

- the follow-up visit V11 *for subjects on trial product who decide not to continue in the extension phase*
- the follow-up prematurely discontinuation visit V11A
- the last date on trial product +38 days
- the end-date for the in-trial observation period

*For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) the observation period ends at the last date on trial product +3 days. This will be used in order to ensure specificity to reversible effects of treatment.*

*Extension phase (sustainability)*
*The on-treatment observation period starts at the date of first dose of trial product.*

*For adjudicated events, ECGs, eye examination, and AEs including hypoglycaemic episodes, the observation period ends at the first date of any of the following:*

- *the follow-up visit V20 for subjects on trial product who continue in the extension phase*
- *the follow-up prematurely discontinuation visit V20A*
- *the last date on trial product +38 days*
- *the end-date for the in-trial observation period*

For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) the observation period ends at the last date on trial product +3 days.

*Extension phase (switch)*
*The on-treatment observation period starts at the date of first dose of trial product in the extension phase planned at V10.*

*For adjudicated events, ECGs, eye examination, and AEs including hypoglycaemic episodes, the observation period ends at the first date of any of the following:*

- the follow-up visit V20 for subjects on trial product who continue in the extension phase
- the follow-up prematurely discontinuation visit V20A
- the last date on trial product +38 days
- the end-date for the in-trial observation period

*For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) the observation period ends at the last date on trial product +3 days.*

The follow-up visit (V11/V11A*/V20/V20A*) is scheduled to take place 5 weeks after the last date on trial product corresponding to approximately five half-lives of oral semaglutide. The visit window for the follow-up visit is +3 days.

~~*For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) the observation period ends at the last date on trial product +3 days. This will be used in order to ensure specificity to reversible effects of treatment.*~~

**On-treatment without rescue medication:** This observation period is a subset of the on-treatment observation period, where subjects are considered treated with trial product, but have not initiated any rescue medications.

*Main phase*
*The on-treatment without rescue medication observation period* ~~Specifically it~~ starts at *the* date of first dose of trial product and ends at the first date of any of the following:

- the last dose of trial product +3 days
- initiation of rescue medication

*Extension phase (sustainability)*
*The on-treatment without rescue medication observation period starts at the date of first dose of trial product and ends at the first date of any of the following:*

- *the last dose of trial product +3 days*
- *initiation of rescue medication*

*Extension phase (switch)*
*For the two treatment arms in the extension phase (switch), the current prescribed rescue medication (at V10) in the main phase will be treated as background medication in the extension phase and only data collected after initiation of rescue medication in the extension phase will be excluded.*

*Specifically the on-treatment without rescue medication observation period starts at the date of first dose of trial product in the extension phase, planned at V10, and ends at the first date of any of the following:*

- *the last dose of trial product +3 days*
- *initiation of rescue medication in the extension phase*

The in-trial observation period will be the primary observation period when estimating the primary estimand. The on-treatment without rescue medication observation period will be the primary observation period when estimating the secondary estimand. The on-treatment observation period will be considered supportive for evaluating ~~efficacy~~ *the secondary estimand*. Safety will be evaluated based on the in-trial and the on-treatment observation periods.

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period. For adjudicated events, the onset date will be the EAC adjudicated onset date.

Before data are locked for statistical analysis and the randomisation code is broken, a review of all *available* data will take place. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group.

Exclusion of data from analyses should be used restrictively, and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

**Confirmatory hypotheses**

For the primary $HbA_{1c}$ endpoint the following confirmatory one-sided hypothesis are planned to be tested *where OR refers to the odds ratio* for oral semaglutide versus sitagliptin.

- $H_0$: OR $\leq$ 1 against $H_a$: OR >1

For the confirmatory secondary ~~body weight~~ endpoint *in the main phase (change from baseline to week 52 in body weight), the following* hypothesis is planned to be tested*, where μ refers to the treatment difference between* ~~for~~ *oral semaglutide minus sitagliptin.*

- $H_0$: $\mu \geq 0.0$ kg against $H_a$: $\mu < 0.0$ kg~~, where μ = (oral semaglutide minus sitagliptin)~~

*For the two confirmatory endpoints in the extension phase (switch; change from week 52 to week 104 in $HbA_{1c}$ and change from week 52 to week 104 in body weight), the following confirmatory one-sided hypotheses are planned to be tested for oral semaglutide versus sitagliptin.*

- *$H_0$: $\mu \geq 0.0$ %-point against $H_a$: $\mu < 0.0$ %-point*
- *$H_0$: $\mu \geq 0.0$ kg against $H_a$: $\mu < 0.0$ kg*

Operationally ~~both~~ the confirmatory hypotheses will be evaluated by two-sided tests at the 5% significance level.

**Multiplicity and criteria for confirming hypotheses**

The type I error for testing the ~~two~~*four* confirmatory hypotheses related to the $HbA_{1c}$ and body weight endpoints will be preserved in the strong sense at 5% (two-sided) using an hierarchical testing strategy as outlined in Figure 17-1.

Superiority of the primary hypotheses will be considered confirmed if the odds ratio is supporting the corresponding alternative hypothesis and the two-sided p-value from the primary analysis of the primary estimand is strictly below the 5% two-sided significance level. This is equivalent to using a one-sided p-value (nominal $\alpha = 0.025$) and a one-sided 2.5% overall significance level. If the primary hypothesis is confirmed, the testing strategy will continue *by* testing the *following* confirmatory secondary hypothesis at a 5% two-sided significance level. Superiority of the *following* secondary confirmatory hypotheses will then be considered confirmed if the treatment difference is supporting the corresponding alternative hypothesis and the two-sided p-value from the primary analysis of the primary estimand is strictly below the 5% two-sided significance level *and so on. If for any of the four confirmatory hypotheses, superiority is not confirmed the testing will terminate.*

### 2.27 Section 17.3.1 Primary analyses for the primary estimand

The primary estimand *for the primary endpoint* will be estimated based on the FAS using week 52 measurements from the in-trial observation period.

…..

### 2.28 Section 17.3.2 Primary analysis for the secondary estimand

The secondary estimand *for the primary endpoint* will be estimated based on the FAS using post-baseline measurements up to and including week 52 from the on-treatment without rescue medication observation period.

…..

### 2.29 Section 17.4.1 Confirmatory secondary endpoints

***Main phase***

Change from baseline to week 52 in body weight (kg) ~~will be confirmatory secondary endpoint~~.

The primary and secondary estimands will be estimated using the same approaches as described for the primary $HbA_{1c}$ endpoint without dichotomizing the endpoint and with a linear normal regression model instead of the logistic regression model. Baseline body weight will be used as a covariate instead of baseline $HbA_{1c}$ *for the endpoints related to body weight* in both the multiple imputation and analysis models.

***Extension phase (switch)***

*Change from week 52 to week 104 in $HbA_{1c}$*

*Change from week 52 to week 104 in body weight (kg)*

*The primary estimand will be based on extension phase (switch) FAS using the in-trial extension phase (switch) observation period. Whereas, the secondary estimand will be based on extension phase (switch) FAS using the on-treatment without rescue medication, extension phase (switch) observation period.*

*The estimands will be estimated using the same approaches as described for the primary $HbA_{1c}$ endpoint without dichotomizing the endpoint and with a linear normal regression model instead of the logistic regression model. Baseline body weight will be used as a covariate instead of baseline $HbA_{1c}$ in the analyses of the body weight endpoint, in both the multiple imputation and analysis models.*

*The stratification factors, $HbA_{1c}$ below 7% (yes/no) and if the subject is currently on prescribed rescue medication and continuing rescue medication in the extension phase (yes/no), and the interaction of these will be included as fixed effects in the analyses.*

Superiority will be considered confirmed if the mean treatment difference is supporting the corresponding hypothesis and the two-sided p-value from the analysis of the primary estimand is strictly below its local two-sided significance level resulting from the closed testing procedure in Figure 17-1. Sensitivity analyses similar to the ones pre-specified for testing superiority for the primary $HbA_{1c}$ endpoint will be made to evaluate the robustness of the *confirmatory* body weight results *for the main phase. The tipping point analysis will be used as a sensitivity analysis for the confirmatory results for the extension phase (switch).*

### 2.29.1 Section 17.4.2.1 Efficacy endpoints

***Main phase***

- the primary estimand based on FAS using the in-trial observation period

  …..

***Extension phase (sustainability)***

- *extension phase (sustainability) FAS using the in-trial extension phase (sustainability) observation period*
- *extension phase (sustainability) FAS using the on-treatment without rescue medication, extension phase (sustainability) observation period*

***Extension phase (switch)***

- *the primary estimand based on extension phase (switch) FAS using the in-trial extension phase (switch) observation period*
- *the secondary estimand based on extension phase (switch) FAS using the on-treatment without rescue medication, extension phase (switch) observation period*

No sensitivity analyses are planned for these.

**Continuous efficacy endpoints**

***Main phase***

Change from baseline to week 52 in:

- $HbA_{1c}$

  …..

***Extension phase (sustainability)***

*Change from baseline to week 104 in:*

- *$HbA_{1c}$*
- *FPG*
- *Body weight (kg)*

- *Body weight (%)*
- *BMI*
- *Waist circumference*

***Extension phase (switch)***

*Change from week 52 to week 104 in:*

- *FPG*
- *Body weight (%)*
- *BMI*
- *Waist circumference*

***Main and extension phase (switch)***

The above continuous endpoints will be analysed separately using similar model approaches as for the *confirmatory* secondary endpoint*s for the main phase and the extension phase (switch), respectively,* with the associated baseline response as a covariate. Fasting lipid profile endpoints *(main phase only)* will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

***Extension phase (sustainability)***

*The endpoints will be summarised descriptively by visit.*
*Furthermore, the change from baseline to week 52 in $HbA_{1c}$ and in body weight will be presented using both the main phase FAS and the extension phase (sustainability) FAS to explore differences in $HbA_{1c}$ and in body weight for subjects not continuing in the extension phase (sustainability).*

**Binary efficacy endpoints**

***Main phase***

If a subject after 52 weeks achieves (yes/no):

- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) AACE target

  …..

***Extension phase (sustainability)***

*If a subject after 104 weeks achieves (yes/no):*

- *$HbA_{1c} < 7\%$ (53 mmol/mol) ADA target*
- *$HbA_{1c} \leq 6.5\%$ (48 mmol/mol) AACE target*
- *$HbA_{1c}$ reduction ≥ 1%-point (10.9 mmol/mol)*
- *$HbA_{1c} < 7\%$ (53 mmol/mol) or $HbA_{1c}$ reduction ≥ 1%-point (10.9 mmol/mol)*
- *Weight loss ≥ 5%*

- *$HbA_{1c}$ < 7% (53 mmol/mol) without treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes and no weight gain*

***Extension phase (switch)***

*If a subject after 104 weeks achieves (yes/no):*

- *$HbA_{1c}$ < 7% (53 mmol/mol) ADA target*
- *$HbA_{1c}$ ≤ 6.5% (48 mmol/mol) AACE target*
- *$HbA_{1c}$ reduction ≥ 1%-point (10.9 mmol/mol) compared to week 52*
- *Weight loss ≥ 5% compared to week 52*
- *$HbA_{1c}$ < 7% (53 mmol/mol) without treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes after week 52 and no weight gain compared to week 52*
- *$HbA_{1c}$ < 7% (53 mmol/mol) and no need for rescue medication after week 52*
- *No need for rescue medication after week 52*

***Main and extension phase (switch)***

The above binary endpoints will be analysed separately using similar model approaches as for the primary endpoint with the associated baseline response*, $HbA_{1c}$ or body weight,* as a covariate. *The analysis of the endpoint for rescue medication in extension phase (switch) will not include a baseline covariate as rescue medication in the main phase (yes/no) is used as a stratification factor in the model.*

***Extension phase (sustainability)***

*The endpoints will be summarised descriptively by visit.*

**Time to event endpoint**

***Main phase***

- Time to rescue medication

The *above time to event* endpoint will be analysed based on FAS using both the on-treatment observation period and the in-trial observation period. For the analysis based on the on-treatment observation period, subject*s* without need for rescue medication during the on-treatment observation period will be censored at the time point of the date of last trial product. *Switch to rescue medication at the date of last trial product will be considered as an event.* For the in-trial period subject*s* without need for addition of rescue medication during the in-trial observation period, will be censored at the time point of the date of end of the in-trial observation period. For this analysis, the follow-up period will be excluded from the in-trial observation period, since subjects will have to stop treatment at the end-of-treatment visit and therefore might need addition of rescue medication during the follow-up period.

The *time to event* endpoint will be described and compared for oral semaglutide versus sitagliptin using likelihood ratio tests obtained from a Cox proportional hazards model with treatment, stratification factors, the interaction between the two stratification factors and region as categorical fixed effects and baseline $HbA_{1c}$ as a covariate. From this analysis the estimated ~~H~~*h*azard ratios between oral semaglutide versus sitagliptin will be presented together with 95% confidence intervals and two sided p-values for test of no difference.

***Extension phase (switch)***

- *Time to rescue medication after week 52*

*The endpoint will be analysed based on extension phase (switch) FAS using both the on-treatment extension phase (switch) observation period and the in-trial extension phase (switch) observation period. For the extension phase (switch), rescue medication initiated in the main phase will be treated as background medication in the extension phase and only addition of rescue medication after week 52 (V10) will be counted in the analyses. The same analyses approach as for the main phase will be performed.*

### 2.29.2 Section 17.4.2.2 Safety endpoints

The safety endpoints *for the main phase in the first clinical trial report* will be evaluated based on SAS using the on-treatment observation period and based on SAS using the in-trial observation period unless otherwise stated.

*The safety endpoints for the extension phase in the second clinical trial report will be evaluated based on extension phase (switch) and (sustainability) SAS using the on-treatment extension phase (switch) and (sustainability) observation period and based on extension phase (switch) and (sustainability) SAS using the in-trial extension phase (switch) and (sustainability) observation period unless otherwise stated.*

The following endpoints are used to support the safety objectives.

**Adverse events**

***Main phase***

- Number of TEAEs during exposure to trial product, assessed up to approximately ~~57~~ 52 weeks

***Extension phase (sustainability)***

- *Number of TEAEs during exposure to trial product, assessed up to approximately 109 weeks*

***Extension phase (switch)***

- *Number of TEAEs during exposure to trial product, assessed from week 52 up to approximately 109 weeks*

…..

Supportive summaries of AEs will be made for the in-trial observation period. The development over time in gastrointestinal AEs will be presented graphically.

***Main phase***

*In addition, events reported from week 52 (V10) to week 57 (V11) in subjects who complete treatment in the main phase and do not continue in the extension phase will be listed separately.*

**Other safety endpoints**

***Main phase***

Change from baseline to week 52 in:

- Amylase (part of biochemistry)

  …..

***Extension phase (sustainability)***

*Change from baseline to week 104 in:*

- *Amylase (part of biochemistry)*
- *Lipase (part of biochemistry)*
- *Pulse*
- *Systolic blood pressure*
- *Diastolic blood pressure*

***Extension phase (switch)***

*Change from week 52 to week 104 in:*

- *Amylase (part of biochemistry)*
- *Lipase (part of biochemistry)*
- *Pulse*
- *Systolic blood pressure*
- *Diastolic blood pressure*

***Main and extension phase (switch)***

The above safety endpoints ~~will be evaluated using the primary analysis for the primary estimand based on SAS using the in-trial observation period and using the primary analysis for the secondary estimand based on SAS using the on-treatment observation period. Endpoints~~ will be analysed as

described above for continuous efficacy endpoints. ~~Results will be presented at week 52~~. Amylase and lipase endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

***Extension phase (sustainability)***

*The endpoints will be summarised descriptively by visit.*

***The following other safety endpoints will be calculated similarly as for the above other safety endpoints:***

~~Change from baseline to week 52 in:~~

***Main phase***

*The safety endpoint for the main phase will furthermore be calculated for the following:*

- Haematology
- Biochemistry (except for amylase and lipase)
- Calcitonin
- ECG category
- Physical examination
- Eye examination category

***Extension phase***

*The safety endpoints for the extension phase (switch) and extension phase (sustainability) will furthermore be calculated for the following:*

- *Haematology*
- *Biochemistry (except for amylase and lipase)*
- *Calcitonin*
- *Eye examination category*

The *main and extension phase* ~~above~~ safety endpoints will be summarised descriptively by treatment arm and visit. Categorical safety endpoints will be summarised as counts and relative frequencies. Calcitonin will also be presented by gender.

**Hypoglycaemia**

***Main phase***

- Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately ~~57~~ *52* weeks
- Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately ~~57~~ *52 weeks* (yes/no)

***Extension phase (sustainability)***

- *Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 109 weeks*
- *Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 109 weeks (yes/no)*

***Extension phase (switch)***

- *Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed from week 52 up to approximately 109 weeks*
- *Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed from week 52 up to approximately 109 weeks (yes/no)*

**Classification of hypoglycaemia**

Hypoglycaemic episodes will be summarised for the SAS*, extension phase (sustainability) SAS and extension phase (switch) SAS, using only* ~~and~~ the on-treatment *extension phase (sustainability) and on-treatment extension phase (switch)* observation period*, respectively (referred to as the on-treatment observation periods in the following)*~~only~~.

….

**Analysis of severe or BG-confirmed symptomatic hypoglycaemic ~~endpoints~~ *episodes***

***Main and extension phase (switch)***

The *endpoints related to* number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during the on-treatment period will be analysed using a negative binomial regression model with a log-link function and the logarithm of the duration of the subject's on-treatment observation period as offset. The model will include treatment, stratification factor and region as fixed factors and baseline $HbA_{1c}$ as covariate.

The binary endpoint*s* showing whether a subject has at least one treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episode will be analysed using a logistic regression model with treatment, stratification factor and region as fixed factors and baseline $HbA_{1c}$ as covariate.

*In addition, treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes reported from week 52 (V10) to week 57 (V11) in subjects who complete treatment in the main phase and do not continue in the extension phase will be listed separately.*

***Extension phase (sustainability)***

*The endpoints will be summarised descriptively.*

### 2.30 Section 17.5 Interim analysis

No interim analyses or other analyses of unblinded data will be performed before the database *for the main phase* is locked.

*A database lock for the main phase will be performed when all subjects have completed the main phase to be able to report the results in the first clinical trial report. After completion of the extension phase, there will be a second database lock followed by the reporting of the results of the entire trial in the second clinical trial report.*

### 2.31 Section 17.6 Patient-reported outcomes

***Main phase***

Change from baseline to week 52 *in*:

- SF-36v2™ (acute version) health survey: ~~S~~scores from the 8 domains and the physical component score and mental component score summary scores
- DTSQ*s*: individual items and treatment satisfaction score (6 of the 8 items summed)

***Extension phase (sustainability)***

*Change from baseline to week 104 in:*

- *SF-36v2™ (acute version) health survey: scores from the 8 domains and the physical component score and mental component score summary scores*
- *DTSQs: individual items and treatment satisfaction score (6 of the 8 items summed)*

***Extension phase (switch)***

*Change from week 52 to week 104 in:*

- *SF-36v2™ (acute version) health survey: scores from the 8 domains and the physical component score and mental component score summary scores*
- *DTSQs: individual items and treatment satisfaction score (6 of the 8 items summed)*

The PRO endpoints will be ~~evaluated using the primary analysis for the primary estimand and using the primary analysis for the secondary estimand~~ based on FAS*, extension phase (sustainability) FAS and the extension phase (switch) FAS,* using the on-treatment without rescue medication*,*

*on-treatment without rescue medication extension phase (sustainability) and on-treatment without rescue medication extension phase (switch) observation* period*s, respectively*.

***Main and extension phase (switch)***

All of the above individual items and scores will be analysed separately as the other supportive continuous efficacy endpoints with the associated baseline response as a covariate.

***Extension phase (sustainability)***

*The endpoints will be summarised descriptively by visit.*

### 2.32 Section 18.1.1 Risks and precautions

**Gastrointestinal adverse events**

Consistent with findings with other GLP-1 RAs, the most frequently reported AEs in clinical trials with oral semaglutide have been gastrointestinal disorders (nausea, vomiting, diarrhoea, dyspepsia and constipation). Clinical trials have indicated that a low starting dose and gradual dose-escalation mitigates the risk of gastrointestinal AEs. Consequently, a low starting dose and dose-adjustment every 8 weeks according to $HbA_{1c}$ and tolerability (nausea/vomiting) have been implemented in this trial. *This is also applicable for subjects switching from sitagliptin to oral semaglutide in the extension phase to mitigate possible gastrointestinal AEs related to oral semaglutide.*

### 2.33 Section 18.1.2 Benefits

In this trial, subjects will be randomised to~~ one of two treatment arms involving~~ a treatment regimen anticipated to be more efficacious than the treatment they receive at the time of entry into the trial.

### 2.34 Section 27 References

1. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practise E6*(R2), Step 4. 09 Nov 2016.*~~(R1), Step 4. 10 June 1996.~~
24. Novo Nordisk A/S. Investigator's Brochure for oral semaglutide (NN9924), *edition 8 or any updates hereof. 2017*.~~ Edition 6 or any updates hereof. 2015.~~
45. *Ahrén B, Comas LM, Kumar H, Sargin M, Derving Karsbøl J, Jacobsen SH, et al. Efficacy and Safety of Once-weekly Semaglutide vs Sitagliptin as add-on to Metformin and/or Thiazolidinediones After 56 Weeks in Subjects With Type 2 Diabetes (SUSTAIN 2). European Association for the Study of Diabetes, 52nd meeting, ePoster #767 2016.*

# 3 Changes in Appendices

## 3.1 Appendix B, Section 1.8.1 Assessments in case of suspicion of hypersensitivity reaction

To assist in the diagnostic evaluation it is recommended to draw a blood sample for measurement of tryptase (total and/or mature tryptase, local assessment) within 3 hours of onset of the hypersensitivity reaction, and if this is achieved, a tryptase sample should also be drawn *five weeks after the event* ~~at V11A~~.

Furthermore, a blood sample for assessment of IgE anti-semaglutide antibodies and anti-semaglutide antibodies should be drawn as soon as possible after the event and *again five weeks after the event* ~~at V11A~~ and sent to central laboratory.

# 4 Changes in protocol Attachments

## 4.1 Attachment I – Global list of key staff and relevant departments and suppliers of clinical relevance

| | | |
|---|---|---|
| Sponsor's global medical expert: | Name:<br>Title:<br>Address:<br><br>Tel:<br>E-mail: | [redacted] |
| ~~International Trial Manager:~~ | ~~Name:~~<br>~~Address:~~<br><br>~~Tel:~~<br>~~E-mail:~~ | [redacted] |