Cover Page for Protocol

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Sponsor trial ID:	NN9924-4223
Official title of study:	PIONEER 2 – vs. SGLT-2 Inhibitor A 52-week, randomised, open label, active-controlled trial to investigate the efficacy and safety of oral semaglutide versus empagliflozin in subjects with type 2 diabetes mellitus inadequately controlled on metformin
Document date:	02 October 2018

16.1.1 Protocol and protocol amendments

List of contents

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

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Protocol

Trial ID: NN9924-4223

PIONEER 2 – vs. SGLT-2 Inhibitor

Efficacy and Safety of Oral Semaglutide versus Empagliflozin in Subjects with Type 2 Diabetes Mellitus

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

Trial phase: 3a

Protocol originator

[redacted], [redacted]
[redacted]

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BG	blood glucose
BMI	body mass index
CLAE	clinical laboratory adverse event
CoEQ	control of eating questionnaire
CK	creatine kinase
CRF	case report form
CTR	clinical trial report
DPP-4	dipeptidyl peptidase-4
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
EAC	event adjudication committee
EOT	end-of-treatment
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
HOMA-B	homeostatic model assessment index of beta-cell function
HOMA-IR	homeostatic model assessment index of insulin resistance
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IRB	institutional review board
IWRS	interactive web response system
LDL	low density lipoprotein
LLoQ	lower limit of quantification
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
NSTEMI	non-ST-elevation acute myocardial infarction
NYHA	New York Heart Association
OAD	oral antidiabetic drug
PG	plasma glucose
PK	pharmacokinetics
PP	per protocol
PRO	patient reported outcome
SAE	serious adverse event

SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous(ly)
SGLT-2	sodium-glucose co-transporter-2
SIF	safety information form
SMPG	self-measured plasma glucose
SmPC	summary of product characteristics
SNAC	sodium N-[8-(2-hydroxybenzoyl)amino]caprylate
STEMI	ST-elevation acute myocardial infarction
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse events
TIA	transient ischaemic attack
TMM	Trial Materials Manual
UNL	Upper Normal Limit
UTN	Universal Trial Number
VLDL	very low density lipoprotein

1 Summary

Objectives and endpoints:

Primary objective

To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, on glycaemic control in subjects with type 2 diabetes mellitus.

Secondary objectives

To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, on body weight in subjects with type 2 diabetes mellitus.

To compare the safety and tolerability of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, in subjects with type 2 diabetes mellitus.

Primary endpoint

Change from baseline to week 26 in glycosylated haemoglobin (HbA_{1c})

Key secondary endpoints

Change from baseline to week 52 in HbA_{1c}

Change from baseline to week 26 and week 52 in:
- Body weight (kg)
- Fasting plasma glucose

If a subject after week 26 and week 52 achieves (yes/no):
- HbA_{1c} < 7.0 % (53 mmol/mol) American Diabetes Association target

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, multicentre, multinational trial with 2 arms comparing the efficacy and safety of oral semaglutide with empagliflozin in subjects with type 2 diabetes mellitus inadequately controlled on metformin.

Subjects will be randomised 1:1 to receive one of the following treatments:

- 14 mg oral semaglutide once-daily
- 25 mg empagliflozin once-daily

The total trial duration for the individual subject will be approximately 59 weeks. The trial includes a 2-week screening period, followed by a 52-week randomised treatment period and a follow-up period of 5 weeks.

Trial population:

Number of subjects planned to be randomised: 816 subjects.

Inclusion criteria

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.
3. Diagnosed with type 2 diabetes mellitus ≥ 90 days prior to day of screening.
4. HbA_{1c} of 7.0-10.5 % (53-91 mmol/mol) (both inclusive).
5. Stable daily dose of metformin (≥ 1500 mg or maximum tolerated dose as documented in the subject medical record) ≥ 90 days prior to the day of screening.

Key exclusion criteria

1. 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.
2. Any disorder, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
3. Family or personal history of Multiple Endocrine Neoplasia Type 2 or Medullary Thyroid Carcinoma.
4. History of pancreatitis (acute or chronic).
5. 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).
6. 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.
7. Subjects presently classified as being in New York Heart Association Class IV.
8. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
9. Subjects with ALT > 2.5 x upper normal limit.

10. Renal impairment defined as Estimated Glomerular Filtration Rate < 60 mL/min/1.73 m^2 as per Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI).
11. 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.
12. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomisation.
13. History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and carcinoma *in situ*).
14. History of diabetic ketoacidosis.

Key assessments:

Efficacy

- HbA_{1c}
- Fasting plasma glucose
- Body weight
- PK sampling

Safety

- Adverse events
- Hypoglycaemic episodes

Trial product:

Investigational medicinal products:

- Test product: semaglutide 3 mg, 7 mg and 14 mg tablets
- Reference therapy: empagliflozin (Jardiance®) 10 mg and 25 mg tablets

2 Flow chart

Trial Periods	Screening[a]	Randomi-sation	Treatment									End-of-treatment (EoT)	Follow-up[b]	EoT premature discontinuation[c]	Follow-up premature discontinuation[c]
Visit (V), Phone (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V12A	V13A
Timing of visit (Weeks)	Up to -2 weeks	0	2	4	8	14	20	26	32	38	45	52	57	Day of discontinuation of trial product	5 weeks after discontinuation of trial product
(Days)			±3	±3	±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	x	x
Demography	x														
Tobacco use	x														
Concomitant illness and medical history	x														
Diagnosis of diabetes/ diabetes complications	x														
History of cardiovascular disease	x														
History of gallbladder disease	x														
History of gastrointestinal disease	x														

Trial Periods	Screening[a]	Randomi-sation	Treatment									End-of-treatment (EoT)	Follow-up[b]	EoT premature discontinuation[c]	Follow-up premature discontinuation[c]
Visit (V), Phone (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V12A	V13A
Timing of visit (Weeks)	Up to -2 weeks	0	2	4	8	14	20	26	32	38	45	52	57	Day of discontinuation of trial product	5 weeks after discontinuation of trial product
(Days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	+3
Randomisation		x													
Criteria for premature discontinuation of trial product			x	x	x	x	x	x	x	x	x				
EFFICACY															
HbA_{1c}	x	x		x	x	x	x	x	x	x	x	x		x	
Fasting plasma glucose		x		x	x	x	x	x		x		x		x	
Fasting insulin and proinsulin		x						x				x		x	
Fasting C-peptide		x						x				x		x	
Fasting glucagon		x						x				x		x	
7-point profile		x						x				x		x	
Lipids		x			x			x				x		x	
CRP		x						x				x		x	
Height		x													
Body weight		x		x	x	x	x	x	x	x	x	x		x	
Waist circumference		x				x		x		x		x		x	
PRO questionnaires		x						x				x		x	
Semaglutide PK sampling[d]				x				x				x			

Trial Periods	Screening[a]	Randomi-sation	Treatment									End-of-treatment (EoT)	Follow-up[b]	EoT premature discontinuation[c]	Follow-up premature discontinuation[c]
Visit (V), Phone (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V12A	V13A
Timing of visit (Weeks)	Up to -2 weeks	0	2	4	8	14	20	26	32	38	45	52	57	Day of discontinuation of trial product	5 weeks after discontinuation of trial product
(Days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	+3
SNAC PK sampling[e]				x				x				x			
SAFETY															
Eye examination[f]	x														
Physical examination	x											x		x	
ECG		x						x				x	x	x	x
Vital signs		x		x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test[g]	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Calcitonin		x				x		x		x		x	x	x	x
Biochemistry[h]	x	x		x	x	x		x		x		x	x	x	x
Lactate[i]				x				x				x			
Haematology		x		x	x	x		x		x		x	x	x	x
Antibodies[j]		x		x	x	x		x		x		x	x	x	x
Adverse events[k]		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
Technical complaints			x	x	x	x	x	x	x	x	x	x		x	
TRIAL MATERIAL															
IV/IWRS call	x	x		x	x	x	x	x	x	x	x	x		x	
Drug accountability		x		x	x	x	x	x	x	x	x	x		x	
Dispensing visit		x		x	x	x	x	x	x	x	x				

Trial Periods	Screening[a]	Randomi-sation	Treatment									End-of-treatment (EoT)	Follow-up[b]	EoT premature discontinuation[c]	Follow-up premature discontinuation[c]
Visit (V), Phone (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V12A	V13A
Timing of visit (Weeks)	Up to -2 weeks	0	2	4	8	14	20	26	32	38	45	52	57	Day of discontinuation of trial product	5 weeks after discontinuation of trial product
(Days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	+3
REMINDERS															
Training in dosing instructions	x	x	x	x	x	x	x	x	x	x	x				
Attend visit fasting[l]		x		x	x	x	x	x		x		x		x	
Handout and instruct in BG meter use	x														
Handout ID card	x														
Dispense and/ or collect diary	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 assessment must not exceed 2 weeks prior to randomisation (V2).
x[b]	Subjects, who have discontinued trial product prematurely, are not required to attend V13 (Follow-up).
x[c]	V12A and V13A are only applicable for subjects who have discontinued trial product prematurely.
x[d]	Sample should be taken for all subjects 25 (+/- 5) minutes post dosing. No PK sampling should be done for visits occurring after V13A (subjects who have discontinued trial product prematurely).
x[e]	Samples should be taken for all subjects 25 (+/- 5) minutes and 40 (+/- 5) minutes post dosing. No PK sampling should be done for visits occurring after V13A (subjects who have discontinued trial product prematurely).
x[f]	Dilated fundoscopy/fundus photography performed within 90 days prior to randomisation is acceptable if results are available for evaluation at V2, unless worsening of visual function since last examination.
x[g]	For women of child-bearing potential: Urine pregnancy test should also be performed at any time during the trial if a menstrual period is missed, and/or according to local regulations/law.
x[h]	At V1, only ALT, creatinine and eGFR will be assessed as part of Biochemistry.
x[i]	Samples should be taken for all subjects pre-dose and 25 (+/- 5) and 40 (+/- 5) minutes post-dosing.
x[j]	Samples should be taken for all subjects. At randomisation, the antibody sampling must be done pre-dose. No antibody sampling should be done for visits occurring after V13A (subjects who have discontinued trial product prematurely).
x[k]	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[l]	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

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 whereto 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 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.

[redacted] 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 (NN9924-4233 and this trial) 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 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 (t½) 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 subcutaneous (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 adverse events (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 Empagliflozin

The selected active comparator in this trial is empagliflozin, a selective inhibitor of the sodium-glucose co-transporter-2 (SGLT-2), the predominant transporter responsible for glucose reabsorption from the glomerular filtrate back into the circulation. Inhibition of SGLT-2 reduces BG levels by blocking renal glucose reabsorption, thereby increasing urinary glucose excretion. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on the BG concentration and renal function. Empagliflozin was developed by Boehringer Ingelheim and Eli Lilly and approved in 2014 under the trade name Jardiance® to improve glycaemic control in adults with T2DM.

For further details, please see the current approved label for Jardiance®[25, 26]

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

3.2 Rationale for the trial

Many patients with T2DM are not in glycaemic control with the currently marketed oral anti-diabetic drugs (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 purpose of the present trial is to compare oral semaglutide with empagliflozin, an established OAD within the drug class of SGLT-2 inhibitors, in terms of glycaemic control, weight loss and other efficacy and safety parameters in subjects with T2DM inadequately controlled on metformin.

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary objective

To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, on glycaemic control in subjects with type 2 diabetes mellitus.

4.1.2 Secondary objectives

To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, on body weight in subjects with type 2 diabetes mellitus.

To compare the safety and tolerability of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, in subjects with type 2 diabetes mellitus.

4.2 Endpoints

The confirmatory endpoints are evaluated as a change from baseline to week 26. There will not be an interim analysis at week 26, the evaluation will take place after completion of the trial.

4.2.1 Primary endpoint

Change from baseline to week 26 in HbA_{1c}

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

Change from baseline to week 26 in body weight (kg)

4.2.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

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

Change from baseline to week 52 in:

- HbA_{1c}*
- Body weight (kg)*

Change from baseline to week 26 and week 52 in:

- Fasting plasma glucose (FPG)*
- Fasting C-peptide
- Fasting insulin and proinsulin
- Fasting glucagon
- Insulin resistance (homeostatic model assessment index of insulin resistance [HOMA-IR]) and beta-cell function (homeostatic model assessment index of beta-cell function [HOMA-B])
- 7-point self-measured plasma glucose (SMPG) profile
  - Mean 7 point profile
  - Mean postprandial increment (over all meals)
- Body weight (%)
- Body mass index (BMI)
- Waist circumference
- Fasting lipid profile (total cholesterol, low-density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, free fatty acids)
- C-reactive protein (CRP)
- Patient reported outcomes (PROs)
  - Short Form (SF)-36v2TM (acute version) health survey
  - Control of Eating questionnaire (CoEQ)

If a subject after week 26 and week 52 achieves (yes/no):

- $HbA_{1c} < 7.0$ % (53 mmol/mol) American Diabetes Association (ADA) target*
- $HbA_{1c} \leq 6.5$ % (48 mmol/mol) American Association of Clinical Endocrinologists (AACE) target
- HbA_{1c} reduction ≥ 1 % (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 ≥ 1.0 % (10.9 mmol/mol) and weight loss ≥ 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 blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks*
- Treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks (yes/no)

Change from baseline to week 26 and week 52 in:

- Haematology
- Biochemistry
- Calcitonin
- Pulse
- Systolic blood pressure
- Diastolic blood pressure
- Electrocardiogram (ECG) category
- Physical examination (only week 52)

Change from pre-dose to post-dose (25 and 40 min) at week 4, week 26 and week 52 in:

- Lactate

Any occurrence of anti-semaglutide antibodies (yes/no) up to approximately 57 weeks:

- Anti-semaglutide binding antibodies
- Anti-semaglutide neutralising antibodies
- Anti-semaglutide binding antibodies cross reacting with native GLP-1
- Anti-semaglutide neutralising antibodies cross reacting with native GLP-1

Anti-semaglutide binding antibodies up to approximately 57 weeks:

- Anti-semaglutide binding antibody levels

Supportive secondary pharmacokinetic endpoints

- SNAC plasma concentrations
- Semaglutide plasma concentrations for population PK analyses

5 Trial design

5.1 Type of trial

This is a 52-week, randomised, open-label, active-controlled, parallel-group, multicentre, multinational trial with 2 arms comparing the efficacy and safety of oral semaglutide with empagliflozin in subjects with T2DM inadequately controlled on metformin.

Subjects will be randomised 1:1 to receive one of the following treatments:

- 14 mg oral semaglutide once-daily
- 25 mg empagliflozin once-daily

The total trial duration for the individual subject will be approximately 59 weeks. The trial includes a 2-week screening period, followed by a 52-week randomised treatment period and a follow-up period of 5 weeks.

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

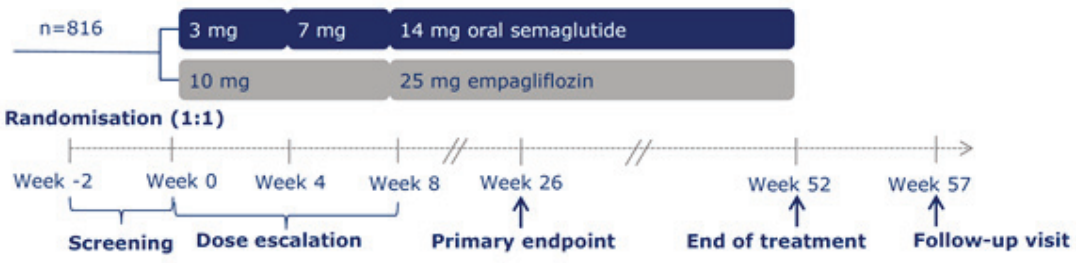


Figure 5–1 Trial design

5.2 Rationale for trial design

The trial has been designed as a parallel-group, 2-armed trial to secure a direct comparison between oral semaglutide and the active comparator empagliflozin. Subjects will be randomised 1:1 between the two treatment arms. Manufacture of placebo tablets resembling empagliflozin was not feasible. Therefore, the trial is open-labelled.

The treatment duration will be 52 weeks to ensure adequate time to compare the full effect and sustainability of both treatments on glycaemic control and body weight.

The confirmatory endpoints will be defined after 26 weeks of treatment where the extent of missing data, use of rescue medication or premature treatment discontinuation is expected to be limited. This allows for a robust estimation of the effect of oral semaglutide on HbA_{1c} and body weight that is considered adequate and meaningful. There will not be an interim analysis at week 26. The subjects will sign up for 52 weeks when they sign the informed consent.

The follow-up period is 5 weeks to allow for wash-out of semaglutide and to prevent interference in the antibody assay.

5.3 Treatment of subjects

Treatment of subjects is summarised in Table 5–1

Table 5–1 Treatment overview

Trial periods		Screening	Treatment period 1	Treatment period 2	Treatment period 3
First visit in each period		V1	V2	V4	V5
Duration of each period		2 weeks	4 weeks	4 weeks	44 weeks
Treatment arm	N				
Oral semaglutide	408	Screening	3 mg	7 mg	14 mg
Empagliflozin	408	Screening	10 mg	10 mg	25 mg

Oral semaglutide treatment

Oral semaglutide is a long-acting GLP-1 RA to be administered orally once-daily. Subjects randomised to oral semaglutide will initiate treatment with 3 mg once-daily and follow a fixed 4-week dose escalation regimen until reaching the maximum treatment dose of 14 mg once-daily, as illustrated in Table 5–1. To mitigate the risk of gastrointestinal AEs, it is important to follow the fixed 4-week dose escalation intervals. The dose must not be changed during the course of the trial once the 14 mg dose of oral semaglutide has been reached.

Empagliflozin treatment

Subjects should be considered suitable for treatment with empagliflozin and the use of empagliflozin should be in accordance with the current, approved label[25]. Renal function and signs and symptoms of volume depletion should be monitored during therapy.

Treatment with empagliflozin will be initiated at 10 mg once-daily. The dose will be escalated after 8 weeks to the recommended maximum dose of 25 mg in subjects tolerating empagliflozin who have an estimated glomerular filtration rate (eGFR) $\geq$ 60 mL/min/1.73 m^2. However, in subjects whose eGFR falls persistently < 60 mL/min/1.73 m^2 (confirmed by retest at central laboratory), the dose of empagliflozin should be reduced to 10 mg once-daily. The dose can be re-escalated to 25 mg once-daily in case the renal function improves (eGFR $\geq$ 60 mL/min/1.73 m^2) during the trial. If

the eGFR falls persistently < 45 mL/min/1.73 m^2 (confirmed by re-test at central laboratory), treatment with empagliflozin should be discontinued (see Section 6.5).

5.3.1 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 tablets 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 (Table 9–2). Furthermore, other oral medication can be taken 30 minutes after administration of trial product.

Empagliflozin

Tablets should be taken once-daily in the morning. The tablet should be swallowed whole with water and it can be taken with or without food.

5.3.2 Background medication

After signing the informed consent, subjects must continue their anti-diabetic background medication (metformin) 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) or a safety concern related to the background medication arises.

In addition, all background medication:

- is considered to be non-investigational medicinal product
- 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

5.4 Treatment after discontinuation of trial product

When discontinuing trial product, 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*). After discontinuation of oral semaglutide, GLP-1 RAs are not allowed before completion of the follow-up visit 5 weeks after the last date on trial product (to avoid interference with the antibody assay for oral semaglutide). Throughout the protocol, last date on trial product is defined as date of the subject's last dosage of trial product.

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

For oral semaglutide, the three dose levels (3, 7 and 14 mg), treatment initiation with the lowest dose and the 4-week dose escalation steps have been chosen based on data from the phase 2 dose-finding trial. This regimen is expected to have the optimal benefit-risk profile for further development for treatment of T2DM in the PIONEER programme.

Empagliflozin has been chosen as active comparator since it is an established OAD within the drug class of SGLT-2 inhibitors and treatment will be initiated with 10 mg in accordance with the current, approved label.

Both oral semaglutide and empagliflozin will be dose escalated to their highest respective maintenance doses to investigate and compare the maximum efficacy of the two drugs when added to metformin.

The duration of randomised treatments is 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: 1360

Number of subjects planned to be randomised: 816

Number of subjects expected to complete the trial on or off trial product: 735

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.
3. Diagnosed with type 2 diabetes mellitus ≥ 90 days prior to day of screening.
4. HbA_{1c} of 7.0-10.5 % (53-91 mmol/mol) (both inclusive).
5. Stable daily dose of metformin (≥ 1500 mg or maximum tolerated dose as documented in the subject medical record) ≥ 90 days prior to the day of screening.

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 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 Greece only: adequate contraceptive measures are defined as combined hormonal contraception (containing oestrogen and progesterone), which suppress ovulation (oral, intravaginal, percutaneous), progesterone-only hormonal contraception which suppress ovulation (oral, injectable, implantable), intrauterine device, hormone-releasing intrauterine system, bilateral tubal occlusion, partner with vasectomy, sexual abstinence.
4. Receipt of any investigational medicinal product within 90 days before screening.
   For Brazil only: Participation in other trials within one year prior to screening visit (V1) 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.
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 hyperglycemia should be offered treatment intensification. To allow time for dose escalation to maximum dose and to observe the expected effect of treatment on glycaemic parameters, rescue criteria will be applied from week 8 and onwards. If any of the FPG values (including fasting SMPG) exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified, a confirmatory FPG (at the central laboratory) should be obtained by calling the subject for a re-test. If the confirmatory FPG also exceeds the value described below, the subject should be offered rescue medication (i.e. intensification of anti-diabetic background medication and/or initiation of new anti-diabetic medication):

- 14.4 mmol/L (260 mg/dL) from week 8 to the end of week 13
- 13.3 mmol/L (240 mg/dL) from week 14 to the end of week 25
- 11.1 mmol/L (200 mg/dL) from week 26 to the end of treatment

In addition, subject should be offered rescue medication if:

- HbA_{1c} (at central laboratory) >8.5% (69.4 mmol/mol) from week 26 to end of treatment.

It is important for trial integrity that only subjects actually needing treatment intensification (as defined above) are started on rescue medication. Subjects that are started on rescue medication should continue to follow the protocol-specified visit schedule. 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[27] and[28] (excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues in the oral semaglutide arm and excluding SGLT-2 inhibitors in the empagliflozin arm). Rescue medication and any changes hereto should be captured on the concomitant medication form in the electronic case report form (eCRF), see Section 8.2.4.

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
- 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

The trial population will include subjects with T2DM treated with stable doses of metformin for at least 90 days prior to screening as changes in the background medication shortly before trial participation may potentially impact the data interpretation. The HbA_{1c} limits of 7.0-10.5 % (53-91 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 impairment will be excluded due to restrictions in the labels of empagliflozin and metformin. As SGLT-2 inhibitors have been associated with euglycaemic diabetic ketoacidosis, subjects with a history of diabetic ketoacidosis will also be excluded from this trial. 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: 23 weeks

Planned FSFV: 10 Aug 2016

Planned LSLV: 13 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[29] it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[30], the Food and Drug Administration Amendment Act (FDAAA)[31], European Commission Requirements[32, 33] 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 flowchart (Section 2) for number and timing of visits and specific assessments to be performed.

Each subject will attend 12 site visits and 1 phone visit. It is the responsibility of the investigator to ensure that all site visits 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.

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 several 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. Note that for all subjects, the required fasting period is longer at visits with PK sampling and lactate assessments (see Section 8.6).

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 the fasting blood samples done within the visit window for the relevant visit.

Fasting samples:

- FPG
- fasting C-peptide
- fasting insulin and proinsulin
- fasting glucagon
- fasting lipid profile (total cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol, triglycerides, free fatty acids)
- lactate
- SNAC PK
- semaglutide PK

8.1.3 Randomisation and trial product administration

Eligible subjects will be randomised into one of two treatment arms. The randomisation session must be performed 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 product (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, please 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 12) and Follow-up (visit 13)

Subjects, who stay on trial product throughout the trial, must attend the end-of-treatment visit (V12) 52 weeks after randomisation and the follow-up visit (V13) 5 weeks after the last date on trial product (+3 days visit window). A completion call must be performed in the IWRS after completion of V12 (see Section 10).

In case the subject cannot be reached (by clinic visit or phone contact) at the scheduled V13, 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 (V12A and V13A)

Subjects, who discontinue trial product prematurely, should attend V12A scheduled to take place on the day of discontinuation of trial product (+ 3 days visit window). V13A 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 V12A (see Section 10).

If premature discontinuation of trial product is decided during a scheduled visit, the visit will be converted into a V12A and trial procedures must be performed accordingly.

Subjects should continue with the originally scheduled site contacts after V13A and up to and including V12. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after V13A. 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 V8 (week 26) and V12 (end-of-treatment) as these visits 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 V12, should not be considered withdrawn from the trial. In case the subject cannot be reached (by clinic visit or phone contact) at the scheduled V12, 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 (for withdrawal procedures, see Section 8.1.6).

8.1.6 Withdrawals

If a subject considers withdrawing from the trial, the investigator must aim to undertake procedures for V12A as soon as possible and V13A 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 and fundoscopy/fundus photography 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 8.2.3).

8.2.3 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 incl. 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 in source documents such as subject's medical record. If a subject is not from the investigator's 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.

8.2.4 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
- only applicable for anti-diabetic medication; start date of current dose and total daily dose

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.

8.2.5 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 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 Greece only: Adequate contraceptive measures are defined as combined hormonal contraception (containing oestrogen and progesterone), which suppress ovulation (oral, intravaginal, percutaneous), progesterone-only hormonal contraception which suppress ovulation (oral, injectable, implantable), intrauterine device, hormone-releasing intrauterine system, bilateral tubal occlusion, partner with vasectomy, sexual abstinence.

8.2.6 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 laboratory process see Section 8.5.

Blood samples will be drawn according to 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 (see Section 8.3.1.1)
- Fasting insulin and proinsulin
- Fasting glucagon
- Fasting C-peptide

Fasting lipid profile:
- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- VLDL-cholesterol
- Free fatty acids
- Triglycerides

Other parameters:
- CRP

8.3.1.1 Fasting plasma glucose

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).

8.3.2 Self-measured plasma glucose

At V1, 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 SMPG measurement.

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.

The subject will be instructed to perform a 7-point SMPG profile three times during the trial period (see Section 2) using the BG meter provided for the trial. The 7-point SMPG profile should be performed on a day where the subject does not anticipate unusual strenuous exercise. The 7-point SMPG profile should preferably be taken within a week prior to the visit.

The record of each SMPG measurement should include the following seven time points:

- before breakfast
- 90 minutes after start of breakfast
- before lunch
- 90 minutes after start of lunch
- before dinner
- 90 minutes after start of dinner
- at bedtime

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 inches 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 Patient reported outcomes questionnaires

PRO will be assessed using the questionnaires:

- SF-36v2™ (acute version) health survey[34-36]
- CoEQ[37-40]

The SF-36v2™ questionnaire is a commonly used instrument to evaluate PROs, also in the T2DM area. The CoEQ has not been developed to be used in clinical trials. However, it has previously been included in clinical trials on an item per item basis, among others in a T2DM population.

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 AEs 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-36 acute version

SF-36v2™ acute version 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™ contains 36 items.

Control of Eating Questionnaire

The CoEQ has its origins in the Food Craving Record. It comprises 21 items designed to assess the intensity and type of food cravings, as well as subjective sensations of appetite and mood. For this study a version with only 19 items will be included.

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 involved
- Classification of medication error
- 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 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 aminotransferase

In case any of these events fulfil the criteria for a SAE, 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 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

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

If dilated fundoscopy/fundus photography 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 dilated fundoscopy/fundus photography 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 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 an AE or a 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 (see Section 12.7.2).

8.4.6 Laboratory assessments for safety

For overall laboratory process see Section 8.5.

Blood samples will be drawn according to 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:

- ALT
- Albumin
- Alkaline phosphatase
- Amylase
- AST
- Bilirubin, total
- Calcium, total
- Creatinine
- eGFR per CKD-EPI[41]
- CK
- Lipase
- Potassium
- Sodium
- Urea
- Lactate (see Section 8.6.1)

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.

Other parameters:

- Anti-semaglutide antibodies (see Section 8.4.8)

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 8.2.5.

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 Anti-semaglutide antibodies

Blood samples will be drawn for measurement of antibodies against semaglutide at selected visits (see Section 2). Positive anti-semaglutide binding antibody samples will be further characterised for cross reactivity to native GLP-1. Samples which are positive for anti-semaglutide binding antibodies will be further characterised for *in vitro* neutralising effect towards semaglutide. In addition, samples which are positive for antibodies cross-reacting with native GLP-1 will be further analysed for *in vitro* neutralising effect towards native GLP-1.

Furthermore, samples drawn at randomisation may be used for calculations of the neutralising effect in the *in vitro* neutralising antibody assays. The *in vitro* neutralising assays will be performed by Novo Nordisk.

At randomisation, the antibody sampling must be done pre-dose.

Antibody samples will be stored as described in Section 24.2.

8.4.9 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[42].

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 also 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[42].

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[43] (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?

The Investigator must review the diary for low SMPG values not reported as hypoglycaemic episodes (see Section 2 for relevant visits). The subject must be questioned whether any of the low values were severe i.e. whether the subject was able to self-treat or not. If the subject was not able to self-treat, it has to be reported as a severe hypoglycaemic episode on a hypoglycaemic episode form.

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data[44, 45].

The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies low SMPG values not reported as hypoglycaemic episodes.

If the hypoglycaemic episode fulfils the criteria for an SAE, then an AE form and a safety information form (SIF) must also be filled in, see Section 12.

8.5 Laboratory assessments

The laboratory analyses will mainly be performed by a central laboratory. Anti-semaglutide antibodies, *in vitro* neutralising effect, IgE anti-semaglutide antibodies and PK samples will be analysed by a special laboratory and Novo Nordisk A/S (see Sections 8.4.8 and 8.6.2). For some of the analyses related to suspicion of acute pancreatitis and hypersensitivity reactions, 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 and special 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, anti-semaglutide antibody and semaglutide plasma concentration results will not be available to the investigator during the trial. These results will be provided to the investigator upon request after the completion of the clinical trial report (CTR).

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 8.2.4 and Section 12.

For Brazil only: all laboratory samples will be communicated to the investigators.

Laboratory samples will be destroyed at the latest at the completion of the CTR, or according to local regulations, except samples obtained for antibody analysis.

8.6 Other assessments

8.6.1 Lactate

Assessment of lactate levels will be included in this trial as a biomarker for impaired cellular respiration (see Section 3.1.4.2). At selected visits (see Section 2), three samples should be drawn for lactate assessment at the following time points in relation to dosing of trial product:

- pre-dose*
- 25 (+/- 5) minutes post dosing
- 40 (+/- 5) minutes post dosing

*Trial product can be taken from the dosepack dispensed at the previous visit or at the current visit.

Correct pre-analytical handling of these samples is extremely important to ensure valid results.

The subject must be fasting for the assessment and remain fasting until the last sample has been taken, that is, at least 40 minutes after dosing. Also, the subject should have rested for at least 30 minutes in a sitting position prior to sampling. During sampling, use of tourniquet should be avoided (if possible). If blood pressure measurement has been performed prior to sampling, blood should preferably be drawn from the opposite arm.

The blood samples must be kept on ice and centrifuged within 15 minutes of collection. Further handling and transportation of the samples are described in the laboratory manual supplied by the central laboratory (see attachment I).

8.6.2 Pharmacokinetics

8.6.2.1 Semaglutide and SNAC plasma concentrations

Blood samples will be drawn for assessment of plasma concentration of semaglutide and SNAC at selected visits (see Section 2). The semaglutide concentrations will be used for population PK analysis.

At each of these visits, samples for semaglutide analysis will be drawn 25 minutes post dosing (+/-5 minutes), and samples for SNAC analysis will be drawn 25 and 40 min post dosing (+/-5 minutes).

The date and time of the latest trial product administration prior to the PK sampling must be recorded and transcribed into the eCRF.

The exact date and time for sampling the blood for PK analysis must be recorded on the lab requisition form.

Blood samples for PK assessments must be collected, handled and shipped according to the description in the laboratory manual supplied by the central laboratory (see attachment I).

The PK responsible laboratory will be provided with the randomisation list and only samples from subjects treated with oral semaglutide will be analysed for semaglutide and SNAC plasma concentrations. However, at V4, 10% of the samples from subjects receiving empagliflozin will also be analysed for semaglutide and SNAC plasma concentrations for compliance evaluation. If any of the samples show values higher than the lower limit of quantification (LLoQ), the full range of collected samples from that subject will be analysed.

Semaglutide PK and SNAK PK samples will be stored at the specialised laboratory until final CTR in case Novo Nordisk requests further analysis of the PK samples.

8.6.3 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
- SMPG 7-point profile

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 record.

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 Investigational medicinal products

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Semaglutide 3 mg tablet	3 mg	Tablet	Oral	Blister card[a]
Semaglutide 7 mg tablet	7 mg			
Semaglutide 14 mg tablet	14 mg			
Empagliflozin 10 mg tablet	10 mg	Tablet	Oral	Blister card[b]
Empagliflozin 25 mg tablet	25 mg			

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

[b]One dosepack contains one blister card with 10 tablets

Metformin and rescue medication are considered non-investigational medicinal products and will not be supplied by Novo Nordisk. However, metformin 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[46], local regulations and trial requirements.

Each trial site will be supplied with sufficient trial product 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 for investigational medicinal products

Trial product	Storage conditions (not-in-use)	In-use conditions
Semaglutide 3 mg tablet	Do not store above 30ºC (86ºF) Do not refrigerate Do not freeze Store in the original package	Take the tablet immediately after dispensation from blister card Take the tablets whole: Do not break or chew
Semaglutide 7 mg tablet		
Semaglutide 14 mg tablet		
Empagliflozin 10 mg tablet	EU: store below 25°C US: store between 59°F – 77°F Do not refrigerate Do not freeze Store in the original package	Take the tablet immediately after dispensation from blister card
Empagliflozin 25 mg tablet		

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 product including expired or damaged products must be accounted for at the latest at closure of 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 A/S 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 carried out for all subjects using the IWRS.

At the randomisation visit (V2), subjects meeting all eligibility criteria will be randomised to one of two treatment arms as described in Section 5.1.

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 8.4.9.

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 criteria 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 AEs 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 > 10x UNL	Yes	No
Hepatic event defined as: ALT or 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.	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 Sections 8.4.1.2, 12.2 and 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 (V13) for subjects on trial product or until the end of trial (V12 or V13A, 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 (SIF) must be completed in addition to the AE form. A SIF is a form to collect supplementary clinical information. If several symptoms or diagnoses occur as part of the same clinical picture, one SIF 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 SIF **within 5 calendar** days of the investigator's first knowledge of the SAE.

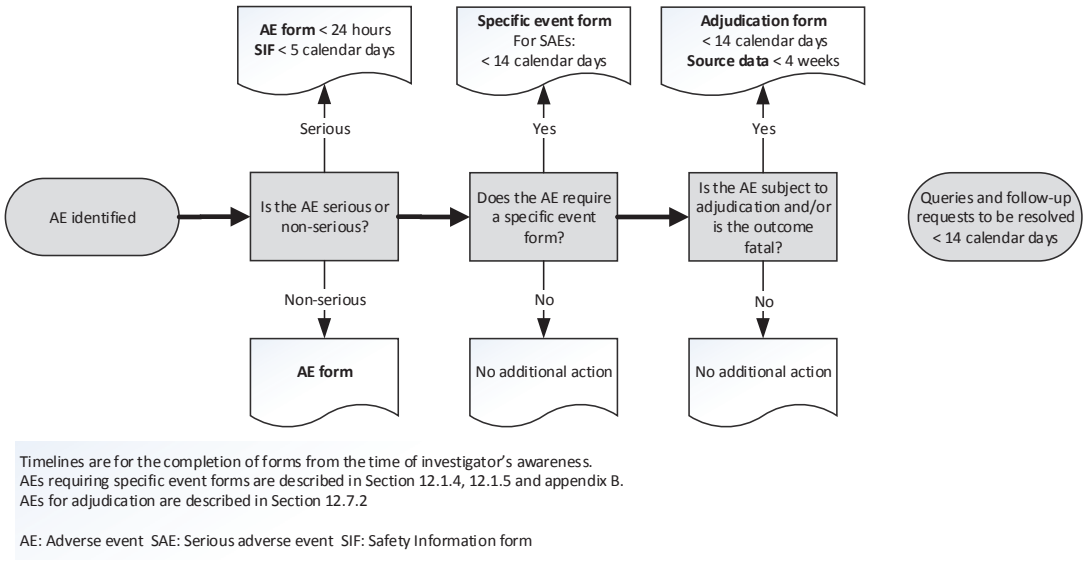
  Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

  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: adjudication form should be completed within 14 calendar days of the 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.



Timelines are for the completion of forms from the time of investigator's awareness.
AEs requiring specific event forms are described in Section 12.1.4, 12.1.5 and appendix B.
AEs for adjudication are described in Section 12.7.2

AE: Adverse event SAE: Serious adverse event SIF: Safety Information form

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)[24] and Jardiance® (empagliflozin) SmPC and prescribing information[25, 26]; 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:
If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the SIF. 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
- empagliflozin 10 mg tablets
- empagliflozin 25 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 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

12.5.1 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), and 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 practise.

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[47].

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) • Non-Cardiovascular death
Acute Coronary Syndrome	Acute Coronary Syndrome conditions include: • ST-elevation acute myocardial infarction (STEMI) • Non-ST elevation acute myocardial infarction (NSTEMI) • Silent MI • Unstable angina pectoris	• Acute MI (STEMI or NSTEMI), silent MI • 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 • Transient ischaemic attack 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 • Haemorrhagic stroke • Undetermined stroke • Transient ischaemic attack
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: • 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 UNL • Characteristic findings of acute pancreatitis on imaging	Acute pancreatitis • Mild • Moderately severe • Severe
Malignant neoplasm	Malignant neoplasms are defined as • 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 Thyroid neoplasms are excluded in this event	• Malignant neoplasm

	category	
Thyroid disease, if malignant thyroid neoplasm or C-cell hyperplasia	Malignant thyroid neoplasms are defined as • 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 • C-cell hyperplasia, defined as hyperplasia of the parafollicular C-cells of the thyroid gland	• Malignant thyroid neoplasm • C-cell hyperplasia
Acute kidney injury	Acute kidney injury[48] is defined as any of the following (not graded): • Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours, or • Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, or • 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 in the eCRF 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 the 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 case report forms (CRF):

- 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
- SIFs
- 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 last subject last visit (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 CTR 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 of the completed diaries and/or PROs must not be removed from the trial site, unless they form part of the eCRF 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.

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 LLoQ will be set to ½LLoQ. Number of values below LLoQ by treatment and visit will be summarised if deemed relevant.

The primary and confirmatory efficacy endpoints will be evaluated at week 26. This approach is expected to result in a lower proportion of missing data, use of rescue medication and premature treatment discontinuation, compared to the expected proportion of missing data, use of rescue medication and premature treatment discontinuation at week 52, and therefore considered a meaningful representation and confirmation of the effect of oral semaglutide.

Results from a statistical analysis will as a minimum be presented by the estimated treatment contrasts for oral semaglutide 14 mg vs. empagliflozin 25 mg 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 at week 26 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 empagliflozin 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 at week 26 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 empagliflozin. It is considered a clinically relevant estimand as it provides information to treating clinicians about the expected glycaemic efficacy of oral semaglutide compared to empagliflozin 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 26

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 10% based on the oral semaglutide phase 2 trial (NN9924-3790). Thus, missing data will 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%) since data collected after discontinuation of trial product or initiation of rescue medication(s) will be set to missing. The 10% of missing data, which is due to discontinuation of trial product or initiation of rescue medication(s), is based on the empagliflozin assessment report[49] and the oral semaglutide phase 2 trial (NN9924-3790) indicates that a low starting dose with gradual dose escalation diminishes gastrointestinal AEs compared with more aggressive dosing regimens. The main reasons for missing data in the two treatment arms are expected to be early treatment discontinuation due to AEs (particular gastrointestinal AEs for the oral semaglutide arm) and initiation of rescue medication. A higher proportion of subjects is expected to discontinue treatment due to AEs in the oral semaglutide arm compared to empagliflozin whereas initiation of rescue medication is expected to be more frequent in the empagliflozin 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 is change from baseline to week 26 in HbA_{1c}. For HbA_{1c}, both non-inferiority and superiority of oral semaglutide versus empagliflozin are planned to be tested. The confirmatory secondary endpoint, change from baseline to week 26 in body weight, is planned to be tested for superiority of oral semaglutide versus empagliflozin.

The sample size calculation is made to ensure a power of at least 90% for testing HbA_{1c} superiority of oral semaglutide versus empagliflozin out of the three pre-specified confirmatory hypotheses shown in Figure 17–1. The closed testing procedure described in Bretz et al 2011[50] is used to control the overall type-I error at a nominal two-sided 5% level.

The statistical testing strategy is based on the principle that glycaemic effect must be established in terms of HbA_{1c} non-inferiority before testing for added benefits in terms of HbA_{1c} superiority and/or body weight superiority.

The sample size is calculated using the calcPower function in the R package, gMCP[51] using 10000 simulations. All of the three pre-specified confirmatory tests are assumed to be independent. Since some of the tests are positively correlated, the assumption of independence is viewed as conservative.

The sample size assumptions for treatment effects (TE), adjusted treatment effects and the standard deviations (SD) are given in Table 17–1. These assumptions are primarily based on the oral semaglutide phase 2 results (NN9924-3790), empagliflozin assessment report[49] and supported by results from the s.c. semaglutide phase 2 trial (NN9535-1821).

To assess the effect of empagliflozin on glycaemic effect, a similar trial (NCT01159600) where empagliflozin was used as add on to metformin was reviewed. Based on this trial, the chosen margin of 0.4 provides assurance that oral semaglutide has a clinically relevant effect greater than zero. With regards to the constancy assumption, controlled clinical trials have consistently established that empagliflozin is an effective anti-diabetic drug. Therefore, lack of trial sensitivity with empagliflozin as comparator is not anticipated to be an issue in this trial.

With regards to preserving an acceptable proportion of the effect of empagliflozin, the broader margin of 0.4, has been chosen instead of 0.3 because of the anticipated body weight advantage of oral semaglutide compared to empagliflozin. The trial has been powered to meet HbA_{1c} superiority of oral semaglutide versus empagliflozin. With the anticipated added benefit on body weight, it is considered acceptable to use a non-inferiority margin of 0.4.

Since the equalising effect of rescue medication will be included in the primary analysis as well as a conservative approach for handling of missing data will be performed, an adjustment in treatment effect will be implemented for the 10% of subjects who are expected to discontinue trial product or

initiate rescue medication and for the 10% of subjects who are expected to have actual missing data. The treatment effects used in the sample size calculation will be adjusted according to a 75% smaller effect in these subjects. For the 10% of the subjects with missing data, the non-inferiority margin of 0.4% for HbA_{1c} is added to the imputed values, when testing for non-inferiority. The adjusted treatment effects for testing non-inferiority (HbA_{1c} only) and superiority are as described below:

- Non-inferiority
  - $0.8 \times TE + 0.2 \times TE \times 0.25 + \text{non-inferiority margin} \times 0.1$
- Superiority
  - $0.8 \times TE + 0.2 \times TE \times 0.25$

Table 17–1 Assumptions used in the for sample size calculation

Parameter	Treatment effect (TE)	Adjusted TE, non-inferiority	Adjusted TE, superiority	Standard deviation	Non-inferiority margin
HbA_{1c}	-0.3%	-0.215%	-0.255%	1.1%	0.4%
Body weight	-1 kg		-0.85 kg	4 kg	

With the above assumptions, allocating 408 subjects to each of the two arms provides 90% power to confirm HbA_{1c} superiority of oral semaglutide versus empagliflozin. In total $2 \times 408 = 816$ subjects are planned to be randomised. Calculated powers for individual hypotheses are presented in Table 17–2.

Table 17–2 Calculated powers for individual hypotheses

	HbA_{1c} non-inferiority	HbA_{1c} superiority	Body weight superiority
Power	> 99%	90%	85%

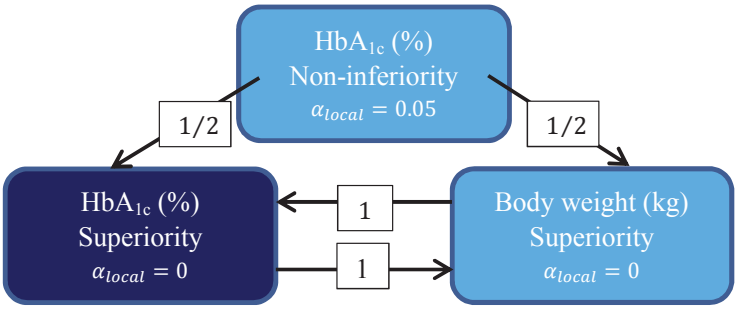


Figure 17–1 Graphical illustration of the closed testing procedure

The overall significance level of α = 0.05 (two-sided) is initially allocated to the HbA_{1c} non-inferiority test of oral semaglutide vs. empagliflozin. The local significance level (α-local) will be reallocated if a hypothesis is confirmed according to the weight given by the directed edges between nodes (hypotheses). The sample size is based on the hypothesis in the dark box.

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".

Per protocol (PP) analysis set: Includes all subjects in the FAS who fulfils the following criteria

- have not violated any inclusion criteria
- have not fulfilled any exclusion criteria
- have a baseline HbA_{1c} measurement
- is exposed to trial product and have at least one HbA_{1c} measurement at or after week 14

Subjects in the PP analysis set will, as in the SAS, contribute to the analysis "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 (V13) for subjects on trial product
- the latest occurring visit of the end-of-treatment visit (V12) or the follow-up premature discontinuation visit (V13A), 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 week after planned last dose of trial product at the follow-up visit.
- 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 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, anti-semaglutide antibodies, and AEs including hypoglycaemic episodes, the observation period ends at the first date of any of the following:

- the follow-up visit (V13)
- the follow-up prematurely discontinuation visit (V13A)
- the last date on trial product +38 days
- the end-date for the in-trial observation period

The follow-up visit 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. The on-treatment without rescue medication observation period starts at first date on trial product and the observation period ends at the first date of any of the following:

- the last dose of trial product +3 days
- the date of 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, 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 and the confirmatory secondary body weight endpoint the following confirmatory one-sided hypotheses are planned to be tested for oral semaglutide versus empagliflozin. Let the mean treatment difference be defined as μ = (oral semaglutide minus empagliflozin):

- HbA_{1c} non-inferiority, using a non-inferiority margin of 0.4%
  - H_0: $\mu \geq 0.4\%$ against H_a: $\mu < 0.4\%$

- HbA_{1c} superiority
  - H_0: $\mu \geq 0.0\%$ against H_a: $\mu < 0.0\%$

- HbA_{1c} body weight superiority
  - H_0: $\mu \geq 0.0$kg against H_a: $\mu < 0.0$kg

Operationally the hypotheses will be evaluated by two-sided tests.

Multiplicity and criteria for confirming hypotheses

The type I error for testing the three confirmatory hypotheses related to the HbA_{1c} and body weight endpoints will be preserved in the strong sense at 5% (two-sided) using the weighted Bonferroni-based closed testing procedure described in Bretz et al 2011[50] and outlined in Figure 17–1

The first hypothesis to be tested is non-inferiority of HbA_{1c}. It will be tested at the overall significance level (5%) while allocating 0% local significance level to the remaining of the hypotheses. For this hypothesis, and in general, if a hypothesis is confirmed the significance level will be reallocated according to the weight and the direction of the edges going from the confirmed hypothesis to the next hypotheses as specified in Figure 17–1. Each of the following hypotheses will be tested at their local significance level (α-local). This process will be repeated until no further hypotheses can be confirmed.

Non-inferiority and/or superiority will be considered confirmed if the mean 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 its local two-sided significance level as defined by the closed testing procedure in Figure 17–1. This is equivalent to using a one-sided p-value (nominal $\alpha = 0.025$) and a one-sided 2.5% overall significance level in the closed testing procedure.

17.3 Primary endpoint

The primary endpoint is change from baseline to week 26 in HbA_{1c}.

17.3.1 Primary analysis for the primary estimand

The primary estimand will be estimated based on the FAS using week 26 measurements from the in-trial observation period. The primary statistical analysis will be a pattern mixture model using multiple imputation to handle missing data assuming that the missing data mechanism is missing at random (MAR) within the groups used for imputation. Imputation of missing data at week 26 will be done within 4 groups of subjects defined by randomised treatment arm, and whether subjects at week 26; (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 26 are similar in terms of randomised treatment arm and treatment adherence/rescue medication status.

Missing values for each group will be imputed as follows:
An analysis of covariance (ANCOVA) with region as a categorical fixed effect and baseline HbA_{1c} measurement as a covariate will be fitted to observed values of the change from baseline in HbA_{1c} at week 26.

The estimated parameters for location and dispersion will be used to impute 100 values for each subject with missing week 26 data based on region and baseline HbA_{1c}. Thus, 100 complete data sets will be generated including observed and imputed values.

Analysis used for confirming superiority versus empagliflozin at week 26:

For each of the 100 (now complete) imputed data sets, the change in HbA_{1c} from baseline to week 26 will be analysed using an ANCOVA with treatment and region as categorical fixed effects, and baseline HbA_{1c} as covariate. The results obtained from analysing the datasets will be combined using Rubin's rule[52] to draw inference.

Analysis used for confirming non-inferiority versus empagliflozin at week 26:

Prior to analysing the data using the same model and approach as used for confirming superiority (see above), a value of 0.4% (the non-inferiority margin) will be added to imputed values at week 26 for the oral semaglutide treatment arms only[53]. For evaluating non-inferiority versus empagliflozin unadjusted two sided p-value for testing no difference from the non-inferiority margin 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 26 from the on-treatment without rescue observation period. The primary analysis for the secondary estimand will be a Mixed Model for Repeated Measurements (MMRM). A restricted maximum likelihood will be used. The model will include all post baseline HbA_{1c} measurements collected at scheduled visits up to and including week 26 as dependent variables. The independent effects included in the model will be treatment and region 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[54] and with a report from the US National Research Council[55], these analyses will primarily evaluate the sensitivity of the results due to the impact of missing data.

Since conservatism, i.e. avoiding bias in favour of oral semaglutide, depends on the context, separate sensitivity analyses will be made for non-inferiority and superiority testing.

The evaluation of the robustness of the primary analysis results will primarily be based on a pattern mixture model approach using multiple imputation. An overview of the sensitivity analyses for each of the estimands are specified below followed by a more detailed description of the three different pattern mixture models used. Finally, three additional sensitivity analyses for the primary analysis will be described that are not based on the pattern mixture model approach (see Section 17.3.3.2).

Sensitivity analyses for the primary estimand

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

- A comparator multiple imputation analysis based on FAS using the in-trial observation period (superiority).
- A comparator multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely based on FAS using the in-trial observation period (superiority).
- A tipping-point multiple imputation analysis based on FAS using the in-trial observation period (non-inferiority and superiority).
- A MMRM analysis (the primary analysis for the secondary estimand) based on FAS using the in-trial observation period (non-inferiority and superiority).

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 (superiority).
- A comparator multiple imputation analysis based on FAS using the on-treatment observation period (superiority). This sensitivity analysis aims to compare oral semaglutide versus empagliflozin for subjects who adhere to treatment regardless of whether or not rescue medication has been initiated.
- A comparator multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely based on FAS using the on-treatment without rescue medication observation period (superiority).
- A tipping-point multiple imputation analysis based on FAS using the on-treatment without rescue medication observation period (non-inferiority and superiority).

17.3.3.1 Pattern mixture models

Common for the three pattern mixture model sensitivity analyses is that they all aim to stress-test the primary HbA_{1c} results by changing the assumptions for part or all missing data in the oral semaglutide treatment arm, while maintaining the missing data assumption for the empagliflozin arm.

- *Comparator multiple imputation analysis:* In this sensitivity analysis missing data at week 26 for all subjects will be imputed to resemble the distribution of the week 26 values observed in the empagliflozin treatment arm. In effect, this imputation approach removes the treatment difference between oral semaglutide and empagliflozin for all subjects randomised to oral semaglutide, given that oral semaglutide is better than empagliflozin. Due to the potential lack of sensitivity for testing non-inferiority this sensitivity analysis will only be used to evaluate the robustness of HbA_{1c} superiority conclusions.
- *Comparator multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely:* In this sensitivity analysis missing data at week 26 for subjects who discontinue oral semaglutide treatment due to treatment related AE(s) will be imputed to resemble the distribution of the week 26 values observed in the empagliflozin treatment arm. Treatment related AEs are defined as AEs classified as possible or probable related to trial product as reported by the investigator. In effect this imputation approach removes the treatment difference between oral semaglutide and empagliflozin for this selected group of subjects randomised to oral semaglutide. This sensitivity analysis is less conservative as compared to the first sensitivity analysis. Due to the potential lack of sensitivity for testing non-inferiority this sensitivity analysis will only be used to evaluate the robustness of HbA_{1c} superiority conclusions.
- *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 26. The approach is to gradually increase this penalty until the 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. This sensitivity analysis will be used for evaluating the robustness of the HbA_{1c} non-inferiority and superiority conclusions.

17.3.3.2 Other sensitivity analyses

The following additional sensitivity analyses will be specified

- *Per-protocol analysis:* This sensitivity will be based on the per-protocol analysis set. Data from the on-treatment without rescue medication observation period will be analysed using the primary analysis approach for the primary estimand. This sensitivity analysis will be used to evaluate the robustness of the HbA_{1c} non-inferiority conclusions.
- *Complete case analysis:* This sensitivity analysis will be based on the on-treatment without rescue medication observation period and include subjects in the FAS who have a valid HbA_{1c}

measurement at week 26. The change from baseline to week 26 in HbA_{1c} will be analysed by a linear normal model (ANCOVA) with treatment and region as categorical fixed effects and baseline HbA_{1c} as a covariate. This sensitivity analysis will be used to evaluate the robustness of the HbA_{1c} non-inferiority conclusions.

- *Last observation carried forward analysis:* This sensitivity analysis will be based on the FAS using the on-treatment without rescue medication observation period. The change from baseline to week 26 in HbA_{1c} will be analysed by a linear normal model (ANCOVA) with treatment and region as categorical fixed effects and baseline HbA_{1c} as a covariate. This sensitivity analysis will be used for evaluating the robustness of the HbA_{1c} non-inferiority and superiority conclusions.

17.3.3.3 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 large number of sensitivity analyses and their 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 26 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. Body weight will only be tested for superiority. Baseline body weight will be used as a covariate instead of baseline HbA_{1c} in both the multiple imputation and analysis model.

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}
- Body weight (kg)

Change from baseline to week 26 and week 52 in:

- Body weight (%)
- FPG
- Fasting C-peptide
- Fasting insulin and proinsulin
- Fasting glucagon
- Insulin resistance (homeostatic model assessment index of insulin resistance [HOMA-IR]) and beta-cell function (homeostatic assessment index of beta-cell function [HOMA-B])
- BMI
- Waist circumference
- Fasting lipid profiles (total cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol, triglycerides, free fatty acids)
- C-reactive protein (CRP)

BMI will be calculated based on body weight and height based on the formulae:

$$\text{BMI kg/m}^2 = \text{body weight (kg)/(Height (m) x Height (m)) or (kg/m}^2 = [\text{lb/in}^2 \text{ x } 703])$$

Change from baseline to week 26 and week 52 in 7-point SMPG profile:

- Mean 7-point profile; defined as the area under the profile, calculated using the trapezoidal method, divided by the measurement time
- Mean postprandial increment (over all meals)

The above continuous endpoints will be analysed separately using similar model approaches as for the primary 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.

For evaluation of the primary estimand, the analysis will be performed separately for week 26 and week 52. For the analysis at week 52, the imputation of missing data will be further differentiated by whether subjects have discontinued trial product or initiated rescue medication prior to week 26 or at or after week 26. This will result in imputation of missing data within 8 groups of subjects instead of the 4 groups as described for the week 26 evaluation in Section 17.3.1. If less than 5 subjects have available data in one of the 8 groups, the imputation will be made within the 4 groups specified for the primary evaluation. The frequency of missing data is expected to be slightly larger at week 52 compared to week 26. The rate of missing data is expected to decline over time.

For evaluation of the secondary estimand, the MMRM based primary analysis will include all scheduled post-baseline measurement up to and including week 52. From this model the estimated treatment differences (ratios) will be presented at week 26 (except for HbA_{1c} and body weight), and week 52 with 95% confidence intervals and two-sided p-values for test of no difference.

Binary efficacy endpoints

If a subject after week 26 achieves (yes/no):

- $HbA_{1c} < 7.0\%$ (53 mmol/mol) (ADA) target
- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) (AACE) target
- HbA_{1c} reduction $\geq 1\%$ (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 hypoglycaemic episodes) and no weight gain
- HbA_{1c} reduction $\geq 1\%$ (10.9 mmol/mol) and weight loss $\geq 3\%$

The above eight endpoints will also be evaluated after week 52.

The above eight binary endpoints will be analysed using a logistic regression model with treatment and region as fixed effects and baseline response as covariate (i.e. baseline HbA1c for binary HbA1c endpoints, baseline weight for weight endpoints and both baseline HbA1c and baseline weight for the binary endpoint that combines both parameters). To account for missing data, the analysis will be made using a sequential multiple imputation approach as described below:

- Multiple imputed data sets (100) will be created in which missing values for the underlying continuous assessments are imputed by treatment group and treatment adherence/rescue status assuming MAR and as described in section 17.3.1 for the primary estimand and by treatment group assuming MAR and as described in section 17.3.2 for the secondary estimand.
- The binary endpoint will be created for each of the 100 complete data sets
- Each of the created complete data set will be analysed with the logistic model and inference will be drawn using Rubin's rule[52].

Time to event endpoint

- Time to rescue medication

Subjects completing the study without need for rescue medication will be censored at the time point of the (actual) last date on trial product. The start time is the first date on trial product. Time to rescue medication will be described and compared for oral semaglutide versus empagliflozin using likelihood ratio tests obtained from a proportional Cox hazards model with treatment and region as categorical fixed effects, and baseline HbA_{1c} as covariate. From this analysis the estimated Hazard ratios between semaglutide versus empagliflozin will be presented together with 95% confidence intervals and two-sided p-values for test of no difference.

Pharmacokinetic endpoints

- SNAC plasma concentrations
- Semaglutide plasma concentrations for population PK analyses

The SNAC plasma concentrations and semaglutide plasma concentrations collected in this trial will be evaluated using relevant summary statistics. In addition, the semaglutide plasma concentration will be part of a meta-analysis across the oral semaglutide phase 3a trials, see Section 17.6.

17.4.2.2 Safety endpoints

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

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 26 and week 52 in:

- Amylase
- Lipase
- 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 separately as described above for continuous efficacy endpoints. Results will be presented at week 26 and 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 26 and week 52 in:

- Haematology
- Biochemistry (except for amylase and lipase)
- Calcitonin
- ECG evaluation
- Physical examination (week 52 only)

Change from pre-dose to post-dose (25 and 40 min) at week 4, 26, and 52 in:

- Lactate

Any occurrence of anti-semaglutide antibodies (yes/no) up to approximately 57 weeks:

- Anti-semaglutide binding antibodies
- Anti-semaglutide neutralising antibodies
- Anti-semaglutide binding antibodies cross reacting with native GLP-1
- Anti-semaglutide neutralising antibodies cross reacting with native GLP-1

Anti-semaglutide binding antibodies up to approximately 57 weeks:

- Anti-semaglutide binding antibody levels

The above safety endpoints will be summarised descriptively by treatment arm and visit. The binary 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

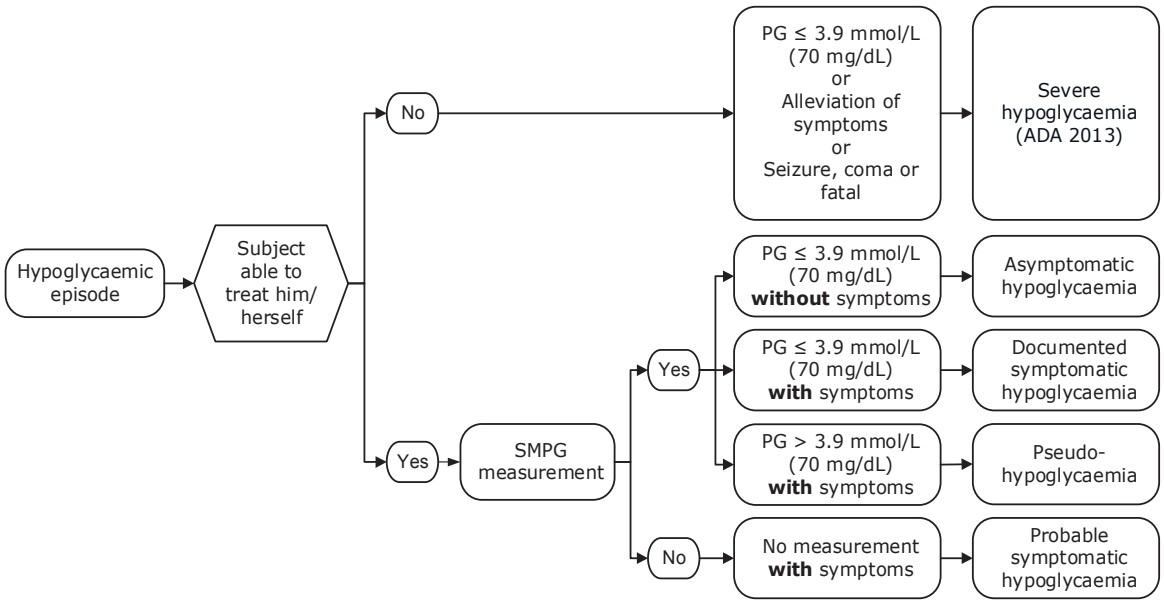
In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L (56 mg/dL)[56]. Therefore, Novo Nordisk has included hypoglycaemia with PG levels below this cut-off point in the definition of BG-confirmed hypoglycaemia.

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[42] or BG-confirmed by a PG value < 3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia.

ADA classification of hypoglycaemia[42]

- 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

Figure 17–2 ADA classification of hypoglycaemia

PG: plasma glucose. SMPG: Self-measured plasma glucose

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 will be evaluated for the on-treatment period 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 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 and region as fixed factors and baseline HbA_{1c} as covariate.

17.5 Interim analysis

No interim analyses will be performed before the database is locked.

17.6 Pharmacokinetic and/or pharmacodynamic modelling

Data from this trial will be evaluated using population pharmacokinetic analysis and exposure-response for semaglutide. The purpose of the population pharmacokinetic analysis will be 1) to describe the covariate factors (such as weight, age, gender, race and ethnicity) that influence semaglutide exposure, 2) to estimate a steady-state exposure level for each subject with pharmacokinetic data in order to facilitate subsequent exposure-response analyses. The purpose of the exposure-response analyses will be to support the recommended doses by investigating response and potentially side effects across the exposure range.

The population pharmacokinetic and exposure-response analyses will be conducted as a meta-analysis, including all relevant Phase 3a trials with PK assessment relevant oral semaglutide phase 3 trials. A separate modelling analysis plan will be prepared before database lock, outlining details of the analyses. The modelling will be performed by Quantitative Clinical Pharmacology at Novo Nordisk A/S and will be reported separately from the CTR.

17.7 Patient reported outcomes

Change from baseline to week 26 and week 52 in:

- SF-36v2™ (acute version) health survey: Scores from the 8 domains and the physical component score and mental component score summary scores
- CoEQ: Scores from the 4 domains and scores from 19 individual items

The PRO endpoints will be evaluated using the primary analysis for the primary estimand based on FAS using the in-trial observation period and using the primary analysis for the secondary estimand based on FAS using the on-treatment without rescue medication period. All of the above 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 escalation with 4 week dose-escalation steps have been implemented in the 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.

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 in 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[27, 28] (excluding GLP-1 RAs, DPP-4 inhibitors, amylin analogues and SGLT-2 inhibitors).

It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2014 Standards of Medical Care in Diabetes[57].

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

18.1.1.1 Empagliflozin

Subjects should be considered suitable for treatment with empagliflozin and the use of empagliflozin should be in accordance with the current, approved label. It is important to monitor renal function and for signs and symptoms of volume depletion during therapy. Serum creatinine will be measured regularly for monitoring of renal function.

The most common adverse reactions reported with empagliflozin are hypoglycaemia (when used with sulphonylurea or insulin), genital infections, pruritus (generalised) and increased urination. Uncommon adverse reactions are volume depletion and dysuria[25]. SGLT-2 inhibitors have recently been associated with a risk of ketoacidosis and urinary tract infections[58]. Symptoms of ketoacidosis include nausea, vomiting, abdominal pain, tiredness, general malaise and shortness of breath. Ketoacidosis associated with the use of SGLT-2 inhibitors can occur even if the blood sugar level is not elevated. If ketoacidosis is suspected, the SGLT-2 inhibitor should be discontinued and treatment instituted promptly.

18.1.2 Benefits

In this trial, subjects will be randomised to one of two treatment arms involving an active add-on treatment regimen anticipated to be more efficacious than the treatment they receive at the time of entry into the trial (metformin only).

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 empagliflozin is expected to provide clinically relevant improvements in glycaemic control[25]. 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. The phase 2 results indicate that oral semaglutide will provide clinically relevant improvements in glycaemic control and body weight.

Empagliflozin 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/empagliflozin 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 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 summary of product characteristics (SmPC) or similar product information for Jardiance® (empagliflozin)
- 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)
- 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 will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications [59].

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[4].

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[59] (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 may be retained for later analysis for further characterisation of antibody responses towards drug if required by health authorities or for safety reasons.

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

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 and bio-repository personnel 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.

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

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 CTR 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 Poland only: Novo Nordisk carries liability for the trial exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal of Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the trial, Novo Nordisk and the investigators are covered by the insurance policy issued according to applicable Polish law.

For Russia only: Federal law of 12 April 2010 No. 61-FZ 'On Medicinal Drugs' Circulation.

27 References

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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.

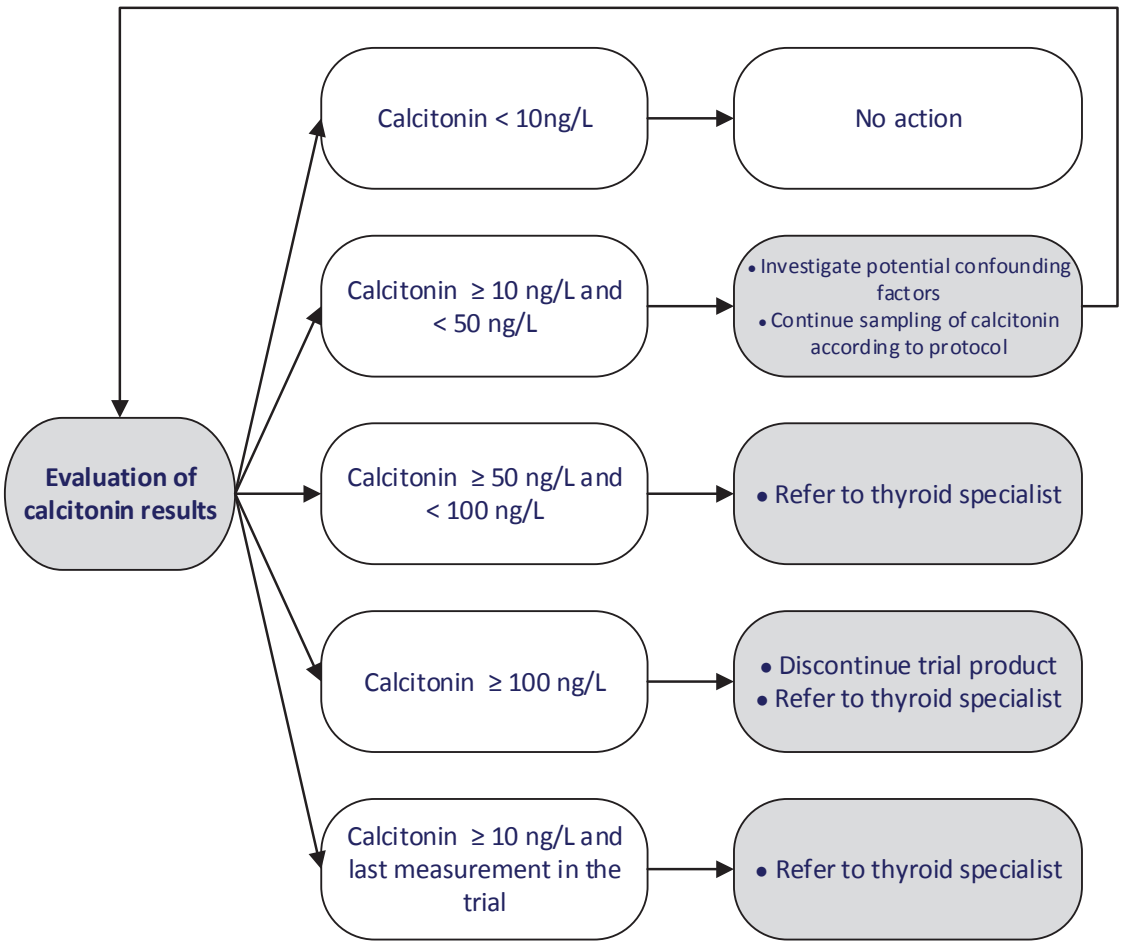

Figure 1 Flow of calcitonin monitoring

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

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Appendix B

Adverse events requiring additional data collection

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 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) > 10x UNL
- Hepatic event:
  - ALT or 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 aminotransferase (ALT) or aspartate aminotransferase (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 Section 12.1.2.

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

Acute coronary syndrome

If an event of acute coronary syndrome (ranging from unstable angina pectoris to myocardial infarction) 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

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

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
- NYHA Class
- Supportive imaging
- Supportive laboratory measurements
- Initiation or intensification of treatment for this condition

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

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).

Neoplasm

All events of neoplasms (excluding thyroid neoplasms, 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

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

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

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

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 V13A. Furthermore, a blood sample for assessment of anti-semaglutide IgE antibodies should be drawn as soon as possible after the event and at V13A 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.

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

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.

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

Creatine kinase > 10x UNL

If an event of CK > 10x 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

Assessments in case of increased levels of creatine kinase

In case of CK > 10x upper limit of normal (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 the possible cause of the observed CK elevation.

Hepatic event

- ALT or 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

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

Assessments in case of increased levels of aminotransferases

Both events should prompt repeat testing (at central laboratory) including ALT, AST, ALP and total bilirubin and discontinuation of trial product should be considered. Thereafter, repeat testing (at central laboratory) of ALT, AST, alkaline phosphatase 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.

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

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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

Protocol Amendment

no 1
to Protocol, final version 2.0
dated 14 March 2016

NN9924-4223

Efficacy and Safety of Oral Semaglutide versus Empagliflozin in Subjects with Type 2 Diabetes Mellitus

Trial phase: 3a

Applicable to all countries

Amendment originator:

[redacted], [redacted]

[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. Investigator's responsibility in ensuring evaluation and management of certain risk factors and complications
3. Clarification of the criteria for completion, withdrawal and lost to follow-up
4. Other minor corrections and clarifications

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, *17.2*, 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[ref x1,x2,x3]. 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[Ref x4]. 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 and 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.

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

Updated protocol Section: 8.4.2, 8.4.4. and 18.1

[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.

1.3 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.

1.4 Clarification of criteria for premature discontinuation of trial product

Updated protocol Section 6.5

For subjects randomised to emplagliflozin, it has been emphasized that trial product should be prematurely discontinued if the eGFR falls persistently < 45 mL/min/1.73 m2 (confirmed by re-test at central laboratory), for subjects randomised to empagliflozin. This was only stated in Section 5.3 previously.

1.5 Risks and Precautions for empagliflozin

Updated protocol Section 18.1.1

Empagliflozin's label has been updated why additional information has been added to section 18.1.1 to reflect this update and to guide investigators.

1.6 Other minor adjustments, clarifications and correction of typographical errors

1.6.1 Laboratory analysis

Updated protocol Section: 8.5

The protocol currently specifies that the in vitro neutralising antibody assays will be performed by Novo Nordisk, however it may be decided by Novo Nordisk that the laboratory currently responsible for antibody binding analysis (Celerion) will perform the assay.

1.6.2 Lactate

Updated protocol Section: 8.6.1.

The protocol has been updated to specify the importance of remaining resting throughout the lactate assessments, as this was not obvious from the previous protocol text.

1.6.3 Statistical considerations

Updated protocol Sections: 17.3.1, 17.4.2.1 and 17.4.2.2.

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. In addition, an error in the number of groups used for imputation is corrected.

1.6.4 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 (UAP) requires hospitalisation to qualify for event adjudication.

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]	Randomi-sation	Treatment									End-of-treatment (EoT)	Follow-up[b]	EoT premature discontinuation[c]	Follow-up premature discontinuation[c]
Visit (V), Phone (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V12A	V13A
Timing of visit (Weeks)	Up to -2 weeks	0	2	4	8	14	20	26	32	38	45	52	57	Day of discontinuation of trial product	5 weeks after discontinuation of trial product
(Days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	+3
SAFETY															
Eye examination[f]	x											*x*		*x*	

Footer	Description
x[f]	Dilated fundoscopy/fundus photography performed within 90 days prior to randomisation is acceptable if results are available for evaluation at V2, unless worsening of visual function since last examination. *Fundus photography or dilated fundoscopy must be performed again:* • *at V12 or within 5 weeks thereafter for subjects completing treatment* • *at V12A or within 5 weeks thereafter, and again within 5 weeks prior to V12, for subjects who have prematurely discontinued trial product*

2.2 Section 4.2.2.2 Supportive secondary safety endpoints

Change from baseline to week 26 and 52 in:

- Haematology
- Biochemistry
- Calcitonin
- Pulse
- Systolic blood pressure
- Diastolic blood pressure
- Electrocardiogram (ECG) category
- Physical examination (only week 52)
- *Eye examination category (only week 52)*

2.3 Section 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
- Calcitonin ≥ 100 ng/L
- *For subjects randomised to empagliflozin only: If the eGFR falls persistently < 45 mL/min/1.73 m^2 (confirmed by re-test at central laboratory) (see Section 5.3)*

2.4 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)*

2.5 Section 8.1.4 End-of-treatment (visit 12) and Follow-up (visit 13)

At V12 the subject should be reminded about the importance of attending the follow-up visit (V13). If the subject, nonetheless, does not attend V13, 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 V13. (For subjects who discontinued trial product, see Section 8.1.*5).

~~In case the subject cannot be reached (by clinic visit or phone contact) at the scheduled visit 19, 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.~~

2.6 Section 8.1.5 Premature discontinuation of trial product and follow-up (visits 12A and 13A)

~~Subjects, who only agree to attend or provide health status at the planned V12, should not be considered withdrawn from the trial. In case the subject cannot be reached (by clinic visit or phone contact) at the scheduled V12, 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 V12 (or V13A if it is scheduled after V12). The site should in due time prepare for establishing contact with the subject within the visit window of the scheduled V8 and V12 respectively, if the subject has agreed to attend these visits.

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* ~~from the trial~~ (for withdrawal procedures, see Section 8.1.6).

2.7 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: V13 for subjects who have completed treatment, whereas for subjects who have discontinued trial product prematurely the last visit is V12 (or V13A if it is scheduled after V12). Only if contact with the subject is not regained by the end of the visit window of the last scheduled visit window, can the subject be considered lost to follow-up (see Section 6.6).

2.8 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 (myocardial infarction or 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 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 aminotransferase (ALT) or aspartate aminotransferase (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.

2.9 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[Ref x5], and adapted to local treatment guidelines if applicable*

2.10 Section 8.4.4 Eye examination

Fundus photography or dilated fundoscopy will be performed as per 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).

2.11 Section 8.4.8 Anti-semaglutide antibodies

Furthermore, samples drawn at randomisation may be used for calculations of the neutralising effect in the in vitro neutralising antibody assays. The *in vitro* neutralising assays will be performed by Novo Nordisk *or the special laboratory responsible for antibody binding analysis*.

2.12 Section 8.6.1 Lactate

The subject must be fasting for the assessment and remain fasting until the last sample has been taken, that is, at least 40 minutes after dosing. Also, the subject should have rested for at least 30 minutes in a sitting position prior to sampling, *and should remain resting until the last sample has been taken.*

2.13 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*

2.14 Section 12.2 Reporting of adverse events

Novo Nordisk assessment of AE expectedness:
Novo Nordisk assessment of expectedness is performed according to the following reference documents: IB for oral semaglutide (NN9924)[24] and Jardiance® (empagliflozin) SmPC ~~and prescribing information~~[25,26]; current version and any updates thereto.

2.15 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: • ST-elevation acute myocardial infarction (STEMI) • Non-ST elevation acute myocardial infarction (NSTEMI) • Silent MI • Unstable angina pectoris (UAP*) requiring hospitalisation*	• Acute myocardial infarction (STEMI or NSTEMI), silent MI • Unstable angina pectoris requiring hospitalisation

2.16 Section 17.2 Definition of analysis sets

For adjudicated events, ECGs, *eye examination category,* anti-semaglutide antibodies, and AEs including hypoglycaemic episodes, the observation period ends at the first date of any of the follwing:

2.17 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 as a categorical fixed effect and baseline HbA_{1c} measurement as a covariate will be fitted to observed values of the change from baseline in HbA_{1c} at week 26.

The estimated parameters for location and dispersion will be used to impute ~~100~~ *1000* values for each subject with missing week 26 data based on region and baseline HbA_{1c}. Thus, ~~100~~ *1000* complete data sets will be generated including observed and imputed values.

Analysis used for confirming superiority versus empagliflozin at week 26:

For each of the ~~100~~ *1000* (now complete) imputed data sets, the change in HbA_{1c} from baseline to week 26 will be analysed using an ANCOVA with treatment and region as categorical fixed effects, and baseline HbA_{1c} as covariate. The results obtained from analysing the datasets will be combined using Rubin's rule[52] to draw inference.

2.18 Section 17.4.2.1 Efficacy endpoints

For evaluation of the primary estimand, the analysis will be performed separately for week 26 and week 52. For the analysis at week 52, the imputation of missing data will be further differentiated by whether subjects have discontinued trial product or initiated rescue medication prior to week 26 or at~~or~~/after week 26. This will result in imputation of missing data within ~~8~~ *6* groups of subjects instead of the 4 groups as described for the week 26 evaluation in Section 17.3.1. If less than 5 subjects have available data in one of the ~~8~~ *6* groups, the imputation will be made within the 4 groups specified for the primary evaluation. The frequency of missing data is expected to be slightly larger at week 52 compared to week 26. The rate of missing data is expected to decline over time.

Binary efficacy endpoints

- Multiple imputed data sets (~~100~~ *1000*) will be created in which missing values for the underlying continuous assessments are imputed by treatment group and treatment adherence/rescue status assuming MAR and as described in section 17.3.1 for the primary estimand and by treatment group assuming MAR and as described in section 17.3.2 for the secondary estimand.
- The binary endpoint will be created for each of the ~~100~~ *1000* complete data sets
- Each of the created complete data set will be analysed with the logistic model and inference will be drawn using Rubin's rule[52].

2.19 Section 17.4.2.2 Safety endpoints

Other safety endpoints

Change from baseline to week 26 and week 52 in:

- Haematology
- Biochemistry (except for amylase and lipase)
- Calcitonin
- ECG evaluation
- Physical examination (week 52 only)

- *Eye examination category (week 52 only)*

2.20 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[Ref x1, x2, x3]. 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[Ref x6, x7] even in intensively treated patients who experienced early worsening[Ref x2]. 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[Ref x4]. 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[57].

General precautions

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[27, 28] (excluding GLP-1 RAs, DPP-4 inhibitors, amylin analogues and SGLT-2 inhibitors).

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*[57] ~~according to the principles outlined in Diabetes Care 2014 Standards of Medical Care in Diabetes~~[57].

Section 18.1.1.1 Empagliflozin

Subjects should be considered suitable for treatment with empagliflozin and the use of empagliflozin should be in accordance with the current, approved label[25,26]. It is important to monitor
renal function and for signs and symptoms of volume depletion during therapy. Serum creatinine will be measured regularly for monitoring of renal function.
The most common adverse reactions reported with empagliflozin are hypoglycaemia (when used with sulphonylurea or insulin), genital infections, pruritus (generalised) and increased urination.

Uncommon adverse reactions are volume depletion and dysuria[25]. SGLT-2 inhibitors have recently been associated with a risk of ketoacidosis and urinary tract infections[58]. Symptoms of ketoacidosis include nausea, vomiting, abdominal pain, tiredness, general malaise and shortness of breath. Ketoacidosis associated with the use of SGLT-2 inhibitors can occur even if the blood sugar level is not elevated. If ketoacidosis is suspected, the SGLT-2 inhibitor should be discontinued and treatment instituted promptly. *Treatment should always be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses*.

2.21 Section 27 References

Reference numbers will change throughout the updated protocol when new references in the amendment are inserted.

New references in this amendment are marked with an x, i.e. Ref [x1]. The following references are new references:

1. *Ref[x1]; 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. *Ref[x2]; 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. *Ref[x3]; 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):e37-9.*
4. *Ref[x4]; 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.*
5. *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*
6. *Ref[x5]; 53 in PIONEER 8*
7. *Ref[x6]; 54 in PIONEER* 8

Ref[26] will be deleted from protocol Section 12.2: ~~Jardiance: US Prescribing Information. 2015~~.

Reference[57] in protocol version 2.0 will be updated:
~~Diabetes Care 2014, Standards of Medical Care in Diabetes~~.
American Diabetes Association. Standards of medical care in diabetes - 2016. Diabetes Care. 2016;39 (Suppl. 1):S1-S109.

2.22 Appendix B, 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 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) > 10x UNL
- Hepatic event:
  - ALT or 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 aminotransferase (ALT) or aspartate aminotransferase (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.

2.23 Appendix B, new section

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*