Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02906930
Sponsor trial ID:	NN9924-4233
Official title of study:	Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only
Document date:	20 June 2018

16.1.1 Protocol and protocol amendments

List of contents

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

.

Protocol

Trial ID: NN9924-4233

PIONEER 1 - Monotherapy

Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only

A 26-week, randomised, double-blind, placebo-controlled trial

Trial phase: 3a

Protocol originator

[redacted]

[redacted]

Table of Contents

Table of Figures

Table of Tables

List of abbreviations

AACE	American Association of Clinical Endocrinologists
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
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLAE	clinical laboratory adverse event
CRF	case report form
CRP	c-reactive protein
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
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 agonists
HbA_{1c}	glycosylated haemoglobin
HDL	high-density lipoprotein
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IB	investigator's brochure
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IND	investigational new drug
IWQOL-Lite	Impact of Weight on Quality of Life
IRB	institutional review board
IWRS	interactive web/voice 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
MI	myocardial infarction
MedDRA	Medical Dictionary for Regulatory Activities
MEN 2	multiple endocrine neoplasia type 2
MMRM	mixed model for repeated measurements
MTC	medullary thyroid carcinoma
NIMP	non-investigational medicinal product
NYHA	New York Heart Association
PG	plasma glucose
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Status
PK	pharmacokinetic
PRO	patient reported outcome
SAE	serious adverse event
SAS	safety analysis set
s.c.	Subcutaneous(ly)
SF-36	short form-36
SIF	safety information form
SMPG	self-measured plasma glucose
SNAC	N-[8-(2-hydroxybenzoyl) amino]caprylate
STEMI	ST-elevation acute myocardial infarction

SUSAR	suspected unexpected serious adverse reaction
TE	treatment effect
TEAE	treatment-emergent adverse events
T2DM	type 2 diabetes mellitus
UNL	upper normal limit
UTN	Universal Trial Number

1 Summary

Objectives and endpoints:

Primary Objective

To compare the effects of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) versus once-daily placebo on glycaemic control in subjects with type 2 diabetes mellitus treated with diet and exercise only.

Secondary Objectives

To compare the effects of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) versus once-daily placebo on body weight in subjects with type 2 diabetes mellitus treated with diet and exercise only.

To compare the safety and tolerability of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) versus once-daily placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only.

Primary endpoint

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

Key secondary endpoints

Change from baseline to week 26 in:

- Body weight (kg)
- Fasting plasma glucose

If a subject after week 26 achieve (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 31 weeks.

Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 31 weeks.

Trial design:

This is a 26-week, randomised, double-blinded, placebo-controlled, four-armed, parallel-group, multi-centre, multi-national trial comparing the efficacy and safety of three dose levels of once-daily oral semaglutide and placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only.

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

- 3 mg oral semaglutide once daily
- 7 mg oral semaglutide once daily
- 14 mg oral semaglutide once daily
- placebo once daily

The randomisation will be stratified based on descent (Japanese subjects/non-Japanese subjects).

The total trial duration for the individual subject will be approximately 33 weeks, including a 2-week screening period followed by a 26-week randomised treatment period and a 5-week follow-up period.

Trial population:

Number of subjects planned to be randomised: 704

Inclusion criteria

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

- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
- Male or female, age above or equal to 18 years at the time of signing informed consent.
  For Japan only: Male or female, age ≥ 20 years at the time of signing informed consent.
  For Algeria only: Male or female, age ≥ 19 years at the time of signing informed consent.
- Diagnosed with type 2 diabetes mellitus ≥ 30 days prior to day of screening.
- HbA_{1c} between 7.0-9.5% (53-80 mmol/mol) (both inclusive).
- Treatment with diet and exercise for ≥30 days prior to day of screening.

Key exclusion criteria

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

- 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 Japan only: Adequate contraceptive measures are abstinence (not having sex), diaphragm, condom (by the partner), intrauterine device, sponge, spermicide or oral contraceptives.
- Any disorder, which in the investigator’s opinion might jeopardise subject’s safety or compliance with the protocol.

- Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinomas.
- History of pancreatitis (acute or chronic).
- History of major surgical procedures involving the stomach potentially affecting absorption of trial product (e.g. subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery).
- Any of the following: myocardial infarction, stroke or hospitalisation for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening and randomisation.
- Subjects presently classified as being in New York Heart Association Class IV.
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
- Subjects with alanine aminotransferase > 2.5 x upper normal limit.
- Renal impairment defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 as per Chronic Kidney Disease Epidemiology Collaboration formula.
- Treatment with any medication for the indication of diabetes or obesity in a period of 90 days before the day of screening. An exception is short-term insulin treatment for acute illness for a total of ≤ 14 days.
- Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomisation.
- History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and *in-situ* carcinomas).

Key assessments:

Efficacy

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

Safety

- Adverse events
- Hypoglycaemic episodes

Trial products:

Investigational medicinal products:

- Test product: Semaglutide 3 mg, 7 mg and 14 mg tablets
- Reference therapy: Placebo tablets

2 Flow chart

Trial Periods	Screening[a]	Randomisation	Treatment					End-of-treatment	Follow-up[b]	End-of-treatment premature discontinuation[c]	Follow-up premature discontinuation[c]
Visit (V), Phone contact (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V8A	V9A
Timing of visit (weeks)	-2	0	2	4	8	14	20	26	31	Day of discontinuation of trial product	5 weeks after discontinuation of trial product
Visit window (days)			±3	±3	±3	±3	±3	±3	+3	+3	+3
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
Demography	x										
Tobacco use	x										
Concomitant illness and medical history	x										
Diagnosis of diabetes/diabetes complications	x										
History of gastrointestinal disease	x										
History of cardiovascular disease	x										
History of gallbladder disease	x										
Randomisation		x									
Criteria for premature discontinuation of trial product			x	x	x	x	x				
EFFICACY											
Height		x									

Trial Periods	Screening[a]	Randomisation	Treatment					End-of-treatment	Follow-up[b]	End-of-treatment premature discontinuation[c]	Follow-up premature discontinuation[c]
Visit (V), Phone contact (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V8A	V9A
Timing of visit (weeks)	-2	0	2	4	8	14	20	26	31	Day of discontinuation of trial product	5 weeks after discontinuation of trial product
Visit window (days)			±3	±3	±3	±3	±3	±3	+3	+3	+3
Body weight		x		x	x	x	x	x		x	
Waist circumference		x				x		x		x	
Fasting plasma glucose		x		x	x	x	x	x		x	
HbA_{1c}	x	x		x	x	x	x	x		x	
Semaglutide PK				x	x	x		x	x	x	x
SNAC PK[d]				x		x		x			
7-point SMPG profile		x						x		x	
Lipids		x			x			x		x	
Fasting insulin and proinsulin		x						x		x	
Fasting C-peptide		x						x		x	
Fasting glucagon		x						x		x	
CRP		x						x		x	
PRO questionnaires		x[e]			x			x		x	
SAFETY											
Adverse events[f]		x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes		x	x	x	x	x	x	x	x	x	x
Physical examination	x							x		x	
Eye examination[g]	x										
Vital signs		x		x	x	x	x	x	x	x	x

Trial Periods	Screening[a]	Randomisation	Treatment					End-of-treatment	Follow-up[b]	End-of-treatment premature discontinuation[c]	Follow-up premature discontinuation[c]
Visit (V), Phone contact (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V8A	V9A
Timing of visit (weeks)	-2	0	2	4	8	14	20	26	31	Day of discontinuation of trial product	5 weeks after discontinuation of trial product
Visit window (days)			±3	±3	±3	±3	±3	±3	+3	+3	+3
ECG		x						x	x	x	x
Biochemistry[h]	x	x		x	x	x		x	x	x	x
Haematology		x		x	x	x		x	x	x	x
Calcitonin		x				x		x	x	x	x
Antibodies[i]		x		x	x	x		x	x	x	x
Pregnancy test[j]	x	x		x	x	x	x	x	x	x	x
Lactate[k]				x				x			
Technical complaints			x	x	x	x	x	x		x	
TRIAL MATERIAL											
Dispensing of trial product		x		x	x	x	x				
Drug accountability		x		x	x	x	x	x		x	
IWRS call	x	x		x	x	x	x	x		x	
REMINDERS											
Attend visit fasting[l]		x		x	x	x	x	x		x	
Training in dosing instructions	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

2.1 Flow chart explanatory descriptions

Footer	Description
a	Subject can be randomised as soon as all inclusion and exclusion criteria are confirmed. The screening assessments must not exceed 2 weeks prior to randomisation (V2).
b	Subjects, who have discontinued trial product prematurely, are not required to attend V9 (Follow-up).
c	V8A and V9A are only applicable for subjects who have discontinued trial product prematurely. After visit 9A, samples for antibodies, PK and lactate assessment should not be taken.
d	Samples should be taken 25 (+/-5) minutes and 40 (+/-5) minutes post dosing.
e	The PGI-C should not be answered at V2.
f	Adverse events reporting includes adverse events from the first trial-related activity after the subject has signed the informed consent at V1.
g	Fundus photography or dilated fundoscopy 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.
h	At V1 only ALT, creatinine and eGFR will be assessed as part of Biochemistry.
i	At randomisation, the antibody sampling must be done pre-dose. No antibody sampling should be done for visits occurring after V9A (subjects who have discontinued trial product prematurely).
j	For women of child-bearing potential: Urine pregnancy test should also be performed at any time during the trial if menstrual period is missed, and/or according to local regulations/law.
k	Samples should be taken pre-dose and 25 (+/-5) minutes and 40 (+/-5) minutes post dosing.
l	Fasting for blood sampling is defined as no food or liquid within the last 8 hours prior to sampling, however water is allowed up until 2 hours prior to 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.

For Mexico only: the above will include the following responsibilities for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility: a) Investigation follow-up b) Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the Subject; c) Timely compliance of the terms in which the authorization of a research for health in human beings had been issued; d) To present in a timely manner the information required by the Health Authority.

3.1 Background information

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

3.1.1 Type 2 diabetes mellitus

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

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

3.1.2 Glucagon-like peptide-1

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

upon chronic exposure[14-16]. These mechanisms of action make GLP-1 receptor agonists (GLP-1 RA) 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), acylation of the peptide backbone with a spacer and C-18 fatty di-acid chain to lysine in position 26[20]. The fatty di-acid side chain and the spacer mediate strong binding to albumin, thereby reducing renal clearance. The amino acid substitution at position 8 makes semaglutide less susceptible to degradation by dipeptidyl peptidase-4 (DPP-4). The change in position 34 from a lysine to an arginine is included to have only one lysine in the sequence where to a spacer can be attached.

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

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

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

3.1.4 Non-clinical data

3.1.4.1 Semaglutide

The non-clinical programme for semaglutide was designed according to the ICH M3 guideline[21] to support the clinical development. The standard non-clinical 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 monkeys, 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 non-clinical 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 non-clinical 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 (NN9924-4223 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 adverse event (AE) requiring additional data collection, please refer to section 8.4.1.2, section 12.1.5 and appendix B.

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

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

3.1.5 Clinical data for oral semaglutide

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

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

3.1.5.1 Pharmacokinetics

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

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

Exposure of semaglutide exhibits a substantially greater dose-to-dose variation following oral administration compared to 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]

[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. 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.

3.2 Rationale for the trial

Many patients with T2DM are not in glycaemic control with the currently marketed oral anti-diabetic drugs. 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 aim of this 26-week, confirmatory phase 3a trial is to demonstrate superiority with three doses of oral semaglutide versus placebo on HbA_{1c} and body weight in T2DM subjects treated with diet and exercise only, and to evaluate the efficacy and safety of oral semaglutide in a monotherapy setting.

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary Objective

To compare the effects of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) versus once-daily placebo on glycaemic control in subjects with type 2 diabetes mellitus treated with diet and exercise only.

4.1.2 Secondary Objectives

To compare the effects of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) versus once-daily placebo on body weight in subjects with type 2 diabetes mellitus treated with diet and exercise only.

To compare the safety and tolerability of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) versus once-daily placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only.

4.2 Endpoints

Baseline refers to randomisation, and week 26 refers to 26 weeks after randomisation.

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 asterix (*)

Change from baseline to week 26 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))
- C-reactive protein (CRP)
- 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, high-density lipoprotein (HDL) cholesterol and triglycerides)
- Patient-reported outcomes (PROs) based on:
  - Short Form (SF)-36v2^{TM} (acute version) health survey
  - Impact of Weight on Quality of Life (IWQOL-Lite) Clinical Trial Version
  - Patient Global Impression of Status (PGI-S) Items
  - Patient Global Impression of Change (PGI-C) Items

If a subject after week 26 achieve (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 $\geq$ 1%-point (10.9 mmol/mol)
- Body weight loss $\geq$ 3%
- Body weight loss $\geq$ 5%
- Body weight loss $\geq$ 10%
- $HbA_{1c} < 7.0\%$ (53 mmol/mol) without hypoglycaemia (treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes) and no body weight gain
- HbA_{1c} reduction $\geq$ 1%-point (10.9 mmol/mol) and body weight loss $\geq$ 3%

Time to event:

- Time to rescue medication

Supportive secondary safety endpoints

- Number of treatment-emergent adverse events (TEAEs) during exposure to trial product, assessed up to approximately 31 weeks*
- Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 31 weeks*
- Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 31 weeks (yes/no)

Change from baseline to week 26 in:

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

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

- Lactate

Any occurrence of anti-semaglutide antibodies (yes/no) up to approximately 31 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 31 weeks:

- Anti-semaglutide binding antibody levels

Supportive secondary pharmacokinetic endpoints

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

5 Trial design

5.1 Type of trial

This is a 26-week, randomised, double-blinded, placebo-controlled, four-armed, parallel-group, multi-centre, multi-national trial comparing the efficacy and safety of three dose levels of once-daily oral semaglutide and placebo in subjects with T2DM treated with diet and exercise only.

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

- 3 mg oral semaglutide once daily
- 7 mg oral semaglutide once daily
- 14 mg oral semaglutide once daily
- Placebo once daily

The randomisation will be stratified based on descent (Japanese subjects/non-Japanese subjects).

The total trial duration for the individual subject will be approximately 33 weeks, including a 2-week screening period followed by a 26-week randomised treatment period and a 5-week follow-up period. The trial design is illustrated in Figure 5–1.

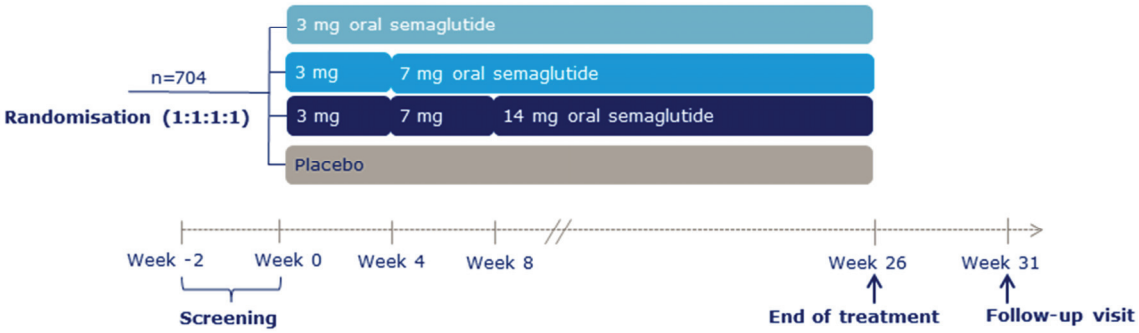


Figure 5–1 Trial design

5.2 Rationale for trial design

The trial has been designed as a parallel-group, 4-armed superiority trial to compare three doses of oral semaglutide with placebo in a monotherapy setting. Subjects will be randomised and the trial will be double blinded.

There will be strict rescue criteria in place to ensure acceptable glycaemic control during the trial for all treatment arms, including the placebo arm (see Section 6.4).

The treatment duration of 26 weeks is considered adequate to evaluate the efficacy of semaglutide versus placebo, and furthermore, for the assessment of safety and tolerability.

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

Subjects will be randomised to oral semaglutide or placebo. Subjects randomised to oral semaglutide will initiate treatment with 3 mg once daily. Subjects randomised to a treatment dose of 7 or 14 mg, will follow a fixed 4-week dose-escalation regimen until reaching the maximum randomised dose, as illustrated in Table 5–1. All dose levels, including the dose-escalation, will be blinded. To mitigate the risk of gastrointestinal AEs, it is important to follow the fixed 4-week dose escalation intervals.

Table 5–1 Treatment of subjects

Trial periods		**Screening**	**Treatment period 1**	**Treatment period 2**	**Treatment period 3**	**Follow-up**
First visit in each period		**V1**	**V2**	**V4**	**V5**	**V9**
Duration of each period		**2 weeks**	**4 weeks**	**4 weeks**	**18 weeks**	**5 weeks**
Treatment arm	**N**					
Oral semaglutide (3 mg)	176	Screening	3 mg	3 mg	3 mg	Follow-up
Oral semaglutide (7 mg)	176	Screening	3 mg	7 mg	7 mg	Follow-up
Oral semaglutide (14 mg)	176	Screening	3 mg	7 mg	14 mg	Follow-up
Placebo	176	Screening	Placebo	Placebo	Placebo	Follow-up

5.3.1 Dosing instructions

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. Trial product can be taken with up to half a glass of water (approximately 120 mL/4 fluid oz). The tablet must be swallowed whole by the subject and must not be broken or chewed (see Table 9–2). Furthermore, other oral medication can be taken 30 minutes after administration of trial product.

5.3.2 Background medication

As the present trial is a monotherapy trial no anti-diabetic medications are allowed 90 days before visit 1 and during the trial. Please see Section 6.4 with regards to rescue medication.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products, either at the scheduled end-of-treatment visit (see Section 8.1.4) or if trial product is discontinued prematurely (see Section 8.1.5), the subject should be switched to a suitable marketed product at the discretion of the investigator. After discontinuation of trial product, 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.

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 4-week dose escalation step have been chosen based on the data from the phase 2 dose-finding trial NN9924-3790. The regimen is expected to have the optimal benefit risk profile for further development for treatment of T2DM in the PIONEER programme.

Subjects randomised to 14 mg oral semaglutide will be dose escalated to the highest dose level to investigate and establish maximum efficacy and safety in subjects in a monotherapy setting.

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 (number of subjects providing informed consent): 1050

Number of subjects planned to be randomised: 704

Number of subjects expected to complete the trial on or off trial product: 634

For Japan only: 100 Japanese subjects are planned to be randomised with an approximate equal distribution across the 4 treatment arms.

For Mexico only: 45 subjects are planned to be randomised/started on trial product in Mexico

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.
   For Japan only: Male or female, age ≥ 20 years at the time of signing informed consent.
   For Algeria only: Male or female, age ≥ 19 years at the time of signing informed consent.
3. Diagnosed with type 2 diabetes mellitus ≥ 30 days prior to day of screening.
4. HbA_{1c} between 7.0-9.5% (53-80 mmol/mol) (both inclusive).
5. Treatment with diet and exercise for ≥30 days prior to 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 Japan only: Adequate contraceptive measures are abstinence (not having sex), diaphragm, condom (by the partner), intrauterine device, sponge, spermicide or oral contraceptives.
4. Receipt of any investigational medicinal product within 90 days before screening.
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 carcinomas (MTC).
7. History of pancreatitis (acute or chronic).
8. History of major surgical procedures involving the stomach potentially affecting absorption of trial product (e.g. subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery).
9. Any of the following: myocardial infarction, stroke or hospitalisation for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening and randomisation.
10. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
11. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
12. Subjects with alanine aminotransferase (ALT) > 2.5 x upper normal limit (UNL).
13. Renal impairment defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 as per Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI).
14. Treatment with any medication for the indication of diabetes or obesity 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 in-situ carcinomas).

6.4 Rescue criteria

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification. To allow time for dose escalation 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 values described below, the subject should be offered rescue medication (i.e. initiation of anti-diabetic medication):

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

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

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.

Rescue medication is considered to be non-investigational medicinal product (NIMP) and will not be provided by Novo Nordisk.

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 the trial product or unacceptable intolerability
- Included in the trial in violation of the inclusion and/or exclusion criteria
- Pregnancy
- Intention of becoming pregnant
- Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product (IMP)
- Calcitonin ≥ 100 ng/L

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

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

6.6 Withdrawal from trial

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

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

For Mexico only: should the subject, his/her family members, parents or legal representative decide to withdraw the consent for participation in the trial, the subject will be entitled to receive appropriate, free of charge medical care and/or trial drug during the follow-up period of the protocol when it will be established with certainty that no untoward medical consequences of the subject´s participation in the research occurred.

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 only diet and exercise for at least 30 days prior to screening in order to evaluate the efficacy and safety of oral semaglutide in a monotherapy setting. Furthermore, no anti-diabetic medication are allowed at least 90 days prior to screening as changes in background treatment shortly before trial participation may potentially impact the data interpretation. The upper HbA_{1c} limit of 9.5% (80 mmol/mol) has been chosen as this is a placebo-controlled trial. FPG will be monitored throughout the trial and rescue medication should be initiated in subjects with persistent, unacceptable hyperglycaemia. Subjects with liver test abnormalities (ALT > 2.5 x UNL) will be excluded to avoid potential confounding of liver safety assessments. Overall, the eligibility criteria will allow for enrolment of a relatively broad trial population resembling the target population in common clinical practice.

7 Milestones

Planned duration of recruitment period FSFV-LSFV: 28 weeks

Planned FSFV: 20-Sep-2016

Planned LSLV: 27-Nov-2017

End of trial is defined as LSLV.

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

8 Methods and assessments

8.1 Visit procedures

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

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

Each subject will attend 8 site visits and 1 phone contact. It is the responsibility of the investigator to ensure that all visits occur according to the flow chart.

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 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.

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.

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 visit 1 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 misplaced), 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 and injectable medications can be administered after blood sampling. Exceptions are visits were samples for SNAC PK and lactate are taken. At these visits, other oral medication must be taken after last blood samples are taken. 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 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, HDL cholesterol, triglycerides)
- Lactate
- SNAC PK

8.1.3 Randomisation and trial product administration

Eligible subjects will be randomised into one of 4 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. It is important to dispense the exact allocated DUNs to the subject. When DUNs are dispensed, please confirm the dispensed date in the IWRS.

All visit 2 assessments must be performed before administration of first dose of trial product.

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

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

8.1.4 End-of-treatment (visit 8) and Follow-up (visit 9)

Subjects, who stay on trial product throughout the trial, must attend the end-of-treatment visit (V8) 26 weeks after randomisation (±3 days visit window) and the Follow-up visit (V9) 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 visit 8 (see Section 10).

In case the subject cannot be reached (by site visit or phone contact) at the scheduled visit 9, the site should consult the contacts provided by the subject (e.g. close relatives), relevant physicians, medical records and locator agencies (if allowed according to local law) to collect health status. If no health status can be collected, the subject should be considered lost to follow-up and this should be specified in the end-of-trial form.

8.1.5 Premature discontinuation of trial product and follow-up (visits 8A and 9A)

Subjects, who discontinue trial product prematurely, should attend visit 8A, scheduled to take place on the day of discontinuation of trial product (+ 3 days visit window). Visit 9A 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 visit 8A (see Section 10).

If premature discontinuation of trial product is decided during a scheduled visit, the visit will be converted into a V8A and trial procedures must be performed accordingly.

Subjects should continue with the originally scheduled site contacts after visit 9A and up to and including visit 8. After visit 9A, samples for antibodies, PK and lactate assessment should not be taken. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after visit 9A. However, as a minimum, these subjects should be asked to attend the scheduled end-of-treatment visit (V8) at week 26 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 scheduled V8, should not be considered withdrawn from the trial. In case the subject cannot be reached (by site visit or phone contact) at the scheduled V8, 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 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.

8.1.6 Withdrawal from trial

If a subject considers withdrawing from the trial, the investigator must aim to undertake procedures for visit 8A as soon as possible and visit 9A should be scheduled 5 weeks (+3 days visit window) after the last date on trial product, if the subject agrees to it.

Subjects who agree to attend or provide health status at the planned V8 should not be considered withdrawn from the trial.

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.

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 fundus photography/dilated fundoscopy 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 visit 1 or assessments revealing baseline conditions at visit 2, the investigator must state a comment in the subject's medical record and record this in the concomitant illness and medical history 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 T2DM
- 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 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 (at visit 1) on the disease specific forms only, i.e. not on the concomitant illness and medical history form:

- **History of cardiovascular disease** (e.g. ischaemic heart disease, myocardial infarction, 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 and a valid fundus photography/dilated fundoscopy if previous assessment is used in source documents such as subject's medical record. If a subject is not from the investigators own practice, the investigator must make reasonable effort to obtain a copy of subject's medical record from relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

8.2.4 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

Contraceptive methods

For Japan only: Adequate contraceptive measures are abstinence (not having sex), diaphragm, condom (by the partner), intrauterine device, sponge, spermicide or oral contraceptives.

8.2.6 Tobacco use

Details of tobacco use must be recorded at visit 1. 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 Blood samples for efficacy

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 (for fasting see Section 8.1.2):

Glucose metabolism:

- HbA_{1c}
- FPG
- Fasting C-peptide
- Fasting insulin and proinsulin
- Fasting glucagon

Fasting lipids profile:

- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides

Other parameters:

- Semaglutide PK (please refer to Section 8.6.2)
- SNAC PK (please refer to Section 8.6.2)
- CRP

8.3.2 Self-measured plasma glucose (SMPG)

At visit 1, 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 should be used for the measurements required in the protocol.

For Japan only: The trial sites are allowed to purchase and supply themselves with BG meters, if possible. BG meters must be the same model as supplied by Novo Nordisk.

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 two 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 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 inch using a non-stretchable measuring tape. The same measuring tape should be used throughout the trial.

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

8.3.5 Patient reported outcomes questionnaires

PRO will be assessed using the questionnaires:

- SF-36v2™ (acute version) health survey[32-34]
- IWQOL-Lite Clinical Trial Version[35, 36]
- PGI-S items
- PGI-C items

The questionnaires SF-36v2™ and IWQOL-Lite Clinical Trial Version are commonly used instruments to evaluate the PROs, also in the T2DM area. The PGI-S items are designed to assess patients' impression of their health status and the PGI-C items are designed to assess patients' impression of change of their health.

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 fifteen minutes to complete the four questionnaires. Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. The completed questionnaires must be reviewed for potential adverse events and missing data while the subject is still at the site. All results from the PRO questionnaires must be transferred into the eCRF.

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

SF-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.

Impact of Weight on Quality of Life Clinical Trial Version

The IWQOL-Lite for Clinical Trials was adapted from the IWQOL-Lite and measures the health-related quality of life. The IQWOL-Lite Clinical Trial Version contains 22 items.

Patients Global Impression of Status Items

The PGI-S assesses patients' impression of physical functioning and mental health status during the clinical trial. The PGI-S contains two items.

Patients Global Impression of Change items

The PGI-C assesses patients' impression of change in physical functioning and mental health during the clinical trial compared to when they entered the trial. Hence, the PGI-C should not be answered at V2. The PGI-C contains two items.

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 and appendix B):

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

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

8.4.1.2 Adverse events requiring additional data collection

For the following AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form (see Section 12.1.5):

- Acute coronary syndrome (myocardial infarction 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 events 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 events leading to trial product discontinuation

*Please note that in case of a hepatic event defined as ALT or AST > 3x UNL and total bilirubin > 2x UNL, where no alternative aetiology exists (Hy's law), this must be reported as an SAE using the important medical event criteria 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 serious adverse event, please report accordingly, see Section 12.

8.4.2 Physical examination

A physical examination will be performed by the investigator according to local procedure (see flow chart, 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

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

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

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

8.4.5 Electrocardiogram (12–lead)

12-lead ECG will be performed as per flow chart (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 myocardial infarction (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 in according to Section 12.

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

All findings suggestive of new MI detected by the central ECG reading will be adjudicated by the Event Adjudication Committee (EAC) (see Section 12.7.2).

8.4.6 Blood samples for safety

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:

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

Hormones:

- Calcitonin

Other parameters:

- Lactate (please refer to Section 8.6.1)
- Anti-semaglutide antibodies (please refer to Section 8.4.8)

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

8.4.7 Pregnancy testing

Females of childbearing potential will have a urine dip-stick pregnancy test performed at site as specified in Section 2 or as required by local law. For definition of female of non-childbearing potential and contraceptive methods, see Section 8.2.5.

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 serum 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 visit 1 to end of trial.

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

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

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

The record should include the following information:

- Start date and time of the hypoglycaemic episode.
- Stop date and time of the hypoglycaemic episode (stop time is the first time the PG value is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved).
  If a stop date and time is not reported, a hypoglycaemic episode will cover a period of 60 minutes.
- The PG level before treating the episode (if available) and any follow-up measurements.
  The lowest value measured during the hypoglycaemic episode will be reported as the PG value for the episode, the remaining values will be kept as source data in the diary.
- Whether the episode was symptomatic (Yes/No).
  A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experience 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 date, time and dose of other anti-diabetic medication prior to the episode.
- Date and time of last main meal (not including snacks) prior to the episode.
- Whether the episode occurred in relation to physical activity.
- Change in any concomitant illness.
- Any sign of fever and/or other acute disease.
- Whether the subject was asleep when the episode occurred.
  - If yes, whether the symptoms of the episode woke up the subject.

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

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

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

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)

- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by another person (i.e. oral carbohydrates, glucagon, intravenous glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet changed, medication error (i.e. overdose, mix-up between products, incorrect use of device), other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[39]
  - 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 [40, 41].

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 to semaglutide and GLP-1, IgE anti-semaglutide antibodies and PK samples (semaglutide and SNAC) 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).

For Mexico only: Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling, transportation and storage of biological samples and information regarding who will perform the assessments, will be described in a trial specific laboratory manual, provided by the central laboratory (for central laboratory details, see attachment 1).

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.

The central laboratory will provide laboratory results to the investigator on an on-going basis. However, anti-semaglutide antibody, semaglutide and SNAC 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.

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 8.2.3 and Section 12.

Laboratory samples will be destroyed no later than at finalisation of the clinical trial report, or according to local regulations, except samples obtained for antibody analysis. Antibody samples will be stored as described in Section 24.2.

8.5.1 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).

8.6 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 18). At selected visits (see flow chart, 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

At visits with lactate sampling trial product must be taken at site. The subject must be fasting and not take any other oral medication until last sample has been taken, that is, at least 40 minutes after dosing (see Section 8.1.2 in case the subject attends the visit in a non-fasting state). 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) and if blood pressure measurement has been performed prior to sampling, blood should preferably be drawn from the opposite arm.

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

The date and exact time of dosing of trial product must be recorded in the medical record and entered into the eCRF. The date and exact time of sampling must be recorded at the laboratory requisition form.

8.6.2 Pharmacokinetics

Blood samples for the semaglutide and SNAC PK will be drawn at selected visits (see flow chart, Section 2) and must be collected, handled and shipped according to the description in the laboratory manual.

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.

Semaglutide PK and SNAC PK samples will be stored at the specialised laboratory until final clinical trial report in case Novo Nordisk request further analysis of the PK samples.

8.6.2.1 SNAC PK sampling

Samples for SNAC PK should be drawn at the following time points in relation to dosing of trial product:

- 25 (+/- 5) minutes post-dosing
- 40 (+/- 5) minutes post-dosing

At visits with sampling of SNAC PK trial product must be taken at site. The subject must be fasting and not take any other oral medication until last sample has been taken (see section 8.1.2 in case the subject attends the visit in a non-fasting state).

The date and exact time of dosing of trial product must be recorded in the medical record and entered into the eCRF. The date and exact time of sampling must be recorded at the laboratory requisition form.

8.6.2.2 Semaglutide PK sampling

Samples for semaglutide PK can be drawn at any time during the visit. For simplicity it is recommended to take the sample for semaglutide PK together with biochemistry samples at all visits requiring semaglutide PK.

The date and exact time of the latest trial product administration prior to semaglutide PK sampling must be recorded in the diary and entered into the eCRF. The date and time of sampling must be recorded at the laboratory requisition form.

8.6.3 Subject diary

The diaries should be handed out at the visits described in the flow chart (see Section 2). The recordings must be reviewed as described in Section 8.1.7 and transcribed into 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
- Date and exact time of last trial product administration on the day prior to sampling of semaglutide PK
- 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 and dosepacks. 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.

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 (IMPs) 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/ packaging materials
Semaglutide 3 mg tablet	3 mg	Tablet	Oral	Dosepack[a]
Semaglutide 7 mg tablet	7 mg			
Semaglutide 14 mg tablet	14 mg			
Placebo tablet	N/A			

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

Rescue medication is considered NIMP and will not be supplied by Novo Nordisk.

For Japan only: During the treatment period, all anti-diabetic medication including rescue medication will be reimbursed by Novo Nordisk Japan according to the local requirement.

The semaglutide tablets and the placebo tablets are identical with regard to visual appearance and all semaglutide tablets are visually identical to each other, irrespective of dose levels.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[42], 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 freeze Do not refrigerate 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		
Placebo 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 Trial Materials Manual.

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.

For Japan only: The head of the study site or the trial product storage manager if assigned by the head of the study site must ensure the availability of proper storage conditions, record and evaluate the temperature.

9.4 Drug accountability and destruction

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

For Japan only: Drug accountability is the responsibility of the head of the study site or the trial product storage manager if assigned by the head of the study site.

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 as unused 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 supply

The following will be provided by Novo Nordisk in accordance with the Trial Material Manual:

- BG meters and BG meter auxiliaries

For Japan only: The trial sites are allowed to purchase and supply themselves with auxiliary supplies, if possible. BG meters must be the same model as supplied by Novo Nordisk.

10 Interactive web/voice 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
- Code break
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

The trial is a double-blinded trial. A randomisation session will be carried out for all subjects using the IWRS. The randomisation will be stratified based on descent (Japanese subjects/non-Japanese subjects) to ensure an even distribution of the four treatment arms (see Section 17).

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

11.1 Breaking of blinded codes

The IWRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

The code for a particular subject may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Whenever a code is broken the person breaking the code must print the Code Break Confirmation Notification generated by the IWRS, record the reason and sign and date the document.

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IWRS is not accessible at the time of code break the IWRS helpdesk should be contacted. Contact details are listed in attachment I. If the code has been broken the subject must discontinue treatment with trial product but be asked to continue in the trial (see Section 8.1.5). A treatment discontinuation session must be completed in the IWRS.

The laboratory responsible for antibody and PK (semaglutide and SNAC) analysis and the responsible development bioanalysis scientist in Novo Nordisk will have access to the unblinding report in the IWRS.

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 clinical laboratory adverse event (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

A 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 adverse events must always be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:

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

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

12.1.3 Non-serious adverse event

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

12.1.4 Medication errors

A medication error concerning trial products is defined as:

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

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

12.1.5 Adverse events requiring additional data collection

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

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

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

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

Event	Specific event form	Event adjudication
Death	No	Yes
Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)	Yes	Yes
Cerebrovascular event (stroke or transient ischaemic attack)	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 reactions	Yes	No
Acute gallstone disease	Yes	No
Medication error	Yes	No
Lactic acidosis	Yes	Yes
CK > 10x UNL	Yes	No
Hepatic events defined as: ALT or AST > 5x UNL and total bilirubin ≤ 2x UNL ALT or AST > 3x UNL and total bilirubin > 2x UNL* Hepatic events leading to trial product discontinuation.	Yes	No

*Please note that in case of a hepatic event defined as ALT or AST > 3x 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 Section 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) 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 (V9) for subjects on trial product, or until the end of trial (V8 or V9A, 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 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 these 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 event adjudication committee (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 investigators first knowledge of the AE.

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

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

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

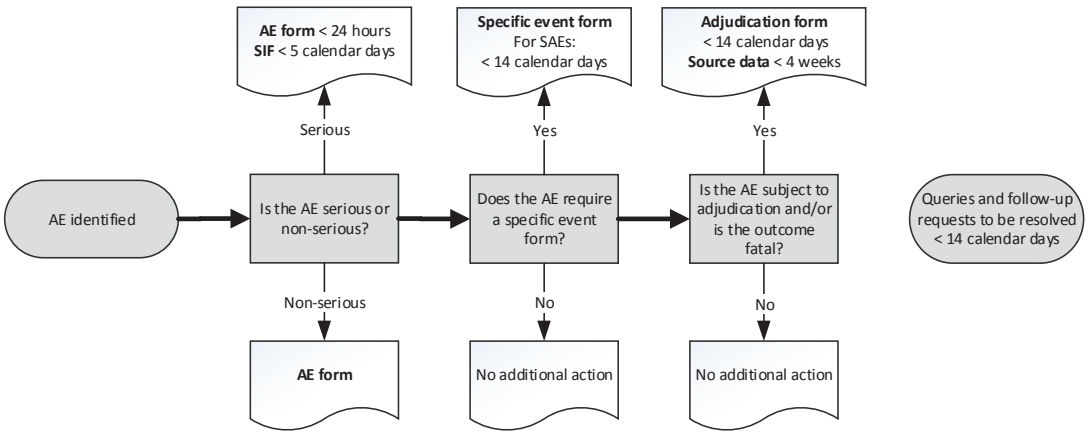


Figure 12–1 Reporting of adverse events

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the following reference documents: IB for oral administration of semaglutide (NN9924) edition 6[24] or any updates hereof.

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 (EMA), of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP[1], unless locally this is an obligation of the investigator.

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

If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as non-investigational medicinal product or concomitant medication in the trial, it is important that the

suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the 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 on-going 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 on-going 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/7 mg/14 mg or placebo 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 code 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 code number and, if available, the DUN. All parts of the DUN should be returned.

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

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

12.5 Pregnancies in female subjects

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

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

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

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

1. **Reporting of pregnancy information**

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

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

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

2. **Reporting of AE information**

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

Forms and timelines for reporting AEs:

Non-serious AEs:

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

SAEs:

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

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 on-going safety surveillance. The oral semaglutide safety committee may recommend unblinding of any data for further analysis and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

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 source 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 FDA requirements[43].

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 (UAP)	• Acute myocardial infarction (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 the UNL • Characteristic findings of acute pancreatitis on imaging	Acute pancreatitis • Mild • Moderately severe • Severe

Events	Description	Adjudication outcome
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 category	• Malignant neoplasm
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[44] 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 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.

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

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 of 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 LSLV at the site in order to ensure the planned lock of the database.

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

14 Monitoring procedures

Monitoring will be conducted under a risk based approach.

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

The monitor must be given direct access to all source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated

printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

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

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

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

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

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

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

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

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

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

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to another data management unit within Novo Nordisk or an external 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 may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The statistical analysis plan will be finalised before database lock.

The blinding of the randomised treatments will be maintained until the database has been released for statistical analysis.

Data from all sites will be analysed and reported together.

The randomisation is stratified based on descent (Japanese subjects/non-Japanese subjects). The information regarding descent will be included based on country details from the IWRS. Descent (Japanese subjects/non-Japanese subjects) will be included in the statistical analyses as part of region.

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

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

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

- Oral semaglutide 14 mg vs. placebo
- Oral semaglutide 7 mg vs. placebo
- Oral semaglutide 3 mg vs. placebo

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

Primary and secondary estimands

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

- Primary estimand
  - de-facto treatment difference (oral semaglutide versus placebo) 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). 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 treatment adherence reflects the behaviour of the target population. Accordingly, data collected regardless of discontinuation of trial product or initiation of rescue medication(s) will be used to draw inference.

- Secondary estimand
  - de-jure treatment difference (oral semaglutide versus placebo) 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. It is considered a clinically relevant estimand as it provides information to treating clinicians about the expected glycaemic efficacy of oral semaglutide 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, is expected to be maximum 10% based on the oral semaglutide phase 2 trial (NN9924-3790). Thus, missing data will mainly be due to withdrawal from trial or lost to follow-up.

When estimating the secondary estimand, the proportion of missing data is expected to be higher (20%) since data collected after discontinuation of trial product or initiation of rescue medication(s) will be set to missing. The 20% of missing data is based on the oral semaglutide phase 2 trial (NN9924-3790), that indicates that a low starting dose with gradual dose escalation diminishes gastrointestinal AEs compared with more aggressive dosing regimens. Across treatment arms the

main reasons for missing data are expected to be early treatment discontinuation due to gastrointestinal AEs and eventually initiation of rescue medication. Initiation of rescue medication is expected to be more frequent in the placebo arm and in the oral semaglutide 3 mg arm than for the two highest dose levels of oral semaglutide. A higher proportion of subjects are expected to discontinue treatment due to AEs in the oral semaglutide 14 mg arm, compared to the other treatment arms. 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

Both the primary endpoint, change from baseline to week 26 in HbA_{1c} and the confirmatory secondary endpoint, change from baseline to week 26 in body weight are planned to be tested for superiority of oral semaglutide vs. placebo at each dose level (3 mg, 7 mg, and 14 mg).

The sample size calculation is made to ensure a power of at least 90% to jointly confirm HbA_{1c} superiority of oral semaglutide vs. placebo at each dose level out of the six pre-specified confirmatory hypotheses shown in Figure 17–1. The closed testing procedure described in Bretz et al.[45] is used to control the overall type I error at a nominal two-sided 5% level. The statistical testing strategy is built on the following two principles:

- Within a dose level, glycaemic effect must be established in terms of HbA_{1c} superiority before testing for added benefits in terms of body weight superiority.
- Glycaemic effect in terms of HbA_{1c} superiority must be established on all higher dose levels before continuing testing hypotheses on lower dose levels.

The sample size is calculated using the calcPower function in the R package, gMCP[46] using 10000 simulations. All of the six 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 common standard deviations used across dose levels are given in Table 17–1. These are primarily based on the oral semaglutide phase 2 results (NN9924-3790) and supported by results from the s.c. semaglutide phase 2 trial (NN9535-1821).

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. The adjusted treatment effects for testing superiority are defined as 0.8×TE + 0.2×TE×0.25.

Table 17–1 Assumptions used in the sample size calculation

Oral semaglutide vs. placebo	HbA_{1c} (%-point)			Body weight (kg)		
Treatment dose	14 mg	7 mg	3 mg	14 mg	7 mg	3 mg
Treatment effect (TE)	-1.0	-0.75	-0.45	-3.0	-2.0	-1.0
Adjusted TE, superiority	-0.85	-0.6375	-0.3825	-2.55	-1.70	-0.85
Standard deviation	1.1	1.1	1.1	4.0	4.0	4.0

With the above assumptions, allocating 176 subjects to each of the oral semaglutide arms and the placebo arm provides 90% power to confirm HbA_{1c} superiority of oral semaglutide vs. placebo at all dose levels. Calculated powers for individual hypotheses are presented in Table 17–2. In total 4×176 = 704 subjects are planned to be randomised.

Table 17–2 Calculated powers for individual hypotheses

Statistical test	HbA_{1c} superiority			Body weight superiority		
Treatment dose	14 mg	7 mg	3 mg	14 mg	7 mg	3 mg
Power (%)	> 99%	> 99%	90%	> 99%	96%	46%

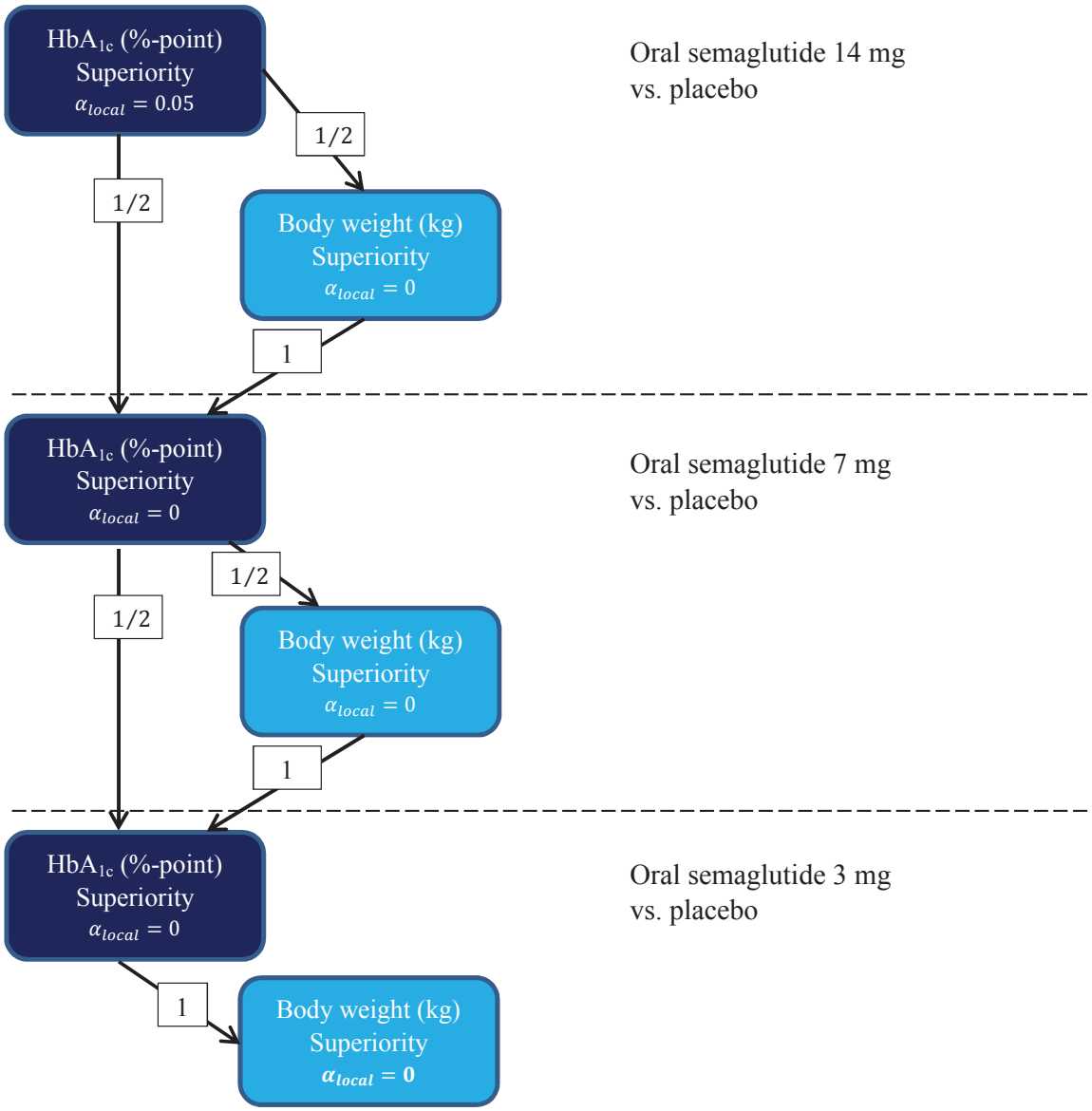


Figure 17–1 Graphical illustration of the closed testing procedure

The overall significance level of α = 0.05 (two-sided) is initially allocated to the HbA_{1c} superiority test on the highest dose level. 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 hypotheses in the dark boxes.

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 based on the trial product received for the majority of the period where they were on treatment. This will be referred to as contributing to the evaluation "as treated".

Data selections and observation periods

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

- The follow-up visit (V9) for subjects on trial product
- The latest occurring visit of the end-of-treatment visit (V8) or the follow-up premature discontinuation visit (V9A), 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 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 IWRS) and ends at the date of:

- The last direct subject-site contact, which is scheduled to take place 5 weeks after planned last dose of trial product at a 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 the trial product. The observation period is a subset of the in-trial observation period. It starts at the date of first dose of trial product. Two slightly different end dates will be needed to cover all assessments appropriately. For adjudicated events, ECGs, 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 (V9)
- The follow-up prematurely discontinuation visit (V9A)
- 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. Specifically it starts at date of first dose of trial product and the end date is the first date of any of the following:

- The last dose of trial product + 3 days
- Initiation of rescue medication

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

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

Before data are locked for statistical analysis and the randomisation code is broken, a review of all data will take place. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group. Exclusion of data from analyses should be used restrictively and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

Confirmatory hypotheses

For the primary HbA_{1c} endpoint and the confirmatory secondary body weight endpoint the following confirmatory one-sided hypotheses are planned to be tested at each dose level of oral semaglutide versus placebo. Let the mean treatment difference be defined as μ = (oral semaglutide minus placebo):

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

- 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 at the 5% significance level.

Multiplicity and criteria for confirming hypotheses

The type I error for testing the six 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.[45] and outlined in Figure 17–1.

The first hypothesis to be tested is superiority of HbA_{1c} at the highest dose level. 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, then 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 updated local significance level (α-local). This process will be repeated until no further hypotheses can be confirmed.

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 8 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 placebo at week 26:

For each of the 100 (now complete) imputed data sets the change from baseline to week 26 in HbA_{1c} 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[47] to draw inference.

From this analysis the estimated treatment differences between each of the oral semaglutide dose levels and placebo together with associated two-sided 95% confidence intervals and unadjusted two-sided p-values for testing no difference from zero 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 medication 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 EMA recommendations[48] and with a report from the US National Research Council[49], these analyses will primarily evaluate the sensitivity of the results due to the impact of missing data.

The evaluation of the robustness of the primary analysis 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, one additional sensitivity analysis for the primary analysis will be described that is 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
- A comparator multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely based on FAS using the in-trial observation period
- A tipping-point multiple imputation analysis based on FAS using the in-trial observation period
- An MMRM analysis (the primary analysis for the secondary estimand) based on FAS using the in-trial observation period

Sensitivity analyses for the secondary estimand

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

- A comparator multiple imputation analysis based on FAS using the on-treatment without rescue medication observation period.
- A comparator multiple imputation analysis based on FAS using the on-treatment observation period. This sensitivity analysis aims to compare oral semaglutide versus placebo 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.
- A tipping-point multiple imputation analysis based on FAS using the on-treatment without rescue medication observation period.

17.3.3.1 Pattern mixture models

Common for the 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 arms, while maintaining the missing at random data assumption for the placebo 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 placebo treatment arm. In effect this imputation approach removes the

treatment difference between oral semaglutide and placebo for all subjects randomised to oral semaglutide, given that oral semaglutide is better than placebo.

- *Comparator multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely:* In this sensitivity analysis only missing data at week 26 for subjects who discontinue oral semaglutide treatment due to treatment related AEs will be imputed to resemble the distribution of the week 26 values observed in the placebo 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 placebo for this selected group of subjects randomised to oral semaglutide.
- *Tipping-point multiple imputation analysis:* In this sensitivity analysis, missing data will first be imputed according to the primary analysis. Secondly, for all oral semaglutide treatment arms a penalty will be added to the imputed values at week 26. The approach is to gradually increase this penalty until all confirmed HbA_{1c} conclusions from the primary analysis are changed. For each hypothesis tested the specific value of the penalty that reverses the conclusion will be used to evaluate the robustness of the primary analysis results.

17.3.3.2 Other sensitivity analyses

The following additional sensitivity analysis will be specified:

- *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.

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 sensitivity analyses inherent conservative nature, it will not be a requirement that all confirmatory hypotheses are consistently confirmed across the sensitivity analyses. Thus, no absolute success criteria will be pre-defined for each sensitivity analysis. The sensitivity results in totality will be used to substantiate the credibility of the trial results.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoints

Change from baseline to week 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. Baseline body weight will be used as a covariate instead of baseline HbA_{1c} in both the multiple imputation and MMRM analysis models.

Superiority will be considered confirmed if the mean treatment difference is supporting the corresponding hypothesis and the two-sided p-value from the analysis of the primary estimand is strictly below its local two-sided significance level resulting from the closed testing procedure in Figure 17–1. Sensitivity analyses similar to the ones pre-specified for 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 26 in:

- 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))
- CRP
- Body weight (%)
- BMI
- Waist circumference
- Fasting lipid profiles (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)

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

BMI kg/m^2 = body weight (kg)/(height (m) × height (m)) or (kg/m^2 = [lb/in^2 × 703])

Change from baseline to week 26 in the below derived endpoints from the SMPG 7-point 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 analyses will be performed at week 26. This will result in imputation of missing data within 8 groups as described for the week 26 evaluation in Section 17.3.1.

For evaluation of the secondary estimand the MMRM based primary analysis will include all scheduled post-baseline measurement up to and including week 26. From this model the estimated treatment differences (ratios) will be presented at week 26 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 ≥ 1 %-point (10.9 mmol/mol)
- Body weight loss ≥ 3 %
- Body weight loss ≥ 5 %
- Body weight loss ≥ 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 ≥ 1 %-point (10.9 mmol/mol) and weight loss ≥ 3 %

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 HbA_{1c} for binary HbA_{1c} endpoints, baseline weight for weight endpoints and both baseline HbA_{1c} and baseline weight for the binary endpoints 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[47].

Time to event endpoint

- Time to rescue medication

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

The endpoint will be described and compared for oral semaglutide versus placebo using likelihood ratio tests obtained from a Cox proportional hazards model with treatment, stratification factors, the interaction between the two stratification factors and region as categorical fixed effects and baseline HbA_{1c} as a covariate. From this analysis the estimated Hazard ratios between oral semaglutide versus placebo will be presented together with 95% confidence intervals and two sided p values for test of no difference.

17.4.2.2 Safety endpoints

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

Adverse events

- Number of TEAEs during exposure to trial product, assessed up to approximately 31 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 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. 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 in:

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

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

- Lactate

Any occurrence of anti-semaglutide antibodies (yes/no) up to approximately 31 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 31 weeks:

- Anti-semaglutide binding antibody levels

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

Hypoglycaemia

- Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 31 weeks
- Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 31 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)[50]. Therefore, Novo Nordisk has included hypoglycaemia with PG levels below this cut-off point in the definition of BG-confirmed hypoglycaemia.

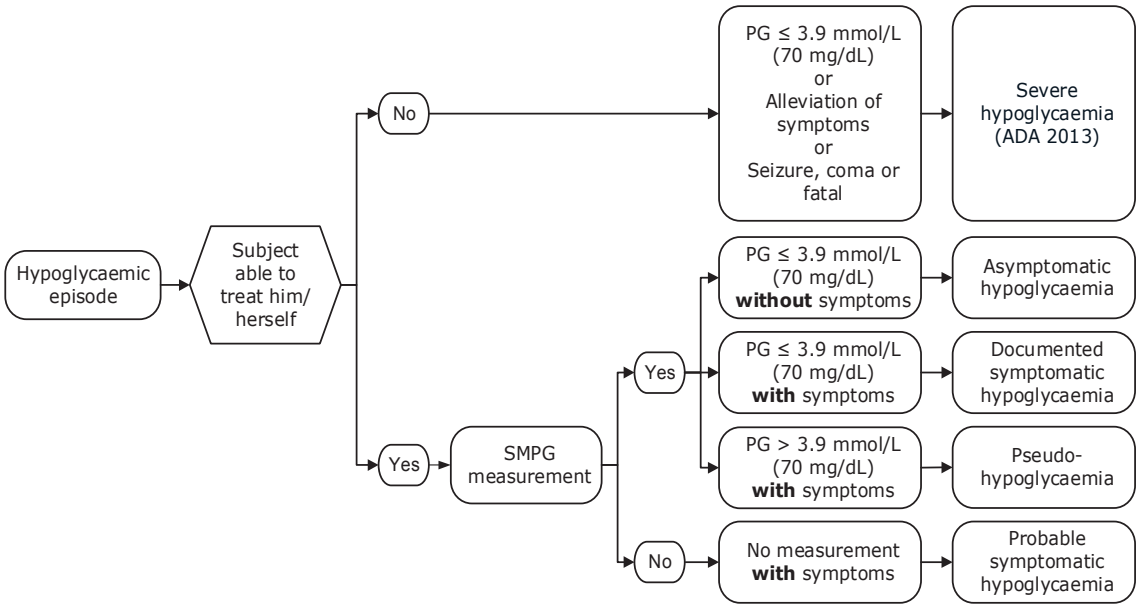
Novo Nordisk uses the following classification in addition to the ADA classification:

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

ADA classification[38] of hypoglycaemia

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

- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured PG concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a PG determination but that was presumably caused by a PG concentration ≤ 3.9 mmol/L (70 mg/dL).



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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–2 ADA classification of hypoglycaemia

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

Analysis of severe or BG-confirmed symptomatic hypoglycaemic endpoints

The number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes in the on-treatment period will be analysed using a negative binomial regression model with a log-link function and the logarithm of the duration of the subject's on-treatment observation period as offset. The model will include treatment 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.

17.4.2.3 Pharmacokinetic endpoints

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

The semaglutide plasma concentrations and SNAC 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 more details in Section 17.6.

17.5 Interim analysis

No interim analyses or other analyses of unblinded data 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:

- To describe the covariate factors (such as weight, age, gender, race and ethnicity) that influence semaglutide exposure
- 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 dose, 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 oral semaglutide phase 3a trials with PK assessments. A separate modelling analysis plan will be prepared before first database lock in the oral semaglutide phase 3a programme, 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 clinical trial report.

17.7 Health economics and/or patient reported outcomes

PRO endpoints

Change from baseline to week 26 in:

- SF-36v2™ (acute version) health survey: Scores from the 8 domains and summary of the physical component score and the mental component score

- IWQOL-Lite Clinical Trial Version: Total score of the 22 items
- PGI-S Items: Scores of the two individual items
- PGI-C Items: Scores of the two individual items

The PRO questionnaire 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. 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

Risks and precautions

The non-clinical 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 non-clinical 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 non-clinical 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 EMA.

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.

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

Other safety considerations

Teratogenicity (embryo-foetal development toxicity)

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

General precautions

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

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

It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2016 Standards of Medical Care in Diabetes[51].

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

18.1.1 Benefits

In this trial, subjects in the semaglutide arms will be treated with a regimen anticipated to be a beneficial and efficient supplement to the treatment they receive at the time of entry into the trial being diet and exercise. 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.

In addition, it is expected that all subjects including those randomised to placebo 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.

18.1.2 Risk and benefit conclusion

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

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 will provide to subjects with T2DM.

18.2 Informed consent

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

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

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

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

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

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

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

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

18.3 Data handling

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

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

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

18.4 Information to subjects during trial

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

18.5 Premature termination of the trial and/or trial site

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

If the trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

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

19 Protocol compliance

19.1 Protocol deviations

Deviations from the protocol should be avoided.

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

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

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

19.2 Prevention of missing data

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

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

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

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

20 Audits and inspections

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

21 Critical documents

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

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of IB

- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

Only applicable for US trial sites:

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

For Japan only: A seal is accepted as signature.

FDA form 1572:

For US sites:

- Intended for US sites
- Conducted under the Investigational New Drug (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.

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 investigators will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[52].

23.1 Communication of results

Novo Nordisk commits to communicating and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[27].

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

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

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures and reports needed to evaluate the planned publication. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

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

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

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[52] (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.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

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

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

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

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

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

Regulatory Authorities:

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

26 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with:

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

For Mexico only:

a) *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, including those applicable provisions on the Mexican United States. If the subject feels that something goes wrong during the course of this trial, the subject should contact the trial staff in the first instance.*

b) *If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the study medication and/or a study procedure that otherwise would not have been part of his/her regular medical care, the subject will receive from the Institution or Medical Care Establishment and free of charge, the appropriate medical treatment as required. In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by the trial sponsor in accordance with the terms provided by all applicable regulations; even if the subject discontinues his/her participation in the study by his own will or by a decision from the investigator.*

c) *By signing the informed consent, the subject will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the trial; any additional expense resulting from the subject's participation in the trial will be covered by the trial sponsor.*

27 References

1. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1), Step 4. 10 June 1996.

2. World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.

3. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am. 2004;88(4):787-835, ix.

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

5. Chuang LM, Tsai ST, Huang BY, Tai TY, Diabcare-Asia Study G. The status of diabetes control in Asia--a cross-sectional survey of 24 317 patients with diabetes mellitus in 1998. Diabet Med. 2002;19(12):978-85.

6. Ford ES, Li C, Little RR, Mokdad AH. Trends in A1C concentrations among U.S. adults with diagnosed diabetes from 1999 to 2004. Diabetes Care. 2008;31(1):102-4.

7. Holst JJ, Vilsboll T, Deacon CF. The incretin system and its role in type 2 diabetes mellitus. Mol Cell Endocrinol. 2009;297(1-2):127-36.

8. Kieffer TJ, Habener JF. The glucagon-like peptides. Endocr Rev. 1999;20(6):876-913.

9. Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsboll T. Impaired regulation of the incretin effect in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011;96(3):737-45.

10. Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic sujbjects. J Clin Invest. 1967;46(12):1954-62.

11. Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia. 1986;29(1):46-52.

12. Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ. Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? Diabetologia. 2011;54:10-8.

13. Hojberg PV, Vilsboll T, Rabol R, Knop FK, Bache M, Krarup T, et al. Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. Diabetologia. 2009;52(2):199-207.

14. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2012;8(12):728-42.

15. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest. 1998;101(3):515-20.

16. Nauck MA, Niedereichholz U, Ettler R, Holst JJ, Orskov C, Ritzel R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. Am J Physiol. 1997;273(5 Pt 1):E981-8.

17. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia. 1993;36(8):741-4.

18. Toft-Nielsen MB, Damholt MB, Madsbad S, Hilsted LM, Hughes TE, Michelsen BK, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. J Clin Endocrinol Metab. 2001;86(8):3717-23.

19. Toft-Nielsen MB, Madsbad S, Holst JJ. Determinants of the effectiveness of glucagon-like peptide-1 in type 2 diabetes. J Clin Endocrinol Metab. 2001;86(8):3853-60.

20. Nauck MA, Petrie JR, Sesti G, Mannucci E, Courreges JP, Atkin S, et al. The once-weekly human GLP-1 analogue semaglutide provides significant reductions in HbA1c and body weight in patients with type 2 diabetes. EASD abstract. 2012.

21. European Medicines Agency. ICH Topic M 3 (R2): Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, Step 3. July 2008.

22. Waser B, Blank A, Karamitopoulou E, Perren A, Reubi JC. Glucagon-like-peptide-1 receptor expression in normal and diseased human thyroid and pancreas. Mod Pathol. 2015;28(3):391-402.

23. Novo Nordisk A/S. Investigators Brochure for s.c. Semaglutide (NN9535), Edition 10 or any updates hereof. 2015.

24. Novo Nordisk A/S. Investigators Brochure for oral Semaglutide (NN9924), Edition 6 or any updates hereof. 2015.

25. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364-79.

26. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015;58(3):429-42.

27. Novo Nordisk Code of Conduct for Clinical Trial Disclosure http:/novonordisk-trial.com/website/content/how-we-disclose-trial-information.aspx. 1/11/2015 2015.

28. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351(12):1250-1.

29. U.S. Department of Health and Human Services, Food and Drug Administration. Food and Drug Administration Amendments Act of 2007.

30. The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and of the Councill of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, article 11. Official Journal of the European Communities. 1 May 2001.

31. Council TEPatCotE. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. Official Journal of the European Communities. April 2001.

32. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.

33. Ware JE, Kosinski M, Dewey JE. How to Score Version Two of the SF-36 Health Survey. Edition 3 ed: Lincoln RI: QualityMetric, Incorporated. 2000.

34. Turner-Bowker DM, Bartley PJ, Ware JE. SF-36® Health Survey & "SF" Bibliography. Lincoln, RI: QualityMetric Incorporated; 2002 Third Edition (1988-2000). 2002.

35. Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity. Obesity Research. 2001;9(2):102-11.

36. RTI Health Solutions. Adaptation of the Impact of Weight on Quality of Life-Lite for Use in Clinical Trials - Draft Instrument Adaptation Report. 22 May 2015.

37. National Kidney F. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. Am J Kidney Dis. 2012;60(5):850-86.

38. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95.

39. McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. Diabet Med. 2001;18(9):690-705.

40. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009.

41. Stull DE, Leidy NK, Parasuraman B, Chassany O. Optimal recall periods for patient-reported outcomes: challenges and potential solutions. Curr Med Res Opin. 2009;25(4):929-42.

42. Commission E. The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 13, Investigational Medicinal Products. Brussels, February 2010.

43. Hicks KA, Hung HMJ, Mahaffey KW, Mehran R, Nissen SE, Strockbridge NL, et al. Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials (Draft). 20 Aug 2014.

44. KDIGO. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney international supplements. 2012;2(1):1-138.

45. Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. Biometrical Journal. 2011;53(6):894-913.

46. Rohmeyer K, Klinglmueller F. gMCP: Graph Based Multiple Test Procedures. R package version 0.8-8. 3 Oct 2014.

47. Little RJA, Rubin DB. Statistical analysis with missing data: New York: John Wiley & Sons. 1987.

48. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1). 2 Jul 2010.

49. National Academy of Sciences (NAS). The Prevention and Treatment of Missing Data in Clinical Trials. Washington D.C.: The National Academies Press. 2010.

50. Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. J Clin Invest. 1987;79(3):777-81.

51. Association AD. Standards of medical care in diabetes -2016. Diabetes Care. 2016;39 Suppl. 1:S13-S22.

52. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals; current version available at www.icmje.org.

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.

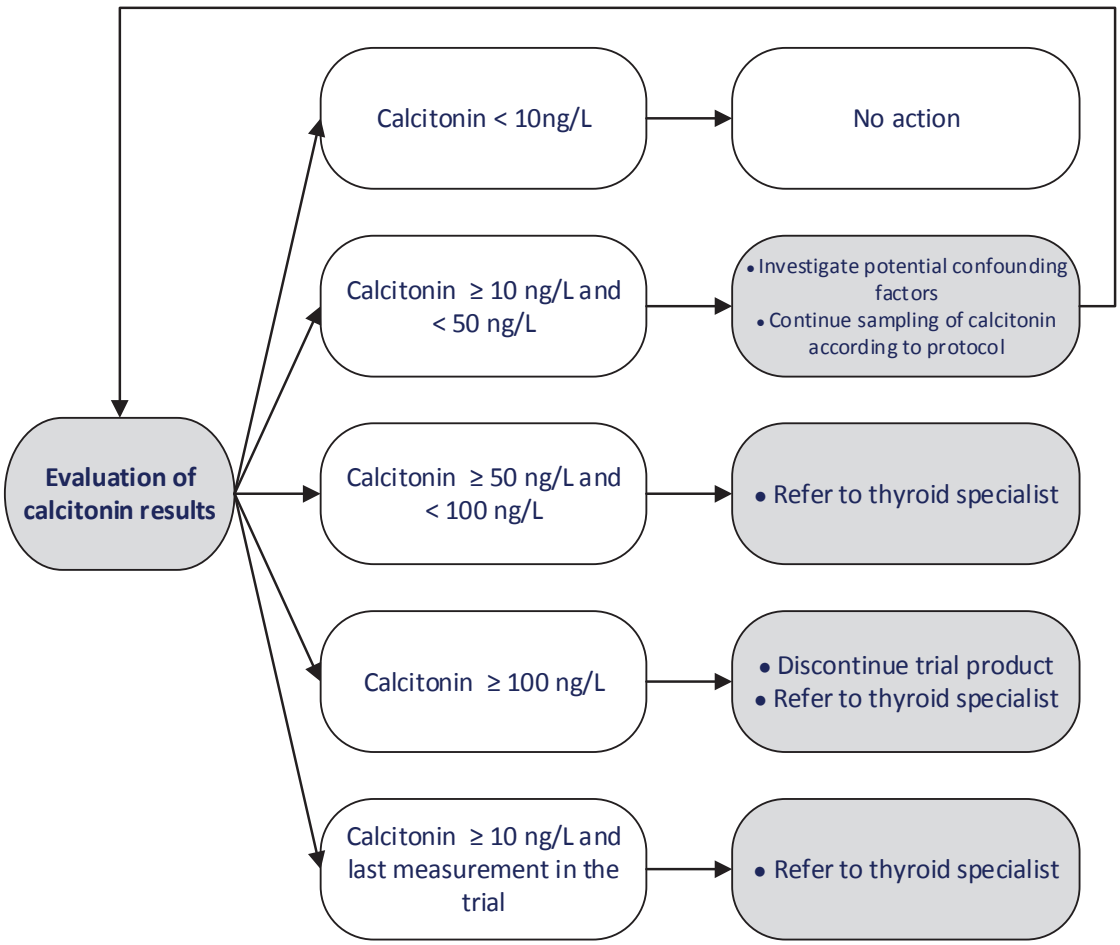


Figure 1 Flow of calcitonin monitoring

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 (re-arranged during transfection) 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 CT > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT > 10 and < 20 ng/L to allow conclusions[2,3].

3 References

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

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

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

Appendix B

Adverse events requiring additional data collection

1 Adverse Events requiring additional data collection

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

- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or 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
  - 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 upper normal limit (UNL)
- Hepatic events:
  - ALT or AST > 5x UNL and total bilirubin ≤ 2x UNL
  - ALT or AST > 3x UNL and total bilirubin > 2x UNL*
  - Hepatic events 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 criteria if no other seriousness criteria are applicable.

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

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

1.1 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

1.2 Cerebrovascular event

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

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

1.3 Heart failure

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

- Signs and symptoms of heart failure
- NYHA Class
- Supportive imaging
- Supportive laboratory measurements
- Initiation or intensification of treatment for this condition

1.4 Pancreatitis

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

- Signs and symptoms of pancreatitis
- Specific laboratory test supporting a diagnosis of pancreatitis
- Imaging performed and consistency with pancreatic disease

- Treatment for and complications of the event
- Relevant risk factors for pancreatic disease
- Family history of pancreatic disease

1.4.1 Assessments in case of suspicion of acute pancreatitis

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

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

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

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

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

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

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

1.5 Neoplasm

All events of neoplasms (excluding thyroid 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

1.6 Thyroid disease

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

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

1.7 Renal event

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

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

1.8 Hypersensitivity reaction

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

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 reactions
- Risk or confounding factors identified

1.8.1 Assessments in case of suspicion of hypersensitivity reaction

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

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 V9A. Furthermore, a blood sample for assessment of anti-semaglutide IgE antibodies should be drawn as soon as possible after the event and at V9A and sent to central laboratory. Tryptase concentrations, if available, should be included in the specific event form when reporting the AE.

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

1.9 Acute gallstone disease

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

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

1.10 Medication error

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

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

For definition of medication error, see protocol Section 12.1.4.

1.11 Lactic acidosis

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

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

1.12 Creatine kinase (CK) > 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

1.12.1 Assessments in case of increased levels of creatine kinase

In case of CK > 10x 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.

1.13 Hepatic events

- ALT or AST > 5x UNL and total bilirubin ≤ 2x UNL
- ALT or AST > 3x UNL and total bilirubin > 2x UNL*
- Hepatic events 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

1.13.1 Assessments in case of increased levels of aminotransferases

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

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

*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 protocol Section 12.1.2).

2 References

1. Banks PA, Freeman ML, Practice Parameters Committee of the American College of G. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101(10):2379-400.

2. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11.

3. Food and Drug Administration. Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products. August 2015.

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 20 April 2016

Trial ID: NN9924-4233

Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only

Trial phase: 3a

Applicable to Czech Republic

Amendment originator:

[redacted]

Table of Contents

Page

1 Introduction including rationale for the protocol amendment

This protocol amendment was issued to incorporate changes requested by the local Regulatory Authority in the Czech Republic to the study protocol version 2.0 dated 20 April 2016.

In this protocol amendment:

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

2 Changes

2.1 Changes to section 1 Summary

Key exclusion criteria

- Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).

For Japan only: Adequate contraceptive measures are abstinence (not having sex), diaphragm, condom (by the partner), intrauterine device, sponge, spermicide or oral contraceptives.

For Czech Republic only: Adequate contraceptive measures are always one highly reliable method (such as intrauterine device, sterilisation of one of the partners, hormonal birth control methods) plus one supplementary barrier method (such as condom, diaphragm) with a spermicide. In justified cases, this combination may be replaced with a double-barrier method with a spermicide. Total sexual abstinence may also be considered contraception. (Please note: hormonal contraception should always be discussed with a gynaecologist).

2.2 Changes to section 6.3 Exclusion criteria

Exclusion criteria

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 Japan only: Adequate contraceptive measures are abstinence (not having sex), diaphragm, condom (by the partner), intrauterine device, sponge, spermicide or oral contraceptives.

For Czech Republic only: Adequate contraceptive measures are always one highly reliable method (such as intrauterine device, sterilisation of one of the partners, hormonal birth control methods) plus one supplementary barrier method (such as condom, diaphragm) with a spermicide. In justified cases, this combination may be replaced with a double-barrier method with a spermicide. Total sexual abstinence may also be considered contraception. (Please note: hormonal contraception should always be discussed with a gynaecologist).

2.3 Changes to section 8.2.5 Childbearing potential

8.2.5 Childbearing potential

Contraceptive methods

For Japan only: Adequate contraceptive measures are abstinence (not having sex), diaphragm, condom (by the partner), intrauterine device, sponge, spermicide or oral contraceptives.

For Czech Republic only: Adequate contraceptive measures are always one highly reliable method (such as intrauterine device, sterilisation of one of the partners, hormonal birth control methods) plus one supplementary barrier method (such as condom, diaphragm) with a spermicide. In justified cases, this combination may be replaced with a double-barrier method with a spermicide. Total sexual abstinence may also be considered contraception. (Please note: hormonal contraception should always be discussed with a gynaecologist).

Protocol Amendment

no *2*
to Protocol, final version *2*
dated 20 April 2016

Trial ID:NN9924-4233

PIONEER 1 – Monotherapy

Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only

Trial phase: 3a

Applicable to all countries

[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 sections in the protocol: 2, 4.2.2.2, 8.4.1.2, 8.4.4, 12.1.5, 17.4.2.2, 18.1, Appendix B; section 1, 1.14

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

[1] Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. Br Med J (Clin Res Ed). 1985;290(6471):811-5.

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

[3] Varadhan L, Humphreys T, Walker AB, Varughese GI. The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. Diabetes Res Clin Pract. 2014;103(3):e37-9.

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

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

Updated sections in the protocol: 8.4.2, 18.1

[redacted], text is added to highlight the investigators 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 sections in the protocol: 6.6, 8.1.4, 8.1.5, 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 Other minor adjustments, clarifications and correction of typographical errors

Updated sections in the protocol: 8.4.8, 12.7.2, 17.2, 17.3.1, 17.4.2.1

Laboratory analysis

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.

Adverse events for Adjudication

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

Statistical considerations

The eye examination category has been added to the list of assessments where the follow-up period is included in the "on-treatment" observation period. This is due to the inclusion of the fundus

photography or dilated fundoscopy at the end of trial visit or within 5 weeks thereafter for subjects completing treatment.

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.

In the section “Time to event endpoint” stratification factors have been added in error and will be deleted.

2 Changes

In this protocol amendment:

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

2.1 Section 2 Flow Chart

Trial Periods	Screening[a]	Randomisation	Treatment					End-of-treatment	Follow-up[b]	End-of-treatment premature discontinuation[c]	Follow-up premature discontinuation[c]
Visit (V), Phone contact (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V8A	V9A
Timing of visit (weeks)	-2	0	2	4	8	14	20	26	31	Day of discontinuation of trial product	5 weeks after discontinuation of trial product
Visit window (days)			±3	±3	±3	±3	±3	±3	+3	+3	+3
Body weight		x		x	x	x	x	x		x	
Waist circumference		x				x		x		x	
Fasting plasma glucose		x		x	x	x	x	x		x	
HbA_{1c}	x	x		x	x	x	x	x		x	
Semaglutide PK				x	x	x		x	x	x	x
SNAC PK[d]				x		x		x			
7-point SMPG profile		x						x		x	
Lipids		x			x			x		x	
Fasting insulin and proinsulin		x						x		x	
Fasting C-peptide		x						x		x	
Fasting glucagon		x						x		x	
CRP		x						x		x	
PRO questionnaires		x[e]			x			x		x	
SAFETY											
Adverse events[f]		x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes		x	x	x	x	x	x	x	x	x	x
Physical examination	x							x		x	
Eye examination[g]	x							x		x	
Vital signs		x		x	x	x	x	x	x	x	x

Footer	Description
g	Fundus photography or dilated fundoscopy 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 V8 or within 5 weeks thereafter for subjects completing treatment* • *at V8A or within 5 weeks thereafter, and again within 5 weeks prior to V8, for subjects who have prematurely discontinued trial product*

2.2 Section 4.2.2.2 Supportive secondary endpoints

Change from baseline to week 26 in:

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

2.3 Section 6.6 Withdrawal from trial

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected. ~~Only subjects who withdraw consent should be considered 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 - 8.1.6.1)*
- *Other (subject deceased or closure of trial site)*

2.4 Section 8.1.4 End-of-treatment (visit 8) and Follow-up (visit 9)

At V8 the subject should be reminded about the importance of attending the follow-up visit (V9). If the subject, nonetheless, does not attend V9, 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 V9. (For subjects who discontinue trial product, see Section 8.1.5)

~~In case the subject cannot be reached (by site visit or phone contact) at the scheduled visit 9, the site should consult the contacts provided by the subject (e.g. close relatives), relevant physicians, medical records and locator agencies (if allowed according to local law) to collect health status. If no health status can be collected, the subject should be considered lost to follow-up and this should be specified in the end-of-trial form.~~

2.5 Section 8.1.5 Premature discontinuation of trial product and follow-up (visits 8A and 9A)

Subjects should continue with the originally scheduled site contacts after ~~visit~~ *V*9A and up to and including ~~visit~~ *V*8. After ~~visit~~ *V*9A, samples for antibodies, PK and lactate assessment should not be taken. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after ~~visit~~ *V*9A. However, as a minimum, these subjects should be asked to attend the scheduled end-of-treatment visit (V8) at week 26 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 scheduled V8, should not be considered withdrawn from the trial. In case the subject cannot be reached (by site visit or phone contact) at the scheduled V8, 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-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 V8 (or V9A if it is scheduled after V8). The site should in due time prepare for establishing contact with the subject within the visit window of the scheduled V8 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).*

2.6 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: V9 for subjects who have completed treatment, whereas for subjects who have discontinued trial product prematurely the last visit is V8 (or V9A if it is scheduled after V8). Only if contact with the subject is not regained by the end of the visit window of the last scheduled visit can the subject be considered lost to follow up (see Section 6.6).

2.7 Section 8.4.1.2 Adverse events requiring additional data collection

For the following AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form (see Section 12.1.5):

- Acute coronary syndrome (myocardial infarction 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 events 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 events leading to trial product discontinuation
- *Diabetic retinopathy and related complications*

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

2.8 Section 8.4.2 Physical examination

A physical examination will be performed by the investigator according to local procedure (see flow chart, Section 2 and 8.1.7). A physical examination must include:

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

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

2.9 Section 8.4.4 Eye examination

Fundus photography/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/dilated fundoscopy will be interpreted by the investigator (see Section 8.1.7).

2.10 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 binding antibody analysis.*

2.11 Section 12.1.5 Adverse events requiring additional data collection

Table 12–1 Adverse events requiring completion of specific event forms and/or are subject to event adjudication [Note: Only shown is the event with updated event description, all other events are unchanged]

Event	Specific event form	Event adjudication
Diabeic retinopathy and related complications	*Yes*	*No*

2.12 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

2.13 Section 17.2 Definition of analysis sets

On-treatment: This observation period represents the time period where subjects are considered treated with the trial product. The observation period is a subset of the in-trial observation period. It starts at the date of first dose of trial product. Two slightly different end dates will be needed to cover all assessments appropriately. For adjudicated events, ECGs, *eye examination category*, 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 (V9)
- The follow-up prematurely discontinuation visit (V9A)
- The last date on trial product + 38 days
- The end-date for the in-trial observation period

2.14 Section 17.3.1 Primary analysis for the primary estimand

Missing values for each group will be imputed as follows:

- An analysis of covariance (ANCOVA) with region 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 placebo at week 26:

For each of the ~~100~~ *1000* (now complete) imputed data sets the change from baseline to week 26 in HbA_{1c} 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[47] to draw inference.

2.15 Section 17.4.2.1 Efficacy endpoints (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[47].

Time to event endpoint

The endpoint will be described and compared for oral semaglutide versus placebo using likelihood ratio tests obtained from a Cox proportional hazards model with treatment~~, stratification factors, the interaction between the two stratification factors~~ and region as categorical fixed effects and baseline HbA_{1c} as a covariate. From this analysis the estimated Hazard ratios between oral semaglutide versus placebo will be presented together with 95% confidence intervals and two sided p values for test of no difference.

2.16 Section 17.4.2.2 Safety endpoints

Other safety endpoints

Change from baseline to week 26 in:

- Haematology

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

2.17 Section 18.1 Benefit-risk assessment of the trial

Other safety considerations

Diabetic Retinopathy complications

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive antidiabetic treatment[52,53,54]. 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[55,56] even in intensively treated patients who experienced early worsening[53]. 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[57]. 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[58].

2.18 Section 18.1 General precautions

It is the responsibility of the investigator to ensure the best possible care *of the subject. This includes adequate glycaemic control, appropriate risk factor modification such as optimal treatment of hypertension, dyslipidaemia and other cardiovascular risk factors, as well as regular monitoring and treatment of diabetic kidney disease and diabetic retinopathy* ~~according to the principles outlined in~~ (Diabetes Care 2016 Standards of Medical Care in Diabetes)[58]

2.19 Section 27 References

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

52. 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.

53. 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.

54. 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.

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

56. The Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Eye Study Group and the Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study Group. Persistent Effects of Intensive Glycemic Control on Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study. Diabetes Care. 2016;39(7):1089-100.

57. 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.

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

~~59. Association AD. Standards of medical care in diabetes--2016. Diabetes Care. 2016;39 Suppl. 1:S13-S22.~~

2.20 Reference Numbers

Will change throughout the protocol when new reference numbers are introduced.

2.21 Appendix B, Section 1 Adverse Events requiring additional data collection

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

- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)

- Cerebrovascular event (stroke or 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
  - 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 upper normal limit (UNL)
- Hepatic events:
  - ALT or AST > 5x UNL and total bilirubin ≤ 2x UNL
  - ALT or AST > 3x UNL and total bilirubin > 2x UNL*
  - Hepatic events leading to trial product discontinuation
- *Diabetic retinopathy and related complications*

2.21.1 Appendix B, new section 1.14 Diabetic retinopathy

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

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

Protocol Amendment

no 3
to Protocol, final version 2.0
dated 20 April 2016

Trial ID: NN9924-4233

Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only

Trial phase: 3a

Applicable to Serbia

Amendment originator:

[redacted]

Table of Contents

Page

1 Introduction including rationale for the protocol amendment

This protocol amendment was issued to incorporate changes requested by the local Regulatory Authority in Serbia to the study protocol version 2.0 dated 20 April 2016.

In this protocol amendment:

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

2 Changes

2.1 Changes to section 6.4 Rescue Criteria

6.4 Rescue criteria

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification. To allow time for dose escalation 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 values described below, the subject should be offered rescue medication (i.e. initiation of anti-diabetic medication):

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

Guidance text requested by Serbian Health Authorities: The safety of the individual subject always has the highest priority. Thus, the rescue criteria represent the minimum criteria for when rescue medication should be initiated. At the investigator's discretion, rescue medication can be initiated in case of FPG values lower than those stated in the rescue criteria or before week 8 in case of a specific safety concern.

It is important for the integrity of the trial that only subjects actually needing treatment intensification (as defined above) are started on rescue medication. Subjects who are started on rescue medication should continue to follow the protocol-specified visit schedule. Rescue medication should be prescribed at investigator's discretion as add-on to randomised treatment and according to ADA/European Association for the Study of Diabetes guidelines25, 26 (excluding GLPRAs, DPP-4 inhibitors and amylin analogues).