

Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02692716
Sponsor trial ID:	NN9924-4221
Official title of study:	PIONEER 6 – Cardiovascular outcomes trial. A trial investigating the cardiovascular safety of oral semaglutide in subjects with type 2 diabetes
Document date:	11 February 2019

16.1.1 Protocol and protocol amendments

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

Protocol
Trial ID: NN9924-4221
UTN: U1111-1173-0750
EudraCT No.: 2015-003563-10

~~CONFIDENTIAL~~

Date: 12 February 2016
Version: 3.0
Status: Final
Page: 1 of 79

Novo Nordisk

Protocol

Trial ID: NN9924-4221

PIONEER 6 – Cardiovascular outcomes
A trial investigating the cardiovascular safety of oral semaglutide in
subjects with type 2 diabetes

Trial phase: 3a

Protocol originator

[REDACTED]

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BG	blood glucose
CRF	case report form
CRO	contract research organisation
DMC	data monitoring committee
DPP-4	dipeptidyl peptidase-4
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	glomerular filtration rate, estimated
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPG	fasting plasma glucose
FSFV	first subject first visit
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA _{1c}	glycosylated haemoglobin
HDL	high density lipoprotein
HR	hazard ratio
IB	Investigator's Brochure

IEC	independent ethics committee
IRB	institutional review board
ITT	intention-to-treat
IV/WRS	interactive voice/web response system
LDL	low density lipoprotein
LLoQ	lower limit of quantification
LSFV	last subject first visit
LSLV	last subject last visit
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MEN 2	multiple endocrine neoplasia type 2
MTC	medullary thyroid carcinoma
NYHA	New York Heart Association
PYO	patient years of observation time
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous(ly)
SDV	source data verification
SGLT2	sodium-glucose cotransporter-2
SMPG	self-measured plasma glucose
SNAC	sodium N-(8-(2-hydroxybenzoyl) amino) caprylate
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TIA	transient ischaemic attack
TMM	Trial Materials Manual
UTN	Universal Trial Number

1 Summary

Objectives and endpoints:

The primary objective is to confirm that treatment with oral semaglutide does not result in an unacceptable increase in cardiovascular risk compared to placebo (rule out 80% excess risk) in subjects with type 2 diabetes at high risk of cardiovascular events.

The primary endpoint is time from randomisation to first occurrence of a major adverse cardiovascular event (MACE) composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The secondary objectives are to compare the efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes at high risk of cardiovascular events.

Key secondary endpoints:

- Time from randomisation to first occurrence of an expanded composite cardiovascular endpoint consisting of: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina requiring hospitalisation or hospitalisation for heart failure
- Time from randomisation to first occurrence of each of the individual components in the expanded composite cardiovascular endpoint
- Time from randomisation to first occurrence of a composite endpoint consisting of: all-cause death, non-fatal myocardial infarction or non-fatal stroke

For the primary and the key secondary endpoints, maximum treatment duration is dependent on event rates and is estimated to be no longer than 19 months.

Trial design:

This trial is a randomised, double-blind, placebo-controlled trial to assess the cardiovascular safety of oral semaglutide versus placebo when added to standard of care in subjects with type 2 diabetes at high risk of cardiovascular events. Subjects will be randomised 1:1 to receive either oral semaglutide or placebo. The trial will be event-driven and will be continued until at least 122 first MACEs confirmed by adjudication have accrued. The treatment period for each subject is estimated to be between 12 and 19 months, depending on the time-point of recruitment and the accrual of first MACEs confirmed by adjudication.

Trial population:

Number of subjects planned to be randomised is 3,176

Key inclusion criteria:

- Male or female diagnosed with type 2 diabetes
- Age ≥ 50 years at screening and presence of cardiovascular disease, or age ≥ 60 years at screening and presence of at least one cardiovascular risk factor

Key exclusion criteria:

- Current or previous (within 90 days prior to screening) treatment with any GLP-1 receptor agonist, DPP-4 inhibitor or pramlintide
- Family or personal history of multiple endocrine neoplasia type 2 (MEN 2) or medullary thyroid carcinoma (MTC)
- 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)
- Subjects presently classified as being in New York Heart Association (NYHA) Class IV heart failure
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening
- Any of the following: myocardial infarction, stroke or hospitalisation for unstable angina or transient ischaemic attack within the past 60 days prior to screening
- Chronic or intermittent hemodialysis or peritoneal dialysis or severe renal impairment (corresponding to eGFR <30 mL/min/1.73 m²)
- History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and carcinoma in situ)

Key assessments:

- Adverse events

Trial products:

- Semaglutide 3 mg tablet
- Semaglutide 7 mg tablet
- Semaglutide 14 mg tablet
- Placebo tablet

Trial Periods	Screening	Randomisation	Treatment														End of treatment	Follow-up
			V1	V2	P3	V4	V5	V6	P7 ²	V8	P9 ²	V10	P11 ²	V12	P13 ²	V14		
Visit (V) Phone (P)	V1	V2	P3	V4	V5	V6	P7 ²	V8	P9 ²	V10	P11 ²	V12	P13 ²	V14	P15 ²	V16	V17 ¹	P18 ¹
Timing of visit (weeks after V2)	Up to -2	0	2	4	8	14	20	26	32	38	44	50	56	62	69	76	83	88
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
IV/WRS call	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomisation		X																
Dispensing of trial product		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug accountability				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
REMINDERS																		
Handout ID card	X																	
Handout and instruct in BG meter use		X																
Attend visit fasting		X		X	X			X				X					X	
End of trial																		X

¹ V17 (End of treatment) and P18 (Follow-up) are applicable for all randomised subjects. P18 can be conducted over the telephone. For a subject who discontinued trial product prematurely (i.e. more than 5 weeks prior to the anticipated V17), V17 can be postponed to the point when P18 is otherwise due.

² Dispensing visit (i.e. a combination of dispensing trial product and collecting relevant information over the telephone. If the subject provides the required information to site staff when collecting trial product, the telephone contact can be omitted).

³ For women of childbearing potential only. In addition to the planned assessment at screening and end-of-treatment, urine dipstick pregnancy test should be performed at site at any time during the trial if a menstrual period is missed, or if pregnancy is suspected, or as required by local law.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP¹ and applicable regulatory requirements, and in accordance with the Declaration of Helsinki.²

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

3.1 Background information

3.1.1 Type 2 diabetes and GLP-1

Type 2 diabetes (T2D) is a progressive metabolic disease primarily characterised by abnormal glucose metabolism. The pathogenesis is heterogeneous, and characterised by chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver³.

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^{4,5}. Subjects with T2D have a decreased incretin effect⁶⁻⁹. 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 supra physiological levels¹⁰. In addition, supra physiological levels of GLP-1 lower body weight due to decreased energy intake induced by reduced appetite¹¹. These mechanisms of action make GLP-1 an attractive pharmacological treatment for T2D¹²⁻¹⁴.

3.1.2 Oral semaglutide

Semaglutide is a long-acting GLP-1 receptor agonist (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 T2D. Compared to human native GLP-1, which has a very short half-life, the semaglutide molecule has three minor but important modifications ensuring protraction of its action: amino acid substitutions at position 8 (alanine to alfa-aminoisobutyric acid, a synthetic amino acid) and position 34 (lysine to arginine), and acylation of the peptide backbone with a spacer and C-18 fatty di-acid chain to lysine in position 26¹⁵. 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 T2D. As the bioavailability of GLP-1 RAs is very low when administered orally, semaglutide has been co-formulated with the absorption enhancing excipient sodium N-(8-(2-hydroxybenzoyl) amino) caprylate (SNAC) based on the [REDACTED] concept developed by [REDACTED] in order to increase

bioavailability. When semaglutide is co-formulated with SNAC, SNAC has the capacity to augment the absorption of semaglutide across the gastrointestinal epithelium. The absorption enhancement by SNAC is dose, size and time-dependent and is believed to take place in close proximity of the tablet in the stomach. The absorption process is hampered if dosed with food, liquid or in the presence of significant stomach content. Throughout this document oral semaglutide will refer to the drug product, that is, semaglutide co-formulated with 300 mg SNAC.

Novo Nordisk is currently also developing semaglutide for once-weekly subcutaneous (s.c.) administration in subjects with T2D.

3.1.3 Non-clinical data

3.1.3.1 Semaglutide

The non-clinical programme for semaglutide was designed according to the ICH M3 guideline 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 low¹⁶.

Embryo–foetal development toxicity

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

potential of semaglutide in this species. These data suggest an important species-dependent mechanism, whereby semaglutide is teratogenic in rats but not in primates.

A review of results from the non-clinical studies can be found in the current edition of the investigator's brochure (IB) for s.c. semaglutide (NN9535)¹⁷, and the current edition of the IB for oral administration of semaglutide (NN9924)¹⁸, or any updates to these documents.

3.1.3.2 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.



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

A review of results from the non-clinical studies can be found in the current edition of the IB for oral administration of semaglutide (NN9924)¹⁸, or any updates thereto.

3.1.4 Clinical data 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 T2D.

For details on the individual trials, please see the current edition of the IB for oral administration of semaglutide (NN9924)¹⁸, or any updates thereto.

3.1.4.1 Pharmacokinetics

In single dose trials, oral semaglutide has demonstrated a long mean terminal half-life ($t_{1/2}$) 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 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 T2D.

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

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. The tablet should be taken with up to half a glass of water (i.e. 120mL/4 fluid oz).



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. 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 T2D. It is extensively metabolized and no accumulation of SNAC has been observed in clinical trials.

3.1.4.2 Efficacy

The efficacy of oral semaglutide in adult subjects with T2D 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 to -6.98 kg).

3.1.4.3 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, common adverse events (AEs) included nausea and vomiting, most of them of mild to moderate 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 administered 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 studies 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) were 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 current edition of the IB for oral administration of semaglutide (NN9924)¹⁸, or any updates thereto.

3.1.5 Oral semaglutide and cardiovascular risk

Based on the nonclinical and clinical data obtained with semaglutide dosed either orally or subcutaneously to date, no adverse safety signals have been identified that indicate an increased risk of cardiovascular events. In addition, although an increase in heart rate has been observed as a class effect for GLP-1 RAs, the extensive amount of clinical data from marketed products have not indicated that this drug class increases risk of cardiovascular events. In support, findings from the recently completed ELIXA™ trial confirmed that treatment with the once daily injectable GLP-1 RA lixisenatide does not increase the risk of MACE as compared to placebo. This trial is the first

cardiovascular outcomes trial within the GLP-1 RA drug class to report and several others (including SUSTAIN™ 6 investigating the cardiovascular safety of s.c. semaglutide) are ongoing.

The absorption enhancer SNAC used in the formulation of oral semaglutide is an excipient with no discernable systemic or pharmacodynamic effects. Accordingly, the potential for adverse effects on the cardiovascular system is considered low. The collective nonclinical and clinical evidence on SNAC from ██████████ and Novo Nordisk has not identified safety signals related to cardiovascular disease. However, information on potential long-term cardiovascular effects of SNAC is not yet available.

For an assessment of benefits and risks of the trial, see section [18.1](#).

3.2 Rationale for the trial

The purpose of this trial is to assess the cardiovascular safety of oral semaglutide in subjects with T2D at high risk of cardiovascular events. This trial has been designed to address the requirements contained in the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance documents^{19,20} which specify how to demonstrate that a new antidiabetic therapy is not associated with an unacceptable increase in cardiovascular risk.

4 Objectives and endpoints

4.1 Objectives

The primary objective is to confirm that treatment with oral semaglutide does not result in an unacceptable increase in cardiovascular risk compared to placebo (rule out 80% excess risk) in subjects with type 2 diabetes at high risk of cardiovascular events.

The secondary objectives are to compare the efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes at high risk of cardiovascular events.

4.2 Endpoints

The primary endpoint is time from randomisation to first occurrence of a MACE composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The confirmatory secondary endpoint is time from randomisation to first occurrence of an expanded composite cardiovascular endpoint consisting of: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina requiring hospitalisation or hospitalisation for heart failure*

The secondary endpoints are:

- Time from randomisation to first occurrence of each of the individual components in the expanded composite cardiovascular endpoint*
- Time from randomisation to first occurrence of a composite endpoint consisting of: all-cause death, non-fatal myocardial infarction or non-fatal stroke*
- Time from randomisation to all-cause death
- Time to permanent discontinuation of trial product due to AE(s)
- Number of serious adverse events (SAEs)

Change from baseline to last assessment of:

- Biochemistry
- Haematology
- Calcitonin
- Pulse
- Systolic and diastolic blood pressure
- Glycosylated haemoglobin (HbA_{1c})
- Body weight
- Lipids

* Key supportive secondary endpoint prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT)

5 Trial design

5.1 Type of trial

This trial is a randomised, double-blind, placebo-controlled trial to assess the cardiovascular safety of oral semaglutide versus placebo when added to standard of care in subjects with T2D at high risk of cardiovascular events. Subjects will be randomised 1:1 to receive either oral semaglutide or placebo. Randomisation will be stratified according to evidence of cardiovascular disease at screening (presence of cardiovascular disease or risk factors only) to ensure even distribution of the two treatment arms within strata. The stratum ‘presence of cardiovascular disease’ consists of subjects at least 50 years of age and recognised as fulfilling **at least one** item of inclusion criterion no. **3a-h** at screening, whereas the stratum ‘presence of cardiovascular risk factors only’ consists of subjects at least 60 years of age and recognised as fulfilling **at least one** item of inclusion criterion no. **3i-l** and **not** fulfilling **any** of the items of inclusion criterion no. **3a-h** at screening (see section [6.2](#)).

All tablets containing oral semaglutide or placebo are identical with regards to visual appearance to maintain the blinding of the trial.

The trial will be event-driven and will be continued until at least 122 first MACEs confirmed by adjudication have accrued. Throughout the remainder of this protocol, MACE will be defined as MACE confirmed by adjudication.

The recruitment period is expected to last 7 months. The treatment period for each subject is estimated to be between 12 and 19 months, depending on the time-point of recruitment and the accrual of first MACEs. The follow-up period is 5 weeks to allow for wash-out of trial drug. A schematic diagram of the trial design is shown in [Figure 5–1](#).

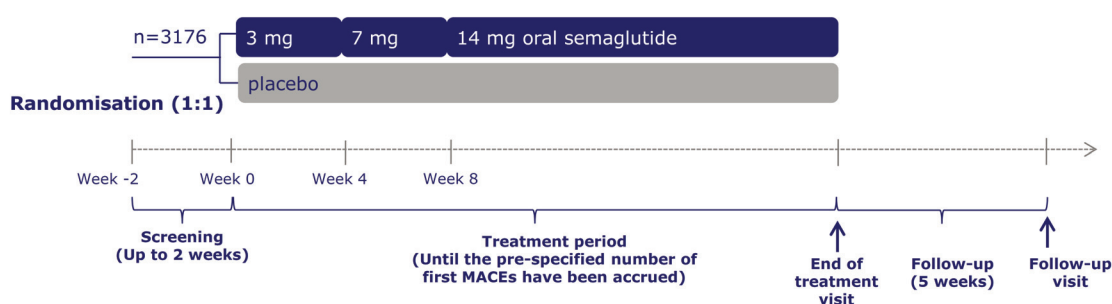


Figure 5–1 Trial design

The trial is designed to evaluate cardiovascular outcomes and will apply a targeted approach to collection of safety data focusing on SAEs, AEs leading to discontinuation of trial product and other selected AEs. An adequate characterisation of the less serious and more common AEs will be evaluated in the other phase 3a trials conducted with oral semaglutide comprising more than 4000 subjects with T2D.

An external event adjudication committee (EAC) will perform ongoing adjudication of predefined cardiovascular events and other selected AEs in an independent and blinded manner.

An independent external data monitoring committee (DMC) will have unblinded access to data from the trial and perform review of accumulating data on an ongoing basis. The DMC will provide recommendation on trial continuation, modification or termination.

5.2 Rationale for trial design

A randomised, double-blind, placebo-controlled trial has been chosen in accordance with the trial objectives and to avoid bias of the results. The planned duration of the trial has been estimated based on the number of subjects randomised and the expected first MACE rate. The treatment period is expected to be between 12 and 19 months. This duration should be adequate to provide data to assess the cardiovascular safety of oral semaglutide.

5.3 Treatment of subjects

Subjects will be randomised in a 1:1 ratio to receive either oral semaglutide or placebo. Randomised subjects will initiate treatment with 3 mg oral semaglutide/placebo once daily and follow a fixed 4-week dose escalation regimen until reaching the maximum dose of 14 mg oral semaglutide/placebo as illustrated in [Table 5–1](#). The 4-week dose escalation intervals are applied in order to mitigate the risk of gastrointestinal adverse events (AEs). Subjects should remain on the 14 mg dose level throughout the maintenance period; however, if treatment with the trial product is associated with unacceptable AEs (as judged by the investigator), dose reductions and extensions of dose escalation periods are allowed. In case the dose is reduced due to unacceptable AEs, the investigator should consider escalating the dose of oral semaglutide once the subject has recovered. Trial product dose and date of change or discontinuation should be recorded in the electronic case report form (eCRF) throughout the trial.

Table 5–1 Treatment of subjects

Trial periods		Screening	Trial period 1	Trial period 2	Trial period 3	Follow-up
Alias for trial period		Screening	Dose escalation	Dose escalation	Maintenance	Follow-up
First visit in each period		V1	V2	V4	V5	V17
Duration of each period		Up to 2 weeks	4 weeks	4 weeks	Up to 75 weeks	5 weeks
Treatment arm	N					
Oral semaglutide	1588	Screening	3 mg	7 mg	14 mg	Follow-up
Placebo	1588	Screening	Placebo	Placebo	Placebo	Follow-up

5.3.1 Missed doses

The trial product should be administered once daily; however, if one or more doses of trial product are missed due to circumstances not related to the safety of the trial product (as judged by the investigator) and treatment with trial product is resumed, the below recommendations for dose adjustment apply:

- If ≤ 21 consecutive doses of 14 mg oral semaglutide/placebo are missed, the once-daily regimen can be resumed as prescribed without dose reduction.
- If 22-35 consecutive doses of 14 mg oral semaglutide/placebo are missed, it is recommended to resume treatment at 7 mg oral semaglutide/placebo and subsequently, escalate to the higher dose after 4 weeks of treatment.
- If ≥ 36 consecutive doses of 14 mg oral semaglutide/placebo are missed, it is recommended to resume treatment at 3 mg oral semaglutide/placebo and subsequently, escalate to the higher doses with 4-week dose escalation steps.

Please refer to section [10](#) for instructions on how to use the interactive voice/web response system (IV/WRS) in relation to subjects discontinuing and resuming trial product treatment.

5.3.2 Dosing instructions

Absorption of oral semaglutide is significantly affected by food and fluid in the stomach, hence subjects should take the oral semaglutide/placebo tablets in the morning in a fasting state and at least 30 minutes before the first meal of the day. The tablets should be taken with up to half a glass of water (approximately 120 mL/4 fluid oz). The tablets must be swallowed whole and must not be broken or chewed. Other oral medication can be taken 30 minutes after the trial product. The tablets should be taken immediately after removal from the blister.

5.3.3 Background medication

The investigator will assume responsibility for the management of glycaemic control in each subject enrolled in the trial. The investigator is responsible for ensuring that glycaemic control is maintained and optimised in each subject while maintaining a low risk of hypoglycaemic episodes. If deemed necessary to achieve glycaemic target, antidiabetic medication (excluding GLP-1 RAs, DPP-4 inhibitors and pramlintide from visit 1 to 17) may be adjusted or added, at the investigator's discretion. The background medication should be used in accordance with standard of care and the current local label.

If episodes of hypoglycaemia require reduction of antidiabetic medication, investigators should reduce or modify the dosing of background medication. In particular, dose reduction of insulin should be done already at randomisation (e.g. 10-20% reduction of the insulin dose) to reduce the risk of hypoglycaemia when introducing an additional glucose lowering agent. Similar considerations should be made for subjects treated with sulphonylureas.

All subjects will be provided with a BG meter at randomisation and glycaemic management will be guided by review of fasting plasma glucose (FPG) and HbA_{1c} results measured at the site as well as self-measured plasma glucose (SMPG) results measured at home by the subject. In addition, it is important that other information such as symptoms of hypo/hyperglycaemia, previous response to dose adjustments and other indicators of the subject's level glycaemic control is taken into consideration when decisions on dose adjustments of the background antidiabetic medication are made. In subjects treated with insulins, close contact should be ensured in the initial 12 weeks after randomisation to allow for adequate adjustment of insulin dose, at the investigator's discretion. Additional phone contacts in the weeks where no site visit is planned should be considered for subjects treated with insulins.

Please note that due to the long half-life of oral semaglutide and the gradual dose escalation, the full effect of the investigational product on glycaemic parameters may not be apparent until several weeks into the maintenance period.

Cardiovascular diseases and risk factors will be treated according to local standard of care at the investigator's discretion.

5.4 Treatment after discontinuation of trial product

When discontinuing trial product at the end of the treatment period, the subject should be switched to a suitable marketed product at the discretion of the investigator. Oral semaglutide will not be available for prescription until marketing authorisation is issued.

For Brazil only: At the end of the trial, subjects will be assured access to the best proved prophylactic, diagnostic and therapeutic methods identified during the trial.

5.5 Rationale for treatment

Blinded treatment with oral semaglutide or placebo offers a robust method for assessment of oral semaglutide's effect on trial endpoints. Gradual dose escalation is applied in order to mitigate the risk of gastrointestinal AEs. Treatment intensification of the background medication is allowed throughout the course of the trial to ensure adequate glycaemic control in all participating subjects. Use of other GLP-1 RAs and DPP-4 inhibitors and pramlintide is not allowed, because these drugs, similarly to oral semaglutide, affect the incretin pathway.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be randomised: 3,176

For Mexico only: Approximately 150 subjects are planned to be randomised 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 diagnosed with type 2 diabetes.

3. Age \geq 50 years at screening and at least one of the below conditions:
- a. prior myocardial infarction
 - b. prior stroke or transient ischaemic attack (TIA)
 - c. prior coronary, carotid or peripheral arterial revascularisation
 - d. $>$ 50% stenosis on angiography or imaging of coronary, carotid or lower extremity arteries
 - e. history of symptomatic coronary heart disease documented by e.g. positive exercise stress test or any cardiac imaging or unstable angina pectoris with ECG changes
 - f. asymptomatic cardiac ischaemia documented by positive nuclear imaging test or exercise test or stress echo or any cardiac imaging
 - g. chronic heart failure New York Heart Association (NYHA) class II-III
 - h. moderate renal impairment (corresponding to an estimated glomerular filtration rate (eGFR) between 30-59 mL/min/1.73 m²)

or

- Age \geq 60 years at screening and at least one of the below risk factors:
- i. microalbuminuria or proteinuria
 - j. hypertension and left ventricular hypertrophy by ECG or imaging
 - k. left ventricular systolic or diastolic dysfunction by imaging
 - l. ankle/brachial index $<$ 0.9

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to the trial product 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 childbearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice. Local country regulations or practices are specified in section 8 of the protocol).
4. Receipt of any investigational medicinal product within 90 days before screening.
For Brazil only: Participation in other clinical trials within one year prior to screening unless there is a direct benefit to the research subject at the investigator's discretion.
5. Participation in another clinical trial of an investigational medicinal product. Participation in a clinical trial which evaluate stent(s) is allowed.
6. Current or previous (within 90 days prior to screening) treatment with any GLP-1 receptor agonist, DPP-4 inhibitor or pramlintide.
7. Any disorder, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

8. Family or personal history of multiple endocrine neoplasia type 2 (MEN 2) or medullary thyroid carcinoma (MTC).
9. History of pancreatitis (acute or chronic).
10. 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).
11. Subjects presently classified as being in New York Heart Association (NYHA) Class IV heart failure.
12. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
13. Any of the following: myocardial infarction, stroke or hospitalisation for unstable angina or transient ischaemic attack within the past 60 days prior to screening.
14. Chronic or intermittent hemodialysis or peritoneal dialysis or severe renal impairment (corresponding to eGFR <30 mL/min/1.73 m²).
15. History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and carcinoma in situ).
16. History of diabetic ketoacidosis.

6.4 Composition of overall trial population

In order to secure sufficient overall cardiovascular risk within the trial population, randomisation of subjects with risk factors only (inclusion criterion no. 3, i-l) will be stopped when 650 of these subjects have been randomised.

6.5 Premature discontinuation of trial product

All efforts should be made to keep the subject on trial product throughout the trial. The subject may, however, decide to discontinue trial product for any reason, or they may be discontinued from trial product due to safety concerns at the discretion of the investigator. In case the trial product is interrupted due to suspicion of acute pancreatitis or a hypersensitivity reaction to the trial product, please see sections [8.2.1](#) and [8.2.2](#).

Furthermore, the subject must discontinue treatment with trial product if any of the following applies:

- pregnancy
- intention of becoming pregnant
- participation in another clinical trial with an investigational medicinal product
- calcitonin \geq 100 ng/L

Discontinuation of treatment with trial product, whether temporary or permanent, must not prompt the investigator to withdraw the subject from the trial. Instead, the subject should maintain adherence to trial visits and procedures to the extent possible. In each separate case, the primary

reason for discontinuation of trial product must be specified in the eCRF. The subject should be encouraged to resume treatment with trial product once they are willing or when the safety concern has ceased, respectively.

A subject who does not fulfil the eligibility criteria (inclusion/exclusion criteria) must not be randomised. If a subject is randomised in error, this will be handled as an important protocol deviation, and the IEC/IRB and regulatory authorities must be notified according to local requirements. If there are no safety concerns, trial treatment may be continued or resumed at the discretion of the investigator following a discussion with the sponsor's global medical expert.

See section [5.3.1](#) for instructions about resuming trial product treatment after a treatment pause.

6.6 Withdrawal of consent

The subject may withdraw at will at any time. If a subject has withdrawn their consent, the investigator must make every effort to establish the subject's vital status at the end of the trial. See section [8.4](#) for further instructions about withdrawals.

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 have withdrawn their consent will not be replaced.

6.8 Rationale for trial population

This trial will include subjects with T2D at high risk of cardiovascular events. This includes subjects with previous cardiovascular disease or well-established risk factors for cardiovascular disease and advanced age, as based on their medical records. The inclusion of subjects with established risk for cardiovascular disease will ensure that the primary objective of the trial can be obtained within a reasonable timeframe.

Subjects with a recent event of myocardial infarction, stroke or hospitalisation for unstable angina or TIA prior to screening are excluded, aiming to avoid any effect of cardiovascular events that are likely to be secondary to another cardiovascular event or intervention.

6.8.1 Determining subject's eligibility

It is the responsibility of the investigator to ensure unequivocal evidence for a subject's eligibility. When determining a subject's eligibility based on medical history, it is at the investigator's

discretion on a case by case basis to decide if further medical records are needed or if the available documentation is adequate. Any laboratory values used to assess eligibility must reflect the subject's current health status.

6.8.2 Microalbuminuria and proteinuria

For the diagnosis of microalbuminuria and proteinuria, local guidelines, if such exist, can be used. Otherwise, commonly accepted guidelines should be used²¹. [Table 6–1](#) shows examples of how albuminuria can be assessed²².

Table 6–1 Measurement of albuminuria

	Normal	Microalbuminuria	Macroalbuminuria	Advantages	Disadvantages
Urine dipstick for protein	-	-	+	Convenience	Dependent on level of hydration
Urine 24-hour protein (mg)	< 150	< 500	≥ 500	Overcomes problem of diurnal variation in excretion	Subject to collection errors
Urine 24-hour albumin (mg)	< 30	30-300	> 300	Overcomes problem of diurnal variation in excretion	Subject to collection errors
Timed urine collection (µg/min)	< 20	20-200	> 200	Overcomes problem of diurnal variation in excretion	Subject to collection errors
Spot urine collection (µg albumin/mg creatinine)	< 30	30-300	> 300	Convenience Not dependent on hydration level Most reproducible	Ratios vary based on gender

6.8.3 Glomerular filtration rate, estimated (eGFR)

To evaluate whether a subject meets inclusion criterion no. [3](#) and exclusion criterion no. [14](#), the creatinine level that best reflects the current status of the subject in the medical records should be used to calculate eGFR. The equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi)²¹ including variables for age, sex, and race should be used to calculate eGFR.

7 Milestones

Planned duration of recruitment period (i.e. FSFV – LSFV): 7 months.

End of trial is defined as Last Subject Last Visit (LSLV).

Novo Nordisk will follow the screening and randomisation rates closely via IV/WRS in order to estimate when to stop screening. Investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened, and IV/WRS will be closed for further screening.

The treatment period for the last randomised subject is expected to be 12 months. The trial duration is, however, decided by the first MACE rate (see section [5.1](#)), and the trial duration will be adjusted as needed. When the trial comes to an end, investigators will be notified and instructed by Novo Nordisk regarding the visit schedules for their subjects.

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure²³, it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors²⁴, the Food and Drug Administration Amendment Act²⁵, European Commission Requirements^{26,27} 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 duration of this trial is decided by the observed first MACE rate (see section [5.1](#)). It is expected that each subject will be asked to attend maximum eighteen visits. Eleven of these are regular clinic visits, two visits can be performed over the telephone, and five visits are dispensing visits. Dispensing visits are a combination of dispensing trial product and collecting relevant information over the telephone (see section [2](#)). If the subject provides the required information to site staff when collecting trial product, the telephone contact can be omitted.

Depending on when a subject entered the trial and the accrual of first MACEs, subject's visit schedule may be shortened. This will imply omission of visit(s) in the treatment period, as, when the trial comes to an end, all subjects should be asked to attend visit 17 and 18. For a subject who discontinued trial product prematurely (i.e. more than 5 weeks prior to the anticipated visit 17), visit 17 can be postponed to the point when visit 18 is otherwise due.

The timing and content of visits and the visit windows are outlined in section [2](#), while procedures and assessments to be carried out at the visits are described in this section.

8.1.1 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP¹ and the requirements in the Declaration of Helsinki².

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. This includes the use of an impartial witness, where required according to local regulations. The subject 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 product.

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.

8.1.2 In/exclusion criteria

Subjects should be assessed for eligibility according to sections [6.2](#) and [6.3](#) at visit 1. For further instructions about determining the eligibility of a subject, see sections [6.8.1](#), [6.8.2](#) and [6.8.3](#).

For inclusion criterion no. [3](#) (section [6.2](#)), the investigator must provide just one answer (yes or no) on the inclusion criteria form in the eCRF for each subject.

For exclusion criterion no. [3](#) (section [6.3](#)), each female of childbearing potential must have a negative pregnancy test in order to be randomised.

8.1.3 Screening

At visit 1, the investigator must perform a screening session in IV/WRS (see section [10](#)), and each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. The investigator must keep a subject screening log, a subject identification code list and a

subject enrolment log. The subject screening log and subject enrolment log may be combined into one list.

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.

Screening failures: If a subject is screened, but for some reason never randomised, the subject is a screening failure. For screening failures, the screening failure form in eCRF must be completed with the reason for not continuing in the trial. SAEs from screening failures must be transcribed by the investigator into the eCRF. Follow-up of SAEs must be carried out according to section [12](#). A screening failure session must be made in the IV/WRS. The case book must be signed electronically. Re-screening is not allowed.

8.1.4 Demography

Demography (date of birth or age, sex, race and ethnicity) will be recorded at visit 1, unless prohibited according to local regulations.

8.1.5 Tobacco use

Details of tobacco use must be recorded at visit 1. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked. If the subject has smoked, record approximately when the subject stopped smoking.

8.1.6 Physical examination

Physical examinations should be performed according to local procedures, when indicated in section [2](#), and will as a minimum include examination of:

- head, ears, eyes, nose, throat, neck
- respiratory system
- cardiovascular system
- gastrointestinal system, incl. mouth
- musculoskeletal system
- central and peripheral nervous system
- skin
- lymph node palpation
- general appearance
- thyroid gland

For each assessment, the investigator should indicate whether the outcome was normal or abnormal, and, if abnormal, indicate whether clinically significant. Relevant findings as a result of screening procedures conducted at visit 1 must be recorded as concomitant illness/medical history in accordance with section [8.1.8](#).

8.1.7 Pregnancy test

Female subjects of childbearing potential will have pregnancy tests (urine dipsticks) performed as per the flow chart in section [2](#). In addition, urine pregnancy test should be performed at any time during the trial if a menstrual period is missed, or if pregnancy is suspected, or as required by local law.

Pregnancy testing will not be required (unless required by local law) for women of non-childbearing potential defined as, but not limited to, women who have undergone hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or who are postmenopausal (i.e. women above the age of 50 with no menstrual periods for at least 1 year). This has to be documented in the medical records.

Contraceptive methods

Female subjects of childbearing potential must use adequate contraceptive methods until 5 weeks after the last date on trial product. Throughout the protocol, last date on trial product is defined as date of the subject's last dosage of trial product.

For Argentina only: Adequate contraceptive measures are: Barrier methods (condom or diaphragm) with spermicide; contraceptive pills or intrauterine devices. Contraceptive methods will be reimbursed by Novo Nordisk Pharma Argentina S.A.

For Brazil only: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.

For Germany only: Adequate contraceptive measures are implants, injectables, combined oral contraceptives, hormonal intrauterine devices, sexual abstinence or vasectomised partner.

For Thailand only: Adequate contraceptive measures are: Diaphragm, condom (by the partner), intrauterine device in place for last three months before trial starts, sponge, cap with spermicide, contraceptive patch, approved hormonal implant (i.e. Norplant), oral contraceptives taken without difficulty for the last three months before trial starts, post-menopausal state or sterilisation.

For United Kingdom only: Adequate contraceptive measures are defined as established use of oral, intravaginal, transdermal, combined estrogen and progestogen hormonal methods of contraception; oral, injected or implanted progestogen only hormonal methods of contraception; placement of an intrauterine device or intrauterine hormone releasing system, bilateral tubal

occlusion, barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository), female sterilisation, vasectomised partner (where partner is sole partner of subject), or true abstinence (when in line with preferred and usual lifestyle).

8.1.8 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at visit 1) or found as a result of a screening procedure.

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 transcribed to the eCRF.

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 assessed at visit 1 and transcribed to disease-specific forms, i.e. not to the medical history/concomitant illness form:

- Diabetes history/diabetes complications (e.g. date of diagnosis, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy)
- History of cardiovascular disease (e.g. ischaemic heart disease, myocardial infarction, heart failure incl. NYHA class²⁸, hypertension, stroke, peripheral arterial disease) including answering yes or no/unknown for each cardiovascular condition/risk factor mentioned in inclusion criterion no. 3 a-1 (see section 6.2)
- 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 assessed according to section 12.1 and reported if applicable as per section 12.2.

8.1.9 Concomitant medication

A **concomitant medication** is any medication, other than the trial product, which is taken during the trial, i.e. as of visit 1 until the time point of visit 18.

Details of any concomitant medication must be recorded at visit 1. Changes in concomitant medication must be recorded at each subsequent visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, indication, total daily dose (only applicable for medication taken to treat diabetes and cardiovascular related disease), start date and stop date or continuation.

For subjects treated with insulin(s), total daily dose administered on the day preceding each trial visit (if available) should be recorded in the eCRF.

8.1.10 Body measurements (height and body weight)

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

Body weight is measured wearing light clothes and no shoes and recorded in the eCRF in kilogram or pound (kg or lb) with one decimal. If possible, the same calibrated weighing scale equipment should be used throughout the trial.

8.1.11 Vital signs

Pulse and systolic and diastolic blood pressure should be assessed 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 measured values should be recorded without rounding. If possible, the same equipment should be used throughout the trial.

8.1.12 Electrocardiogram

12-lead ECGs will be performed at selected visits (see the flow chart in section [2](#)). Investigator's interpretation of each ECG must be documented on the document or in the subject's medical records and abnormalities assessed according to section [12.1](#), and reported if applicable as per section [12.2](#). However, for abnormal clinically significant findings revealing baseline conditions at visit 2 the investigator must record these as concomitant illness/medical history, and, if applicable, update answer(s) related to inclusion criterion [3](#) (see section [8.1.8](#)).

The ECGs will also undergo central assessment and the investigator must forward the ECGs to the central ECG readers as soon as possible. If the central evaluation of a baseline ECG is suggestive of a prior myocardial infarction, the investigator will be notified. Unless already done, the investigator should consider recording the condition as cardiovascular history and update the answer(s) related to inclusion criterion [3](#) (see section [8.1.8](#)). If the central ECG evaluation of a post-baseline ECG is suggestive of new myocardial infarction, the investigator will be notified and a confirmatory ECG should be submitted to central ECG readers. Unless already done, and at the investigator's discretion, the investigator should assess the finding according to section [12.1](#), and if applicable report it as per section [12.2](#).

If additional ECG recordings are performed at the investigator's discretion at other visits than the planned ECG visits, such ECGs should also be submitted to the central ECG readers. The reason for recording an additional ECG should be documented.

Findings suggestive of new myocardial infarction detected by the central ECG readers will be adjudicated by the EAC (see section [12.7.3](#)).

8.1.13 Randomisation, dispensing of trial product and drug accountability

At visit 2, subjects are randomised into one of the two treatment arms. The randomisation session must be performed in IV/WRS and will include allocation of dispensing unit numbers (DUNs) to be dispensed to the subject.

All assessments pertaining to visit 2 must be performed before first dose of trial product is taken. Date of first administration of trial product must be captured in the eCRF.

At each visit where dispensing of trial product is indicated (see section [2](#)), IV/WRS must be used to allocate DUNs according to the subject's assigned treatment group (assigned at randomisation). The allocated DUNs should be dispensed by the site, hospital pharmacy or equivalent.

The investigator must ensure that the subject is reminded about dosing instructions (see section [5.3.2](#)) at every dispensing visit, as needed.

At each visit where the subject returns used, partially used or unused trial product, the investigator will account for the returned trial products in IV/WRS (see section [9.4](#)).

8.1.14 Blood sampling

Laboratory kits and laboratory manual will be provided to each site. The manual will include instructions for handling, storage and shipment of blood samples, and contact information for the central laboratory, including a link to their website where current laboratory certificates can be obtained. Blood samples should be collected according to the flow chart in section [2](#) and the laboratory parameters listed below will be assessed at a central laboratory (see [Attachment I](#)).

Glucose metabolism:

- HbA_{1c}
- FPG

Lipids:

- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides

Biochemistry:

- Alanine aminotransferase (ALT)
- Albumin
- Alkaline phosphatase (ALP)
- Amylase
- Aspartate aminotransferase (AST)
- Bilirubin, total
- Calcium
- Creatinine
 - eGFR will be calculated by the central laboratory
- Lipase
- Potassium
- Sodium
- Urea
- Creatine kinase

Haematology:

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

Hormones:

- Calcitonin

The laboratory results will be made available for the investigator on an ongoing basis. The investigator must sign and date each laboratory report or ensure review is documented in the subject's medical records. For laboratory results outside the reference range, the investigator must indicate as either clinically significant or not clinically significant. Concomitant illnesses and AEs must be assessed and reported according to this protocol, as applicable.

If a calcitonin assessment results in a value ≥ 10 ng/L, the investigator must follow the algorithm in Protocol [Appendix A](#).

FPG levels are monitored to aid investigators in glycaemic management through adjustment of background medication, but will not be included as an endpoint.

Subjects must attend visits fasting when FPG and lipids are assessed (see section [2](#)). Fasting is defined as having consumed only water within the last 8 hours. Administration of trial product is allowed prior to the visit. If a subject attends the visit in a non-fasting state, the visit procedures should be performed, excluding blood sampling, and subjects must be asked to visit the site once more within the visit window to have blood sampling performed.

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. *For Brazil only: All laboratory results will be communicated to the investigators.* The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

Blood samples will be destroyed at completion of the clinical trial report at the latest, except samples obtained for anti-semaglutide antibody analysis in relation to suspicion of hypersensitivity reaction (see section [8.2.2](#) and [24.2](#)).

8.1.15 Hand out and instruct in BG meter use

At visit 2, the subject should be provided with a BG meter including auxiliaries. The subject should be instructed in how to use the device. The instructions should be repeated as necessary during the trial.

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.

The investigator should instruct and encourage the subject to measure and record fasting SMPG according to individual recommendation from the investigator. The SMPG measurements may be recorded anywhere as per the subject's own choice or the investigator's recommendation. The measurements will not be transcribed into the eCRF, i.e. these measurements are only encouraged in order to facilitate good diabetes management at the discretion of the investigator.

8.1.16 Adverse events and technical complaints

AEs and technical complaints must be reported in accordance with the procedures outlined in section [12](#).

8.1.16.1 Hypoglycaemic episodes

All severe hypoglycaemic episodes defined according to the ADA classification²⁹ must be reported as an AE with additional data collection, see section [12.1.4](#), [12.2](#) and [Appendix B](#). The investigator is not required to report a hypoglycaemic episode if the episode is both non-serious and non-severe.

A severe hypoglycaemic episode is defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

If the hypoglycaemic episode fulfils the criteria for an SAE then a safety information form must also be filled in, see section [12](#).

8.1.16.2 Medication errors

If a medication error concerning trial product (see definition in section [12.1.4](#)) is observed during the trial, the following information is required:

- Trial product(s) involved
- Classification of medication error
 - Wrong drug(s) administered
 - Wrong route of administration
 - Wrong dose administered
- Whether the subject experienced any AE(s) as a result of the medication error
- Suspected primary reason for the medication error

8.1.17 End of trial

When a subject completes visit 18, the investigator should fill in the end-of-trial forms in the eCRF.

If a subject proves difficult to reach for visit 18, and vital status is collected via sources other than the subject him/herself (see section [8.4](#)), the investigator should fill in the end-of-trial forms after collecting the vital status. If, before the database lock, the investigator establishes contact with the subject, the investigator will update the end-of-trial forms.

8.2 Other assessments

8.2.1 Assessments in case of suspicion of acute pancreatitis

Most patients with acute pancreatitis experience 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 relief³⁰. 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 pancreatitis³⁰. 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, trial product treatment should be promptly interrupted. Appropriate additional examinations must be performed, including measurement of amylase and lipase.

The diagnosis of acute pancreatitis requires two of the following three features³¹:

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

If acute pancreatitis is ruled out, the subject should resume trial product treatment, at the investigator's discretion.

If acute pancreatitis is confirmed, the investigator should initiate careful monitoring of the subject. The subject must be discontinued from trial product, but should remain in the trial (see section [6.5](#) and [8.4](#)).

The event must be assessed according to section [12.1](#) and reported if applicable as per section [12.2](#).

8.2.2 Assessments in case of suspicion of hypersensitivity reactions to the trial product

In case of suspicion of a severe immediate systemic hypersensitivity reaction³² to the trial product, the subject must be discontinued from trial product but should remain in the trial (see sections [6.5](#) and [8.4](#)).

To assist in diagnosis it is recommended to draw a blood sample for measurement of tryptase (total and/or mature tryptase, to be assessed at a local laboratory) within 3 hours of the hypersensitivity reaction, and, if this is achieved, a tryptase sample should also be collected at next site visit. Furthermore, a blood sample for assessment of anti-semaglutide IgE antibodies and anti-semaglutide antibodies should be drawn as soon as possible after the event and at next site visit and sent to central laboratory for analysis.

In case of suspicion of immune complex disease³², the subject must be discontinued from trial product but should remain in the trial (see sections [6.5](#) and [8.4](#)). It is recommended to collect a

blood sample for assessment of complement levels (C3 and C4) to assist the diagnostic evaluation (to be assessed at a local laboratory).

The event must be assessed according to section [12.1](#) and reported if applicable as per section [12.2](#).

8.2.3 Assessments in case of increased levels of aminotransferases

In case of

1. ALT or AST > 3x UNL **and** total bilirubin > 2x UNL,
2. ALT or AST > 5x UNL **and** total bilirubin ≤ 2x UNL,

the event must be reported as an AE requiring additional data collection (see section [12](#) and [Appendix B](#)).

For both events, prompt repeat testing (at central laboratory) including ALT, AST, ALP and total bilirubin should be done and discontinuation of trial product 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.

8.3 Treatment compliance

Treatment compliance will be assessed by monitoring of drug accountability. Subjects will be asked to bring along all used, partly used and unused trial products including empty packaging at each visit where drug accountability is performed (see sections [2](#) and [9.4](#)). The investigator must assess the amounts of trial product used compared to expected usage since 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 them of the importance of following the instructions given including taking the trial products as prescribed.

8.4 Trial adherence

Throughout the trial, the investigator will remind the subject to follow the trial procedures and requirements. It is the responsibility of the investigator to ensure that the subject's visits occur according to schedule.

If a clinic visit is missed and it is not possible to reschedule, the investigator should ensure that relevant information is collected for example over the telephone. The subject should be asked to attend the next scheduled visit according to the visit schedule.

If extra trial product is needed, the investigator can perform an additional dispensing session in IV/WRS (see section [10](#)).

The subject can remain in the trial regardless of lack of compliance with trial treatment, lack of adherence to the visit schedule, missed assessments, discontinuation of trial treatment for any reason or development of comorbidities or clinical outcomes.

Premature discontinuation of trial product: Subjects who discontinue treatment with trial product should still be followed according to the visit schedule in section [2](#). For subjects who are off trial product, a reduced visit schedule and conversion of site visits to telephone visits may be considered if this becomes a prerequisite for their continued participation in the trial. Reasons for not adhering to the standard visit schedule must be documented in medical records. Premature trial product discontinuation should be registered in the eCRF (see section [5.3](#)) and in IV/WRS (see section [10](#)).

Withdrawals: A subject who explicitly wants to withdraw their consent must be formally 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/willing to come to the trial site. Although a subject is not obliged to give his/her reason(s) for withdrawing from a trial, 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 not completing the trial must be specified on the end-of-trial form in the eCRF.

A subject who agrees to provide information concerning relevant morbidities at the planned end of trial should not be considered withdrawn from the trial.

Regarding subjects who are withdrawn when the trial comes to an end, the investigator must scrutinise publicly available registries for relevant safety information, unless prohibited by local regulations. Vital status must be determined as a minimum, wherever possible.

Lost to follow-ups: If a subject proves difficult to reach for their visit 18, extensive attempts must be made to locate the subject and obtain relevant safety information, in particular related to MACE. This may include consulting contacts provided by the subject (e.g. relatives or emergency contacts), relevant health care professionals/clinics, medical records, local registries and locator agencies. A subject cannot be deemed lost to follow-up until at least the following contacts have been attempted and documented in medical records:

- to subjects: two phone calls and one written contact
- to primary physician and/or other health care professionals: calls until contact is established
- to relatives or other contacts provided by the subject: two phone calls and one written contact
- to relevant publicly available registries

A subject will only be considered lost to follow-up in case vital status cannot be determined at the time of visit 18, or at least before the trial database lock is initiated.

9 Trial supplies

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

Each trial site will be supplied with sufficient trial products for the trial on an ongoing basis controlled by IV/WRS. Trial products will be distributed to trial sites in accordance with subject enrolment rates at the individual site.

Trial product should only be dispensed to persons participating in the trial. If a subject is unable to attend the site for a dispensing visit (see flowchart in section 2), a non-participating person may, however, collect the allocated trial product on behalf of the subject. If trial product is collected by a non-participant, this must be agreed with the subject on beforehand and thoroughly documented at the site e.g. by means of a letter of authorisation issued by the subject, and, on each occasion, the investigator must follow up by contacting the subject.

9.1 Trial products

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

Table 9–1 Investigational medicinal products

Trial product	Strength	Dosage form	Route of administration	Container
Semaglutide 3 mg tablet	3 mg	Tablet	Oral	Dose pack with 1 blister card each containing 7 tablets
Semaglutide 7 mg tablet	7 mg			
Semaglutide 14 mg tablet	14 mg			
Placebo tablet	N/A			

Semaglutide and placebo tablets are white to light yellow oval-shaped tablets, embossed with “M8” on one side. All tablets are visually identical, irrespective of strength.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13³³, local regulations and trial requirements.

9.3 Storage

Storage conditions for the trial products are outlined in [Table 9-2](#) and on the trial product labels.

Table 9-2 Storage conditions for trial products

Trial product	Storage conditions	In-use conditions
Semaglutide 3 mg tablet	Do not store above 30°C (86°F) Do not freeze Do not refrigerate Store in the original package	Take the tablet immediately after dispensation from blister card
Semaglutide 7 mg tablet		
Semaglutide 14 mg tablet		
Placebo tablet		Take the tablets whole: Do not break or chew

The investigator must ensure the availability of proper storage conditions, and also record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. stored in a refrigerator).

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

9.4 Drug accountability and destruction

Subjects must be instructed to bring along all used, partly used and unused trial products including empty packaging material on an ongoing basis. Returned trial product must be stored separately from non-allocated trial product.

Drug accountability is the responsibility of the investigator and should be done at tablet level by means of IV/WRS. All trial products received at site should be accounted for. Non-allocated trial product (expired, damaged and available) should be accounted as unused at closure of the trial site at the latest.

Destruction of expired stock and damaged or returned trial product may be done on an ongoing basis throughout the trial, in accordance with local procedures, after accountability is finalised and reconciled by the monitor. Remaining stock can be destroyed after last end-of-treatment visit has been carried out at the site. On-site destruction may be arranged if local procedures allow. Destruction of trial products must be documented in IV/WRS.

9.5 Auxiliary supplies

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

- BG meters and BG meter auxiliaries

10 Interactive voice/web response system

A trial-specific IV/WRS will be set up which can be accessed at any time via the internet or telephone. Access to the IV/WRS must be restricted to and controlled by authorised persons. IV/WRS user manuals will be provided to each trial site.

IV/WRS is used for:

- Screening
- Screening failure
- Randomisation
- Data change
- Medication arrival
- Dispensing
 - Semaglutide 3 mg / placebo tablets
 - Semaglutide 7 mg / placebo tablets
 - Semaglutide 14 mg / placebo tablets
- Subject treatment status change (treatment pause / treatment resume)
- Code break
- Drug accountability

At the screening session in IV/WRS, the investigator may need to indicate whether the subject fulfils one or more of the criteria a-h in inclusion criterion no. [3](#) (see section [6.2](#)).

In case a subject discontinues trial treatment, or resumes trial treatment after a treatment pause, this should be registered in IV/WRS by means of the ‘subject treatment status change’ session.

When using the ‘subject treatment status change’ session to resume treatment, the investigator will need to decide which trial product dose to prescribe (cf. section [5.3.1](#)). If trial product treatment is resumed at 3 or 7 mg oral semaglutide/placebo, IV/WRS will per default dispense trial product to support the dose escalation steps outlined in section [5.3.1](#), and extraordinary dispensing visits may be needed in order to get the subject back into the ordinary dispensing visit schedule outlined in the flow chart in section [2](#).

At all times during the trial, investigators must have robust procedures in place to ensure they only dispense the DUNs allocated to the particular subject by IV/WRS. This will ensure that:

- The subject receives the trial treatment they are randomised to
- Adequate stock is available at site
- Dispensed trial products can be accounted for

If a subject needs trial product between dispensing visits, the investigator should make an additional dispensing session in IV/WRS. For subjects who withdraw from the trial or pass away during the

trial, final drug accountability will need to be performed. The system will then be updated by Novo Nordisk and the site will no longer be supplied with trial product for the particular subject.

11 Randomisation procedure and breaking of blinded codes

Only eligible subjects are allowed to be randomised. The investigator must use IV/WRS for randomisation of subjects. IV/WRS will ensure random assignment to the two treatment arms in a 1:1 ratio and ensure even distribution of the two treatment arms within the strata described in section [5.1](#).

11.1 Breaking of blinded codes

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 IV/WRS, record the reason, and sign and date the document. The IV/WRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IV/WRS is not accessible at the time of code break the IV/WRS helpdesk should be contacted. Contact details are listed in [Attachment I](#).

The subject may resume or continue trial product treatment although their code was broken.

12 Adverse events, technical complaints and pregnancies

This trial is designed to evaluate cardiovascular outcomes and will apply a targeted approach for collection of safety data focusing on SAEs, AEs leading to discontinuation of trial product and other selected events.

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a 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: 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 considered as AEs:

- Pre-existing conditions, including those found as a result of screening procedures (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.

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 serious adverse event (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 dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

The following events must always be reported as SAEs using the important medical event criterion if no other seriousness criterion is applicable:

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

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 Adverse events requiring additional data collection

Adverse events requiring additional data collection are events which, in the evaluation of safety, have a special focus (e.g. required by the health authorities).

If any of the following AEs are applicable for reporting according to section [12.2](#), additional data collection is required:

- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or TIA)
- Heart failure requiring hospitalisation
- Pancreatitis
- Neoplasm (excluding thyroid neoplasm)
- Thyroid disease (including thyroid neoplasm)
- Renal event
- Hypersensitivity reaction to the trial product
- Lactic acidosis
- Medication error concerning trial product:
 - Administration of wrong drug.
 - Note: Use of wrong DUN is not considered a medication error per se.
 - Wrong route of administration
 - Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
 - Accidental administration of a higher dose than intended. That is a dose of 1 tablet or 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.

If a subject missed one or more doses of trial product, this should not be reported as a medication error.

- Severe hypoglycaemic episode (see section [8.1.16.1](#))
- Hepatic event:
 - 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

Additional assessments should be made for hepatic events (see section [8.2.3](#)).

12.1.5 Technical complaint

A technical complaint is any written, electronic, or oral communication that alleges product 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)
- The packaging material (e.g. cracks or errors in labelling text)

12.2 Reporting of adverse events

In this trial the following events must be collected and reported:

- SAEs
- AEs leading to discontinuation of trial product
- Medication errors
- Severe hypoglycaemic episodes
- Hepatic events
- Pregnancies

Medication errors, severe hypoglycaemic episodes and hepatic events must be reported regardless of seriousness and whether trial product is discontinued.

Events occurring as of the first trial-related activity after the subject signed the informed consent until the end of the follow-up period are in scope for collection and reporting. The events must be recorded in the applicable CRFs 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, for example by asking: "Have you experienced any problems since the last contact?"

All SAEs, AEs leading to discontinuation of trial product, medication errors, severe hypoglycaemic episodes and hepatic events, either observed by the investigator or subject, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the

following reference documents: IB for oral administration of semaglutide (NN9924), current edition¹⁸ or any updates thereto.

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

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

AEs requiring additional data collection must be reported using both the AE form and the specific event form. A specific event form is a form tailored to collect specific information related to the individual event (see [Appendix B](#) for details about the specific event forms and the additional information to report).

Certain events will undergo event adjudication by the Event Adjudication Committee (EAC), please refer to section [12.7.3](#). For such events, the Event Adjudication Form will also have to be completed in the eCRF. The Event Adjudication Form is a checklist of clinical data to be provided from the site.

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the eCRF within the specified timelines:

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

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

- **SAEs fulfilling criteria for additional data collection:** In addition to above, the corresponding specific event form **within 14 calendar days** of investigators knowledge of the event.
- **Events for adjudication:** Event Adjudication Form **within 14 calendar days** of the investigator's first knowledge of the AE.

The investigator should preferably provide the medical documentation within 4 weeks of event identification.

If the eCRF is unavailable, the concerned AE information must be reported on paper forms 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 appropriate forms in the eCRF.

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

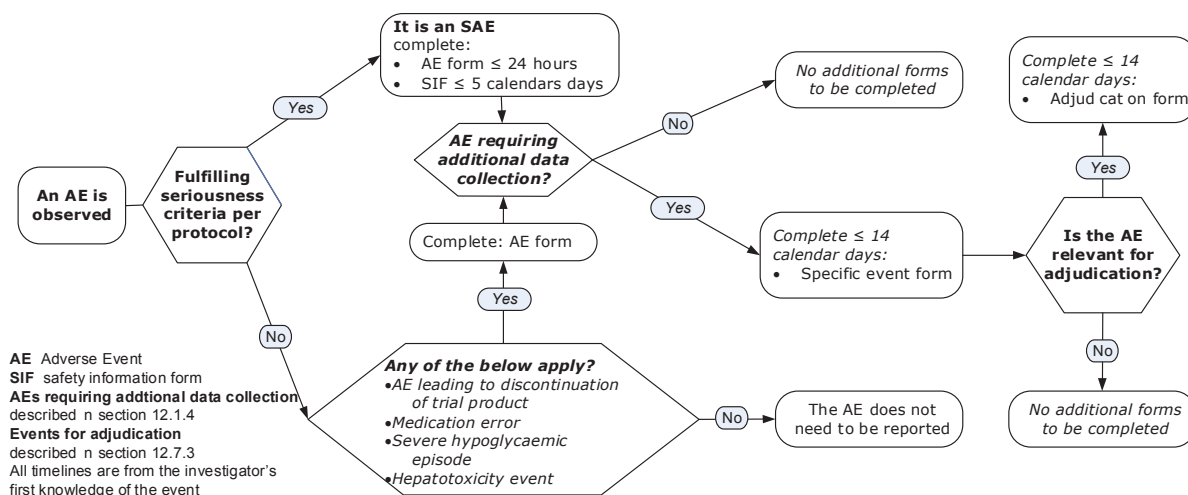


Figure 12–1 Initial reporting of AEs

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 GCP¹. 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 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 GCP¹, unless locally this is an obligation of the investigator.

To avoid introducing bias and to maintain the integrity of the primary analysis, Novo Nordisk will exempt SAEs that are part of the primary endpoint evaluation from unblinding during regulatory reporting, even though the cases fulfil the definition of SUSARs. The DMC (see section 12.7.2) receives unblinded data and makes recommendations to the Novo Nordisk safety committee. This ensures adequate monitoring of safety while maintaining SAE reports related to the primary endpoint blinded for Novo Nordisk.

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

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

Novo Nordisk products used as concomitant medication:

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

12.3 Follow-up of adverse events

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

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

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

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

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

The investigator must ensure that the 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.

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 / placebo tablets
- Semaglutide 7 mg / placebo tablets
- Semaglutide 14 mg / 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. A technical complaint form for each code number or for each DUN 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 sent with the sample.

The investigator must ensure that the technical complaint sample contains the code number and, if available, the DUN.

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. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (see section 9).

12.5 Pregnancies

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

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

The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and newborn infant. When needed, Novo Nordisk will provide paper forms for collection of the relevant information. The investigator must report the requested information to Novo Nordisk - electronically (e.g. in PDF format), or by fax or courier.

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 (mild/moderate) include: hunger, slight headache, nausea, light-headedness, palpitations, and sweating. Severe hypoglycaemia may produce loss of consciousness. Symptoms of non-severe hypoglycaemia should be treated by ingestion of carbohydrates. Severe hypoglycaemia resulting in loss of consciousness should be treated at the investigator's discretion according to best available medical practise.

One case of accidental overdose of oral semaglutide was reported in the [REDACTED] trial in a subject treated with 20 mg oral semaglutide once daily. The subject accidentally took the trial product twice on Day 52 of the trial. No AEs were reported at the same time. The medication error

was discovered at the next scheduled visit. The subject did not report any symptoms and treatment was continued without any change.

One case of accidental overdose has been reported in s.c. semaglutide once weekly treated subjects. The case was classified as moderate in severity and considered probably related to semaglutide and was reported by a subject enrolled in the trial [REDACTED]. No hospitalisation was needed. The subject inadvertently injected 4 mg of semaglutide instead of 0.4 mg, which corresponds to a 2.5-fold higher dose than the maximum dose included in that trial. After 4–5 hours the subject felt nauseated, vomited and had a headache. The subject was instructed to drink sufficient amounts of fluids. Symptoms had improved within one day of dosing, and the subject wished to continue in the trial. Plasma glucose levels, blood pressure and pulse were monitored during the following 5 days, and no symptoms of hypoglycaemia or any other symptoms or signs were noted. The subject was withdrawn from the trial after 19 days of treatment due to an AE (diarrhoea).

For further details please see the IB for oral administration of semaglutide (NN9924), current edition¹⁸, or any updates thereto.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

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

12.7.2 Data monitoring committee

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

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

12.7.3 Event adjudication committee

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

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

The events are reviewed by the EAC in a blinded manner. The EAC will have no authorisation to impact 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 12-1](#) have been selected for adjudication in order to obtain an external independent validation of the diagnosis. In addition, cardiovascular events are being adjudicated in accordance with FDA requirements³⁴.

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication packages (e.g. x-rays, 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.

AEs for adjudication can be identified in four different manners:

- AEs reported by the investigator for adjudication
- Screening of AEs reported by the investigator as not relevant for adjudication
- Unreported AEs detected by the EAC while reviewing source data for other AEs reported by the investigator
- ECGs suggestive of new myocardial infarction (see section [8.1.12](#))

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 independence and in-depth 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.

Table 12–1 Adverse events for adjudication

Events	Description	Adjudication outcomes
Death	<ul style="list-style-type: none"> All-cause death 	<ul style="list-style-type: none"> Cardiovascular death (including undetermined cause of death) Non-cardiovascular death
Acute Coronary Syndrome	<ul style="list-style-type: none"> ST-elevation acute myocardial infarction (STEMI) Non-ST elevation acute myocardial infarction (NSTEMI) Silent myocardial infarction Unstable angina pectoris (UAP) 	<ul style="list-style-type: none"> Acute myocardial infarction (STEMI or NSTEMI), silent myocardial infarction Unstable angina pectoris requiring hospitalisation
Cerebrovascular events	<ul style="list-style-type: none"> 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 (TIA) is defined as a transient episode (<24 hours) of focal neurological dysfunction caused by brain, spinal cord, or retinal ischaemia, without acute infarction 	<ul style="list-style-type: none"> Ischaemic stroke Haemorrhagic stroke Undetermined stroke TIA
Heart failure requiring hospitalisation	<ul style="list-style-type: none"> Hospitalisation with a primary diagnosis of heart failure (new episode or worsening of existing heart failure) 	<ul style="list-style-type: none"> Heart failure requiring hospitalisation
Acute pancreatitis	<p>The diagnosis of acute pancreatitis requires two of the following three features:</p> <ul style="list-style-type: none"> Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) Serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal Characteristic findings of acute pancreatitis on imaging 	<ul style="list-style-type: none"> Acute pancreatitis <ul style="list-style-type: none"> Mild Moderate Severe
Malignant neoplasm	<p>Malignant neoplasms are defined as:</p> <ul style="list-style-type: none"> 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 <p>Thyroid neoplasms are excluded in this event category</p>	<ul style="list-style-type: none"> Malignant neoplasm
Thyroid disease, if malignant thyroid neoplasm or C-cell hyperplasia	<p>Malignant thyroid neoplasms are defined as</p> <ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Malignant thyroid neoplasm C-cell hyperplasia
Acute kidney injury	<p>Acute kidney injury²¹ is defined as any of the following (not graded):</p> <ul style="list-style-type: none"> 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 < .5 mL/kg/h for 6 hours 	<ul style="list-style-type: none"> Acute kidney injury

Events	Description	Adjudication outcomes
Lactic acidosis	Lactic acidosis is characterized by increased blood lactate level in association with metabolic acidosis	• Lactic acidosis

The safety data accumulating during the trial will be screened 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.

The event adjudication vendor or 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 or subjects never randomised for whatever reason.

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

13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRFs). 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 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.

The following will be provided as paper CRFs:

- Pregnancy forms (distributed to site if a pregnancy occurs)

In addition, paper AE forms, safety information forms and technical complaint forms will be provided. These must be used when access to the eCRF is revoked or if the eCRF is unavailable.

On the paper CRFs, 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. Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

Corrections to data on paper CRFs may only be made by drawing a straight line through the incorrect data and then writing the correct data next to the original entry. Each correction must be initialled, dated and explained (if necessary).

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

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.

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 for trial sites with subjects in screening, treatment or follow-up.

The monitor must be given direct access to 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).

The eCRF must not be used for capturing source data, i.e. all data recorded in the eCRF must be verifiable in source documentation. 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.

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

Monitor will review the subject's medical records and other source data to ensure consistency and/or identify omissions compared to the CRF. If discrepancies are found, the investigator will be questioned about these.

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

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a data management unit within Novo Nordisk or a CRO.

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 may use their own electronic systems to capture source data.

17 Statistical considerations

The blinding of the randomised treatments will be maintained until the database has been released for statistical analysis. No interim analyses or other analyses of unblinded or between group data will be performed before the database is locked, with the exception of those highly confidential analyses performed by an external independent statistician to support the deliberations of the DMC (see section [12.7.2](#)) or in direct response to a recommendation by the DMC.

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

Data from all sites will be analysed and reported together.

In statistical analyses where stratification is included, the evidence of cardiovascular disease at screening (presence of cardiovascular disease or risk factors only) will be included based on the actual information collected through the eCRF. In case of missing eCRF information the information collected in IV/WRS will be used.

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

Laboratory values below the lower limit of quantification (LLoQ) will be set to $\frac{1}{2}$ LLoQ. Number of values below LLoQ by treatment and visit will be summarised if deemed relevant.

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

Primary estimand

The trial aims to confirm that treatment with oral semaglutide does not result in an unacceptable increase (80% excess risk) in cardiovascular risk compared to placebo in subjects with T2D at high risk of cardiovascular events. Time from randomisation to first MACE will be the primary endpoint and treatment arms will be compared using the hazard ratio. This is an event-driven trial and information is planned to be collected on all randomised subjects until at least 122 first MACEs have accumulated during the planned trial duration of 19 months.

Primary estimand:

- de-facto estimand comparing oral semaglutide and placebo for all randomised subjects. Subjects who discontinue treatment with trial product should be followed according to the planned visit schedule. Estimation of the primary estimand will include all first MACEs

collected during the trial as defined by the in-trial observation period (see section [17.2](#)) regardless of adherence to randomised treatment.

17.1 Sample size calculation

Firstly, the primary endpoint; time from randomisation to first occurrence of a MACE composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, will be tested for non-inferiority using a 1.8 non-inferiority margin. If the hypothesis is confirmed, the confirmatory secondary endpoint; time from randomisation to first occurrence of an expanded composite cardiovascular endpoint consisting of: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina requiring hospitalisation or hospitalisation for heart failure, will be tested for non-inferiority using a 1.8 non-inferiority margin. The type-I-error will be preserved in the strong sense at 5% (two-sided) when using the hierarchical testing strategy.

The sample size is made to ensure a power of 90% for testing the confirmatory hypothesis for the primary endpoint. Based on a logrank test, a total of 122 first MACEs will provide 90% power to rule out hazard ratios exceeding 1.8, assuming a true hazard ratio of 1.0.

In order to have a total of 122 first MACEs with trial duration of 19 months and 1,588 subjects randomised to each treatment group (1:1 randomisation), in total 3,176 subjects, the following is assumed based on the ongoing trials EX2211-3748 (LEADER[®]) and NN9535-3744 (SUSTAIN[™] 6):

- First MACEs occur at a rate of 3 per 100 patient years of observation time (PYO) in both treatment groups throughout the trial
- Recruitment into the trial occurs uniformly during 7 months
- The lost-to-follow-up rate is 1% per year throughout the trial
- LSLV occurs 19 months after first subject was randomised

[Table 17–1](#) shows expected trial duration for different event rates under the same assumptions as described above for the other parameters.

Table 17–1 Expected trial duration according to event rates

Event rate per 100 PYO in both treatment arms	2.5	2.75	3.0	3.25	3.5
Expected trial duration from randomisation of subject to LSLV (months)	22.2	20.4	19	17.8	16.7

17.2 Definition of analysis sets

The following analysis set is defined:

- Full analysis set (FAS): includes all randomised subjects. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation “as randomised”.

In this trial, two observation periods will be defined. Definition of the observation periods:

- **In-trial observation period:** This observation period will include information assessed from randomisation to the date of the last subject-site contact regardless of adherence to treatment, which is scheduled to take place 5 weeks (with a +3 days visit window) after last planned dose of the trial product. The 5 weeks follow-up period corresponds to approximately five half-lives of oral semaglutide. For subjects lost to follow-up the end-date will be the date of the last contact with the subject (site visit or by telephone). If a subject dies during the trial, the date of death will be the end-date of the in-trial observation period regardless of the above defined end-dates.
- **On-treatment observation period:** This observation period is a subset of the in-trial observation period and will include information assessed on or after the first date of trial product up to and including the first date of (i) last date on trial product +38 days or (ii) 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. In addition, the ascertainment window includes the follow-up visit window of +3 days after last date on trial product.

Subjects not having a MACE within the observation period will be censored at the end of the observation period in the primary analysis assuming independent censoring for subjects lost to follow-up. Hence, a subject censored at a given time should be representative of those still at risk at that time point. For EAC confirmed events the onset date will be the onset date assessed by the EAC. EAC confirmed events with adjudicated onset date prior to randomisation will be described in listings. EAC confirmed events with adjudicated onset date after in-trial observation period but prior to database lock will be evaluated and summarised descriptively. For events not subjected to adjudication or negatively adjudicated, the onset date for the adverse event reported by the investigator will be used.

17.3 Primary endpoint

- Time from randomisation to first occurrence of a MACE composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

The primary estimand will be estimated based on the FAS and the in-trial observation period. The primary statistical analysis of the primary endpoint will be a stratified Cox proportional hazards model with treatment group (oral semaglutide, placebo) as fixed factor. The model will be stratified

by evidence of cardiovascular disease at screening (presence of cardiovascular disease or risk factors only). From this model the estimated hazard ratio (HR) (oral semaglutide/placebo) together with the 2-sided 95% confidence interval will be presented. Non-inferiority of oral semaglutide versus placebo will be considered confirmed if the upper limit of the two-sided 95% confidence interval for the HR is below 1.8 or equivalent if the p-value for the one-sided test of

$$H_0: HR \geq 1.8 \text{ against } H_a: HR < 1.8$$

is less than 2.5% (or equivalent to 5% for a two-sided test).

A Kaplan-Meier plot with number of subjects at risk at specific time points will be presented and used graphically to assess the validity of the assumption of proportional hazards. This will be supported by the use of Schoenfeld residuals.

17.3.1 Sensitivity analysis

To explore the robustness of the primary analysis results the following sensitivity analyses will be performed. The sensitivity analyses will evaluate different de-jure estimands and, thus, will focus on events occurring while subjects to a greater extent compared to the primary estimand are treatment adherent. Different observation periods will be defined considering treatment adherence and different follow-up periods after last date on trial product. All sensitivity analyses will be based on FAS and analysed using the same model as the primary analysis including the censoring rules and the assumption of independent censoring for subjects with shorter observation period than the trial duration.

Sensitivity analysis 1: Including additional covariates

This sensitivity analysis will explore the primary analysis by fitting a stratified Cox regression analysis and estimate of the treatment hazard ratio (oral semaglutide/placebo) with a 2-sided 95% confidence interval while including the additional covariates sex, region, baseline age, diabetes duration, smoking history, and eGFR at baseline. The model will be stratified by evidence of cardiovascular disease at screening (presence of cardiovascular disease or risk factors only). The analysis will be based on the FAS and the in-trial observation period.

Sensitivity analysis 2: Ascertainment window of 38 days after last date on trial product

This sensitivity analysis will include all first MACEs that are collected in the on-treatment observation period.

Sensitivity analysis 3: Ascertainment window of 7 days after last date on trial product

This sensitivity analysis will include all first MACEs that are collected on or after the first date on trial product up to and including the last date on trial product +7 days.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoint

- Time from randomisation to first occurrence of an expanded composite cardiovascular endpoint consisting of: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina requiring hospitalisation or hospitalisation for heart failure

The confirmatory secondary endpoint will be analysed using the same analysis including sensitivity analyses as for the primary endpoint.

17.4.2 Safety endpoints

Time to event endpoints

- Time from randomisation to first occurrence of each of the individual components in the expanded composite cardiovascular endpoint
- Time from randomisation to first occurrence of a composite endpoint consisting of: all-cause death, non-fatal myocardial infarction or non-fatal stroke
- Time from randomisation to all-cause death
- Time to permanent discontinuation of trial product due to AE(s)

The analyses of the above time-to-event composite endpoints (except for the last endpoint) will be the same as the primary analysis. The analysis of time to permanent discontinuation of trial product due to AE(s) will be adjusted for the competing risk of other predefined reasons for discontinuing trial product prematurely. The above analyses will be based on the FAS and performed for both the in-trial and on-treatment observation periods. Cumulative incidence functions will be plotted for all of the endpoints.

Adverse events

- Number of SAEs

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

SAEs 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). The summaries will be based on FAS and performed for both the in-trial and the on-treatment observation periods. Furthermore, events confirmed by adjudication and AEs leading to discontinuation of trial product will be summarised as above.

Continuous safety endpoints

Change from baseline to last assessment of:

- Pulse
- Systolic and diastolic blood pressure

The last available measurement for the above endpoints will be analysed separately in an analysis of covariance (ANCOVA) with treatment group as fixed factors and the corresponding baseline value as a covariate. From the ANCOVAs the estimated treatment differences for oral semaglutide versus placebo together with the corresponding 2-sided 95% confidence intervals will be presented. The analyses will be based on FAS and performed for both the in-trial and the on-treatment observation periods.

Other safety endpoints

- Biochemistry
- Haematology
- Calcitonin

The above assessments will be summarised using descriptive statistics by treatment group for all scheduled visits and for last available assessment based on FAS and performed for both the in-trial and the on-treatment observation periods. Categorical safety endpoints will be summarised as counts and relative frequencies. Calcitonin will also be presented by sex.

17.4.3 Efficacy endpoints

Change from baseline to last assessment of:

- HbA_{1c}
- Body weight
- Lipids

The last available measurement for the above endpoints will be analysed separately in an ANCOVA with treatment group as fixed factors and the corresponding baseline value as a covariate. From the ANCOVAs the estimated treatment differences for oral semaglutide versus placebo together with the corresponding 2-sided 95% confidence intervals will be presented. The analyses will be based on FAS and performed for both the in-trial and the on-treatment observation periods.

18 Ethics

The trial will be conducted in compliance with ICH GCP¹ and applicable regulatory requirements, and in accordance with the Declaration of Helsinki². When treatment with trial product ends, the subject and investigator will decide on the best available treatment for each subject.

18.1 Benefit–risk assessment of the trial

Risks and precautions

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

The sections below describe identified and potential risks and precautions associated with oral semaglutide treatment. These are based on findings in nonclinical 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. In addition, in case a subject experiences unacceptable tolerability issues, dose reduction to a lower treatment dose is allowed.

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 of 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 T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from nonclinical- or clinical trials or postmarketing 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.

Severe 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. In this trial, it is recommended to reduce the dose of insulin and sulphonylurea at randomisation to reduce the risk of hypoglycaemia when introducing an additional glucose lowering agent.

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.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, an allowed background treatment, have also been associated with volume depletion. It is recommended to monitor for signs and symptoms of fluid loss during therapy.

Impaired renal function may increase the risk of metformin associated lactic acidosis when GLP-1 RAs are co-administered with metformin. As a precaution serum creatinine will be measured regularly.

Other

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 intends 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 the site at screening, follow-up and at any time during the trial if a menstrual period is missed, or is required by local law.

General precautions

All subjects will be included after a thorough evaluation in regards to in- and exclusion criteria defined in order to ensure that subjects are eligible for trial treatment. It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2014 Standards of Medical Care in Diabetes³⁵.

Further details with regards to safety of trial product are described in the current edition of the IB for oral semaglutide (NN9924)¹⁸, or any updates thereto.

Benefits

For all participating subjects, the anticipated benefits include a close monitoring of their T2D and an optimised antidiabetic treatment. All subjects will be treated within an antidiabetic regimen anticipated to be better than or equal to the treatment that they receive at the time of entry into the trial. The investigator is responsible for adjusting or adding antidiabetic medication throughout the course of the trial to maintain an adequate level of glycaemic control in each subject. In addition, it is expected that all subjects will benefit from participation through close contact with the trial site including thorough medical examinations and close follow-up of their T2D.

Risk and benefit conclusion

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile for the investigational medicinal product generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of oral semaglutide in accordance with the planned clinical trial.

18.2 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 data collected at follow-up will be retained by Novo Nordisk, entered into the database and used for the 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.

18.3 Information to subject during trial

The site will be offered a communication package to the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subject at the discretion of the investigator. The subject may e.g. receive a “patient newsletter” during trial participation and a “thank you for your participation letter” after the trial has ended.

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.

18.4 Premature termination of the trial and/or trial site

The DMC may recommend premature termination of the trial (cf. section [12.7.2](#)).

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

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 clinical database.

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

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*

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, 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 Investigator's Brochure for oral semaglutide
- Signed and dated Agreement on Protocol
- Signed and dated agreement on protocol amendment, if applicable

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

For US only:

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

FDA form 1572:

For US sites:

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

For sites outside the US:

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

By signing the protocol, each investigator agrees to comply fully with ICH GCP¹, applicable regulatory requirements and the Declaration of Helsinki².

By signing the protocol, 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. 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 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 must ensure adequate supervision of the conduct of the trial at the trial site.

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 should be kept in a secure locked facility, so no unauthorised persons can get access to the data.

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

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

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

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

23 Reports and publications

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

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain

conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

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

One or more investigator(s) will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator(s)) on behalf of all participating investigators. The signatory investigator(s) will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications³⁶.

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 Disclosure²³.

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 Editors³⁷ (sometimes referred to as the Vancouver Criteria).

At the end of the trial, one or more publications (abstracts, posters, manuscripts) will be prepared for submission to scientific congresses and peer-reviewed journals in collaboration between Novo Nordisk and investigator(s) appointed by Novo Nordisk. These investigator(s) must meet the International Committee of Medical Journal Editors authorship criteria to be named authors on publications.

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 trial subjects' data available, and will be provided with the randomisation codes after the end of the trial.

24 Retention of clinical trial documentation and human biospecimens

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 as long as the product is on the market plus 20 years.

The files from the trial site/institution must be retained for 15 years after the completion of the trial, 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 biospecimens

In order to comply with any future requests from health authorities to further characterise the antibody response, antibody samples collected in relation to suspicion of hypersensitivity reactions during the trial may be stored at Novo Nordisk until no further marketing authorisations are pending or maximum 15 years after the trial ended, whichever comes first. Stored antibody samples will be identified only by a subject number, a visit number and a trial identification number. The investigator is responsible for maintaining a list which links each subject number to a subject name. This list must be kept for at least 15 years after the trial ended. The list may be reviewed by Novo Nordisk staff including auditors or representatives from regulatory authorities.

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

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

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

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to IB, SUSARs, 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 Argentina only: Novo Nordisk Pharma Argentina S.A. has contracted insurance as required by local law.

For Germany only: German Drug Law dated August 24, 1976, last amended by article 3 of the law dated December 17, 2014 (Federal Law Gazette I p. 2222).

For Mexico only: Novo Nordisk carries product liability for its products and liability as assumed under the special laws, acts/and/or guidelines for conducting trials in any country, including those applicable provisions on the Mexican United States. If the subject feels that something goes wrong during the course of this trial, the subject should contact the trial staff in the first instance.

If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the 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.

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.

For the Netherlands only: Wetgeving betreffende geneesmiddelen; geneesmiddelenwet 1 juli 2007 (Medicines Law, 1 July 2007). De Wet Medisch-wetenschappelijk Onderzoek met mensen (WMO), 1 maart 2006 (Medical Research Involving Human Subjects Act, 1 March 2006). Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015, 24 november 2014 (Decree compulsory insurance in medical research involving human subjects 2015, 24 November 2014).

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

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Protocol Appendix A
Trial ID: NN9924-4221
UTN: U1111-1173-0750
EudraCT No.: 2015-003563-10

~~CONFIDENTIAL~~

Date:	12 February 2016	Novo Nordisk
Version:	3.0	
Status:	Final	
Page:	1 of 5	

Appendix A

Monitoring of calcitonin

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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, H₂-blockers and glucocorticoids)

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

2 Calcitonin monitoring

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

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

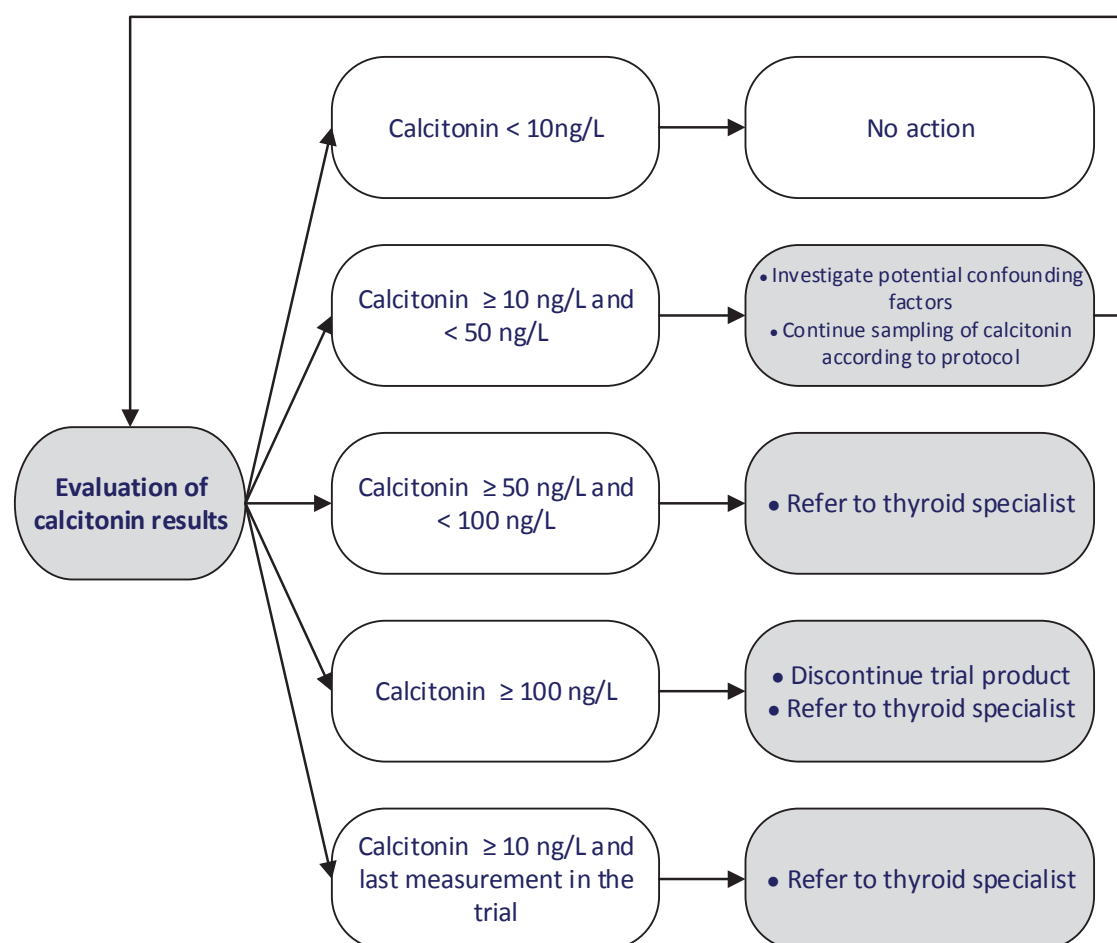


Figure 1 Flow of calcitonin monitoring

2.1 Calcitonin ≥ 100 ng/L

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

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

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

Diagnostic evaluation should include:

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

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

2.2 Calcitonin ≥ 50 and < 100 ng/L

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

Background: These values were found in 8 (0.14%) of the population of 5817 patients with thyroid nodular disease¹. 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 disease¹. 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 al¹ 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}

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Appendix B

Adverse events requiring additional data collection

1 Adverse Events requiring additional data collection

AEs must be assessed according to section [12.1](#) and reported if applicable according to section [12.2](#).

If any of the following AEs are applicable for reporting, 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 requiring hospitalisation
- Pancreatitis
- Neoplasm (excluding thyroid neoplasm)
- Thyroid disease (including thyroid neoplasm)
- Renal event
- Hypersensitivity reaction to the trial product
- Lactic acidosis
- Medication error concerning trial product
- Severe hypoglycaemic episode
- Hepatic event:
 - ALT or AST > 5x UNL and total bilirubin ≤ 2x UNL
 - ALT or AST > 3x UNL and total bilirubin > 2x UNL
 - Hepatic event leading to trial product discontinuation

As specified in section [12.2](#), the majority of events listed above should only be reported if a seriousness criterion is fulfilled or if the event leads to premature treatment discontinuation. Exempts are medication errors, severe hypoglycaemic episodes and hepatic events which must be reported regardless of the seriousness criteria.

Some of the events requiring additional data collection will also undergo event adjudication by the Event Adjudication Committee (EAC), please see section [12.7.3](#) and [Table 12-1](#).

1.1 Acute coronary syndrome

If an event of acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina) is applicable for reporting 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 (stroke or TIA) is applicable for reporting, the following additional information must be reported, if available:

- Type of event (stroke or TIA)
- Contributing condition
- Neurologic signs and symptoms
- History of neurologic disease
- Imaging supporting the condition
- Treatment given for the condition

1.3 Heart failure requiring hospitalisation

If an event of heart failure requiring hospitalisation (admission to an in-patient unit or a visit to an emergency department that results in at least a 24 hour stay) is applicable for reporting 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

If an event of pancreatitis is applicable for reporting 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

Please see section [8.2.1](#) for further details on assessments in case of suspicion of acute pancreatitis.

1.5 Neoplasm

If an event of neoplasm (excluding thyroid neoplasm, which will be reported under thyroid disease) is applicable for reporting 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 applicable for reporting 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 applicable for reporting the following additional information must be reported, if available:

- Signs and symptoms of renal failure
- Specific laboratory test 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 to the trial product

If an event of hypersensitivity reaction to the trial product is applicable for reporting 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

Please see section [8.2.2](#) for further details on assessments in case of suspicion of hypersensitivity reaction to the trial product.

1.9 Lactic acidosis

If an event of lactic acidosis is applicable for reporting the following additional information must be reported, if available:

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

1.10 Medication error concerning trial product

If a medication error concerning trial product is observed during the trial, the following additional information must be reported, if available:

- Trial product(s) involved
- Classification of medication error
 - Wrong drug(s) administered
 - Wrong route of administration
 - Wrong dose administered
- Whether the subject experienced any AE(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication error concerning trial product, see section [12.1.4](#).

1.11 Severe hypoglycaemic episode

If a severe hypoglycaemic episode is observed during the trial, the following additional information must be reported, if available:

- Lowest glucose value recorded
- Whether there were symptoms associated with the event
- Contributing factors (e.g. diet change, physical activity)
- Treatment given for the event

For definition of a severe hypoglycaemic episode, see section [8.1.16.1](#).

1.12 Hepatic event

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

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

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

Please see section [8.2.3](#) for further details on assessments in case of increased levels of aminotransferases.

Oral semaglutide
Trial ID: NN9924 4221
Clinical Trial Report
Appendix 16.1.1

Date:
Version:
Status:

11 February 2019
1.0
Final

Novo Nordisk

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
Trial ID: NN9924-4221
UTN: U1111-1173-0750
EudraCT No.: 2015-003563-10

~~CONFIDENTIAL~~

Date:
Version:
Status:
Page:

18 February 2016
1.0
Final
1 of 2

Novo Nordisk

Protocol Amendment
no 1
to Protocol, final version 3.0
dated 12 February 2016

Trial ID: NN9924-4221

PIONEER 6 – Cardiovascular outcomes
A trial investigating the cardiovascular safety of oral semaglutide
in subjects with type 2 diabetes

Trial phase: 3a

Applicable to Germany

Amendment originator:

[REDACTED]

[REDACTED]

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1 Introduction including rationale for the protocol amendment

This protocol amendment is generated to ensure the protocol requirements about contraception during participation in the clinical trial are in accordance with the current regulatory requirements in Germany.

In this protocol amendment:

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

2 Changes

Section 8.1.7 Pregnancy test

For Germany only: ~~Adequate contraceptive measures are implants, injectables, combined oral contraceptives, hormonal intrauterine devices, sexual abstinence or vasectomised partner. Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or sexual abstinence or vasectomised partner.~~

Protocol Amendment
no 2
to Protocol, final version 3.0
dated 12 February 2016

Trial ID:
NN9924-4221

PIONEER 6 – Cardiovascular outcomes
A trial investigating the cardiovascular safety of oral
semaglutide in subjects with type 2 diabetes

Trial phase: 3a

Applicable to all countries

Amendment originator:

[REDACTED]

[REDACTED]

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1 Introduction including rationale for the protocol amendment

This protocol amendment introduces: 1) A new screening procedure to ensure that a recent fundoscopic examination has been performed for each subject before they are randomised into the trial, 2) an additional exclusion criterion to disallow enrolment of patients with proliferative retinopathy or maculopathy requiring acute treatment, and 3) minor updates and clarifications. The changes are introduced and described in details below.

1.1 A new screening procedure and an additional exclusion criterion related to diabetic retinopathy

Transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive antidiabetic treatment. 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. The majority of the related adverse events were moderate in severity and did not lead to premature discontinuation of trial product. However, as a precaution in this trial, an additional exclusion criterion is added requiring all subjects to have a fundus photography or dilated fundoscopy performed within 90 days prior to screening or within the period from screening to randomisation; moreover, subjects with proliferative retinopathy or maculopathy requiring acute treatment will not be included in the trial. To accommodate the additional screening procedure, the screening period is extended from up to 2 weeks to up to 3 weeks.

1.2 Minor updates and clarifications

The following minor revisions and clarifications are implemented:

- The protocol is updated to reflect results from the recent completion of the cardiovascular outcomes trials for once-weekly s.c. administration of semaglutide (SUSTAIN™ 6 – NN9535-3744) and once-daily subcutaneous administration of liraglutide (LEADER® – EX2211-3748).
- The protocol is updated to clarify the rationale for the selected trial product dose levels.
- Text is added to highlight the investigator's responsibility in ensuring evaluation and management of not only cardiovascular disease but also microvascular complications such as diabetic kidney disease and diabetic retinopathy.
- Text is added to highlight that severe dehydration may be a risk factor for diabetic ketoacidosis in subjects using sodium-glucose cotransporter-2 (SGLT2) inhibitors.

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	Randomisation	Treatment			
			P3	V4	V5	V6
Visit (V) Phone (P)	V1	V2	P3	V4	V5	V6
Timing of visit (weeks after V2)	Up to -32	0	2	4	8	14
Visit window (days)			±3	±3	±3	±3
Informed consent	X					
In/exclusion criteria	X					
Demography, tobacco use	X					
Physical examination	X					
Eye examination ³	X					
Pregnancy test, urine dipsticks ³⁴	X					

³ Fundus photography or dilated funduscopy must be performed within 90 days prior to screening or within the period between screening and randomisation.

³⁴ For women of childbearing potential only. In addition to the planned assessment at screening and end-of-treatment, urine dipstick pregnancy test should be performed at site at any time during the trial if a menstrual period is missed, or if pregnancy is suspected, or as required by local law.

2.2 Section 3.1.5 Oral semaglutide and cardiovascular risk

In support, findings results from the recently completed ELIXA™ LEADER® trial (EX2211-3748) confirmed showed that treatment with the once-daily injectable GLP-1 RA lixisenatide s.c. liraglutide does not increase the risk of MACE as compared to placebo. In fact, treatment with liraglutide reduced the risk of the primary composite endpoint consisting of death from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke by 13% versus placebo³⁸. Also, the SUSTAIN™ 6 trial (NN9535-3744) achieved its primary objective by showing non-inferiority of once-weekly s.c. semaglutide versus placebo on cardiovascular outcomes; moreover, s.c. semaglutide statistically significantly reduced cardiovascular risk versus placebo³⁹. This trial is the first cardiovascular outcomes trial within the GLP-1 RA drug class to report and several others (including SUSTAIN™ 6 investigating the cardiovascular safety of s.c. semaglutide) are ongoing.

2.3 Section 5.1 Type of trial

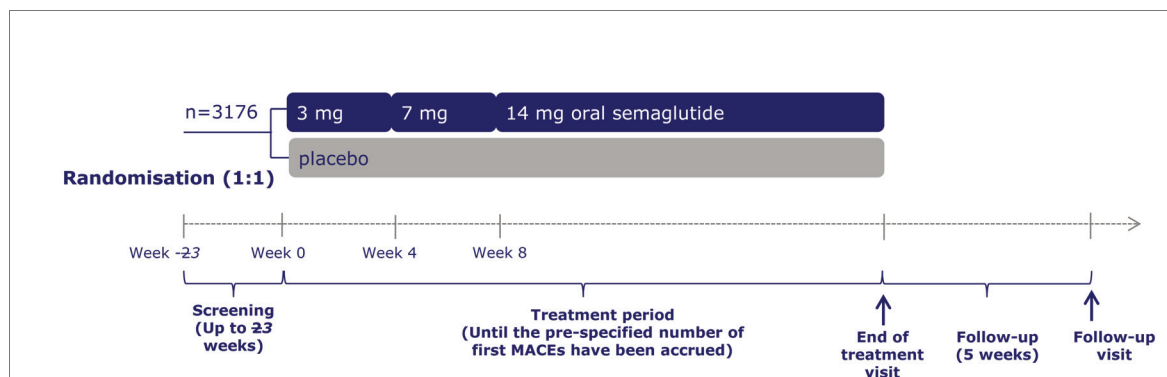


Figure 5-1 Trial design

2.4 Section 5.3 Treatment of subjects

Table 5-1 Treatment of subjects

Trial periods		Screening	Trial period 1	Trial period 2	Trial period 3	Follow-up
Alias for trial period		Screening	Dose escalation	Dose escalation	Maintenance	Follow-up
First visit in each period		V1	V2	V4	V5	V17
Duration of each period		Up to 23 weeks	4 weeks	4 weeks	Up to 75 weeks	5 weeks
Treatment arm	N					
Oral semaglutide	1588	Screening	3 mg	7 mg	14 mg	Follow-up
Placebo	1588	Screening	Placebo	Placebo	Placebo	Follow-up

2.5 Section 5.3.3 Background medication

The investigator is responsible for ensuring ongoing management of cardiovascular diseases and risk factors as well as potential microvascular complications such as diabetic kidney disease and diabetic retinopathy will be treated according to local standard of care at the investigator's discretion.

2.6 Section 5.5 Rationale for treatment

Three treatment doses of oral semaglutide will be investigated in the phase 3a development programme: 3 mg, 7 mg and 14 mg. The selected doses are based on the data derived from the NN9924-3790 dose-finding trial. This dose range is expected to have the optimal benefit-risk profile for further development of oral semaglutide. In addition, the increments between the three doses are expected to provide clinically meaningful differentiation between the effects on glycaemic control while ensuring mitigation of gastrointestinal AEs through gradual dose escalation. For further details regarding the results obtained in the phase 2 dose-finding trial (NN9924-3790), please refer

to the current edition of the IB for oral administration of semaglutide (NN9924)¹⁸, or any updates thereto.

Similar to other cardiovascular outcomes trials, the maximum treatment dose (14 mg oral semaglutide) will be investigated and compared to placebo in the present trial. Blinded treatment with oral semaglutide or placebo offers a robust method for assessment of oral semaglutide's effect on trial endpoints. ~~Gradual dose escalation is applied in order to mitigate the risk of gastrointestinal AEs.~~

2.7 Section 6.3 Exclusion criteria

17. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to screening or within the period between screening and randomisation.

2.8 Section 8.1.2 In/exclusion criteria

For exclusion criterion no. 17 (section 6.3), each subject must have a fundus photography or dilated fundoscopy performed and evaluated before randomisation, in accordance with the instructions in section 8.1.7.

2.9 Section 8.1.7 Eye examination

Results of a fundus photography or dilated fundoscopy must be available and evaluated by the investigator before randomisation. If the subject had a fundus photography or dilated fundoscopy performed within 90 days prior to screening, the investigator may base their evaluation upon the results of that examination. However, the examination must be repeated before randomisation if the subject experienced worsening of visual function since the last examination.

If the subject did not have a fundus photography or dilated fundoscopy performed within 90 days prior to screening, such examination must be performed by the investigator or other qualified health care professional prior to randomisation.

The investigator should indicate whether the outcome of the eye examination was normal or abnormal, and, if abnormal, indicate whether clinically significant. Relevant findings as a result of this screening procedure must be recorded as concomitant illness/medical history in accordance with section 8.1.9.

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

2.10 Section numbers for sections 8.1.7 to 8.1.17

Will change to 8.1.8 to 8.1.18.

2.11 Section 17.1 Sample size calculation

In order to have a total of 122 first MACEs with trial duration of 19 months and 1,588 subjects randomised to each treatment group (1:1 randomisation), in total 3,176 subjects, the following is assumed based on the ongoing trials EX2211-3748 (LEADER[®]) and NN9535-3744 (SUSTAIN[™] 6):

2.12 Section 18.1 Benefit–risk assessment of the trial

Potential risks

Acute renal impairment

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, an allowed background treatment, have also been associated with volume depletion. It is recommended to monitor for signs and symptoms of fluid loss during therapy. *Severe dehydration may be a risk factor for diabetic ketoacidosis.*

Other

Diabetic retinopathy

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive antidiabetic treatment⁴⁰⁻⁴². 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^{43,44} even in intensively treated patients who experienced early worsening⁴¹. 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. As a precaution in this trial, all subjects are required to have a fundus photography or dilated funduscopy performed before enrolment into the trial; moreover, subjects with proliferative retinopathy or maculopathy requiring acute treatment will be excluded.

Benefits

In addition, it is expected that all subjects will benefit from participation through close contact with the trial site including thorough medical examinations and close follow-up of their T2D. *Finally, data from two cardiovascular outcomes trials investigating treatment with GLP-1 RAs compared to placebo have indicated that there might be a potential beneficial effect of these drugs on cardiovascular outcomes when added to standard of care in subjects with T2D at high risk of cardiovascular events (see section 3.1.5).*

2.13 Section 27 References

- 17) Investigators Brochure for s.c. Semaglutide (NN9535), Edition ~~4011~~ or any updates hereof. ~~2015~~2016.
- 18) Investigators Brochure for oral Semaglutide (NN9924), Edition ~~67~~ or any updates hereof. ~~2015~~2016.
- 38) Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. *Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med.* 2016.
- 39) Novo Nordisk A/S. *Company Announcement: SUSTAIN 6.* 2016.
- 40) K Dahl-Jørgensen, O Brinchmann-Hansen, K F Hanssen, L Sandvik, O Aagenaes. *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
- 41) The Diabetes Control and Complications Trial Research Group. *Early Worsening of Diabetic Retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol.* 1998 Jul;116(7):874-86.
- 42) Varadhan L1, Humphreys T2, Walker AB3, Varughese GI4. *The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. Diabetes Res Clin Pract.* 2014 Mar;103(3):e37-9. doi: 10.1016/j.diabres.2013.12.041. Epub 2014 Jan 6
- 43) UK Prospective Diabetes Study (UKPDS) Group. *Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet* 1999 Aug 14;354(9178):602.
- 44) 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 Jun; dc160024. <http://dx.doi.org/10.2337/dc16-0024>

2.14 Reference numbers

Will change throughout the updated protocol when new references numbered 38-44 above are introduced.

Protocol Amendment no. 3
Trial ID: NN9924-4221
UTN: U1111-1173-0750
EudraCT No.: 2015-003563-10

~~CONFIDENTIAL~~

Date:
Version:
Status:
Page:

03 November 2016
1.0
Final
1 of 10

Novo Nordisk

Protocol Amendment
No. 3
to Protocol, final version 4.0
dated 21 July 2016

Trial ID:
NN9924-4221

PIONEER 6 – Cardiovascular outcomes
A trial investigating the cardiovascular safety of oral
semaglutide in subjects with type 2 diabetes

Trial phase: 3a

Applicable to all countries

Amendment originator:

[REDACTED]

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1 Introduction including rationale for the protocol amendment

This protocol amendment introduces:

1. Additional eye examinations and additional data collection for events of diabetic retinopathy or related complications
2. Addition of bicarbonate as a part of the biochemistry laboratory assessments
3. Clarification in relation to physical examination
4. Minor corrections or clarifications

1.1 Additional eye examinations and additional data collection for events of diabetic retinopathy or related complications

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. Based on feedback from the US Food and Drug Administration (FDA) in relation to these findings, additional eye examinations will be implemented in the present trial (NN9924-4221) after approximately one year of treatment and at the end of the treatment period. Also, to further understand this safety signal, the targeted safety reporting in this trial will be broadened to include diabetic retinopathy and related complications. Furthermore, additional information will be collected for events of diabetic retinopathy and related complications reported during the trial.

1.2 Addition of bicarbonate as a part of the biochemistry laboratory assessments

The FDA has requested that bicarbonate is added as a routine laboratory test in trials where sodium-glucose cotransporter-2 (SGLT2) inhibitors are used as background medication, because SGLT2 inhibitors have been associated with a risk for metabolic acidosis.

1.3 Clarification in relation to physical examination

As per agreement with the FDA, text is added to highlight the investigator's responsibility in relation to further evaluation of potential incidental thyroid nodules discovered at the physical examinations.

1.4 Minor corrections or clarifications

Clarification in relation to event adjudication and initial AE reporting.

2.2 Section 4.2 Endpoints

Change from baseline to last assessment of:

- Biochemistry
- Haematology
- Calcitonin
- *Eye examination category*
- Pulse
- Systolic and diastolic blood pressure
- Glycosylated haemoglobin (HbA_{1c})
- Body weight
- Lipids

2.3 Section 8.1.6 Physical examination

Please note that the diagnostic evaluation of thyroid nodules should be in accordance with the American Thyroid Association Management Guidelines or any updates hereof³⁰, adapted to local treatment guidelines.

2.4 Section 8.1.7 Eye examination

Results of a fundus photography or dilated fundoscopy must be available and evaluated by the investigator before randomisation. If the subject had a fundus photography or dilated fundoscopy performed within 90 days prior to screening, the investigator may base their evaluation upon the results of that examination. However, the examination must be repeated before randomisation if the subject experienced worsening of visual function since the last examination. *If the applicable fundus photography or dilated fundoscopy was performed before the subject signed the informed consent form, it must be documented in the medical records that the reason for performing the examination was not related to this trial.*

If the subject did not have a fundus photography or dilated fundoscopy performed within 90 days prior to screening, such examination must be performed by the investigator or other qualified health care professional prior to randomisation.

In addition to the eye examination performed at screening, fundus photography or dilated fundoscopy should be performed at visit 12 and visit 17 as per the flow chart in section 2.

Fundoscopy requires pharmacological dilation of both pupils. The investigator should indicate whether the outcome of the each eye examination was normal or abnormal, and, if abnormal, indicate whether clinically significant. Relevant findings as a result of the this-screening procedure must be recorded as concomitant illness/medical history in accordance with section 8.1.9, and

relevant findings occurring after randomisation should be reported as an AE if applicable according to section 12.2.

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

2.5 Section 8.1.15 Blood sampling

Biochemistry:

- Alanine aminotransferase (ALT)
- Albumin
- Alkaline phosphatase (ALP)
- Amylase
- Aspartate aminotransferase (AST)
- *Bicarbonate*
- Bilirubin, total
- Calcium
- Creatinine
 - eGFR will be calculated by the central laboratory
- Lipase
- Potassium
- Sodium
- Urea
- Creatine kinase

2.6 Section 12.1.4 Adverse events requiring additional data collection

Adverse events requiring additional data collection are events which, in the evaluation of safety, have a special focus (e.g. required by the health authorities).

If any of the following AEs are applicable for reporting according to section 12.2, additional data collection is required:

- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or TIA)
- Heart failure requiring hospitalisation
- Pancreatitis
- Neoplasm (excluding thyroid neoplasm)
- Thyroid disease (including thyroid neoplasm)
- Renal event
- Hypersensitivity reaction to the trial product

- Lactic acidosis
- Medication error concerning trial product:
 - Administration of wrong drug.
 - Note: Use of wrong DUN is not considered a medication error per se.
 - Wrong route of administration
 - Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
 - Accidental administration of a higher dose than intended. That is a dose of 1 tablet or 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.
If a subject missed one or more doses of trial product, this should not be reported as a medication error.
- Severe hypoglycaemic episode (see section [8.1.17.1](#))
- Hepatic event:
 - 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 discontinuationAdditional assessments should be made for hepatic events (see section [8.2.3](#)).
- *Diabetic retinopathy and related complications*

2.7 Section 12.2 Reporting of adverse events

In this trial the following events must be collected and reported:

- SAEs
- AEs leading to discontinuation of trial product
- Medication errors
- Severe hypoglycaemic episodes
- Hepatic events
- *Diabetic retinopathy and related complications*
- Pregnancies

Medication errors, severe hypoglycaemic episodes, ~~and~~ hepatic events *and diabetic retinopathy and related complications* must be reported regardless of seriousness and whether trial product is discontinued.

Events occurring as of the first trial-related activity after the subject signed the informed consent until the end of the follow-up period are in scope for collection and reporting. The events must be recorded in the applicable CRFs 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, for example by asking: "Have you experienced any problems since the last contact?"

All SAEs, AEs leading to discontinuation of trial product, medication errors, severe hypoglycaemic episodes, ~~and hepatic events~~, *and diabetic retinopathy and related complications*, either observed by the investigator or subject, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents: IB for oral administration of semaglutide (NN9924), current edition¹⁸ or any updates thereto.

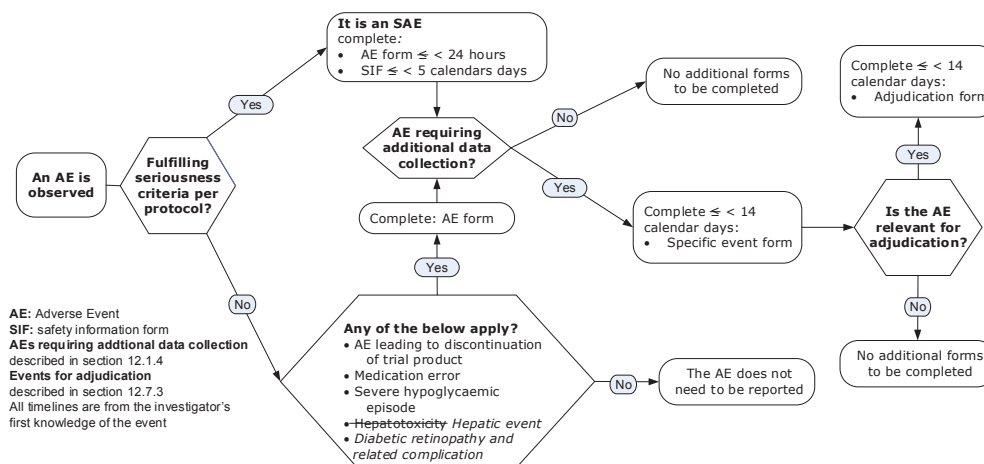


Figure 12–1 Initial reporting of AEs

2.8 Section 12.7.3 Event adjudication committee

Table 12-1 Adverse events for adjudication

Events	Description	Adjudication outcomes
Death	<ul style="list-style-type: none"> All-cause death 	<ul style="list-style-type: none"> Cardiovascular death (including undetermined cause of death) Non-cardiovascular death
Acute Coronary Syndrome	<ul style="list-style-type: none"> ST-elevation acute myocardial infarction (STEMI) Non-ST elevation acute myocardial infarction (NSTEMI) Silent myocardial infarction Unstable angina pectoris (UAP) <i>requiring hospitalisation</i> 	<ul style="list-style-type: none"> Acute myocardial infarction (STEMI or NSTEMI), silent myocardial infarction Unstable angina pectoris requiring hospitalisation

2.9 Section 17.4.2 Safety endpoints

Other safety endpoints

- Biochemistry
- Haematology
- Calcitonin
- *Eye examination category*

2.10 Section 18.1 Benefit-risk assessment of the trial, new subtitle

Diabetic retinopathy complications

2.11 Section 27 References

30. *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.*

2.12 Reference numbers

Reference numbers will change throughout the updated protocol when new reference numbered 30 above is introduced.

2.13 Appendix B, Section 1 Adverse events requiring additional data collection

AEs must be assessed according to section 12.1 and reported if applicable according to section 12.2.

If any of the following AEs are applicable for reporting, 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 requiring hospitalisation
- Pancreatitis
- Neoplasm (excluding thyroid neoplasm)
- Thyroid disease (including thyroid neoplasm)
- Renal event
- Hypersensitivity reaction to the trial product
- Lactic acidosis
- Medication error concerning trial product
- Severe hypoglycaemic episode
- Hepatic event:
 - ALT or AST > 5x UNL and total bilirubin ≤ 2x UNL

- ALT or AST > 3x UNL and total bilirubin > 2x UNL
- Hepatic event leading to trial product discontinuation
- *Diabetic retinopathy and related complications*

2.14 Appendix B, new section

1.13 Diabetic retinopathy and related complications

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

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

Protocol
Trial ID: NN9924-4221
UTN: U1111-1173-0750
EudraCT No.: 2015-003563-10

~~CONFIDENTIAL~~

Date:	03 November 2016	Novo Nordisk
Version:	5.0	
Status:	Final	
Page:	1 of 82	

Protocol

Updated Protocol including:

Protocol, Final version 3.0, dated 12-Feb-2016

Protocol Amendment no. 1, Germany, Final version 1.0, dated 18-Feb-2016

Protocol Amendment no. 2, Global, Final version 1.0, dated 21-Jul-2016

Protocol Amendment no. 3, Global, Final version 1.0, dated 03-Nov-2016

Trial ID: NN9924-4221

PIONEER 6 – Cardiovascular outcomes
A trial investigating the cardiovascular safety of oral semaglutide in
subjects with type 2 diabetes

Trial phase: 3a

Protocol originator

[REDACTED]

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Appendix A – Calcitonin monitoring

Appendix B – Adverse events requiring additional data collection

Attachment I – Global list of key staff and relevant departments and suppliers

Attachment II – Country list of key staff and relevant departments, if applicable for the individual country

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BG	blood glucose
CRF	case report form
CRO	contract research organisation
DMC	data monitoring committee
DPP-4	dipeptidyl peptidase-4
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	glomerular filtration rate, estimated
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPG	fasting plasma glucose
FSFV	first subject first visit
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA _{1c}	glycosylated haemoglobin
HDL	high density lipoprotein
HR	hazard ratio
IB	Investigator's Brochure

IEC	independent ethics committee
IRB	institutional review board
ITT	intention-to-treat
IV/WRS	interactive voice/web response system
LDL	low density lipoprotein
LLoQ	lower limit of quantification
LSFV	last subject first visit
LSLV	last subject last visit
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MEN 2	multiple endocrine neoplasia type 2
MTC	medullary thyroid carcinoma
NYHA	New York Heart Association
PYO	patient years of observation time
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous(ly)
SDV	source data verification
SGLT2	sodium-glucose cotransporter-2
SMPG	self-measured plasma glucose
SNAC	sodium N-(8-(2-hydroxybenzoyl) amino) caprylate
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TIA	transient ischaemic attack
TMM	Trial Materials Manual
UTN	Universal Trial Number

1 Summary

Objectives and endpoints:

The primary objective is to confirm that treatment with oral semaglutide does not result in an unacceptable increase in cardiovascular risk compared to placebo (rule out 80% excess risk) in subjects with type 2 diabetes at high risk of cardiovascular events.

The primary endpoint is time from randomisation to first occurrence of a major adverse cardiovascular event (MACE) composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The secondary objectives are to compare the efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes at high risk of cardiovascular events.

Key secondary endpoints:

- Time from randomisation to first occurrence of an expanded composite cardiovascular endpoint consisting of: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina requiring hospitalisation or hospitalisation for heart failure
- Time from randomisation to first occurrence of each of the individual components in the expanded composite cardiovascular endpoint
- Time from randomisation to first occurrence of a composite endpoint consisting of: all-cause death, non-fatal myocardial infarction or non-fatal stroke

For the primary and the key secondary endpoints, maximum treatment duration is dependent on event rates and is estimated to be no longer than 19 months.

Trial design:

This trial is a randomised, double-blind, placebo-controlled trial to assess the cardiovascular safety of oral semaglutide versus placebo when added to standard of care in subjects with type 2 diabetes at high risk of cardiovascular events. Subjects will be randomised 1:1 to receive either oral semaglutide or placebo. The trial will be event-driven and will be continued until at least 122 first MACEs confirmed by adjudication have accrued. The treatment period for each subject is estimated to be between 12 and 19 months, depending on the time-point of recruitment and the accrual of first MACEs confirmed by adjudication.

Trial population:

Number of subjects planned to be randomised is 3,176

Key inclusion criteria:

- Male or female diagnosed with type 2 diabetes
- Age \geq 50 years at screening and presence of cardiovascular disease, or age \geq 60 years at screening and presence of at least one cardiovascular risk factor

Key exclusion criteria:

- Current or previous (within 90 days prior to screening) treatment with any GLP-1 receptor agonist, DPP-4 inhibitor or pramlintide
- Family or personal history of multiple endocrine neoplasia type 2 (MEN 2) or medullary thyroid carcinoma (MTC)
- 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)
- Subjects presently classified as being in New York Heart Association (NYHA) Class IV heart failure
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening
- Any of the following: myocardial infarction, stroke or hospitalisation for unstable angina or transient ischaemic attack within the past 60 days prior to screening
- Chronic or intermittent hemodialysis or peritoneal dialysis or severe renal impairment (corresponding to eGFR <30 mL/min/1.73 m²)
- History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and carcinoma in situ)

Key assessments:

- Adverse events

Trial products:

- Semaglutide 3 mg tablet
- Semaglutide 7 mg tablet
- Semaglutide 14 mg tablet
- Placebo tablet

Trial Periods	Screening	Ran- domi- sation	Treatment													End of treat- ment	Follow- up					
			P3	V4	V5	V6	P7 ²	V8	P9 ²	V10	P11 ²	V12	P13 ²	V14	P15 ²			V16				
Visit (V) Phone (P)	V1	V2																V17 ¹	P18 ¹			
Timing of visit (weeks after V2)	Up to -3	0																76	83	88		
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaints			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IV/WRS call	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomisation		X																				
Dispensing of trial product		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
REMINDERS																						
Handout ID card	X																					
Handout and instruct in BG meter use		X																				
Attend visit fasting		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
End of trial																						X

¹ V17 (End of treatment) and P18 (Follow-up) are applicable for all randomised subjects. P18 can be conducted over the telephone. For a subject who discontinued trial product prematurely (i.e. more than 5 weeks prior to the anticipated V17), V17 can be postponed to the point when P18 is otherwise due.

² Dispensing visit (i.e. a combination of dispensing trial product and collecting relevant information over the telephone. If the subject provides the required information to site staff when collecting trial product, the telephone contact can be omitted).

³ Fundus photography or dilated funduscopy must be performed within 90 days prior to screening or within the period between screening and randomisation.

⁴ Fundus photography or dilated funduscopy should be performed at Visit 12 and 17 or within 5 weeks prior to those visits.

⁵ For women of childbearing potential only. In addition to the planned assessment at screening and end-of-treatment, urine dipstick pregnancy test should be performed at site at any time during the trial if a menstrual period is missed, or if pregnancy is suspected, or as required by local law.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP¹ and applicable regulatory requirements, and in accordance with the Declaration of Helsinki².

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

3.1 Background information

3.1.1 Type 2 diabetes and GLP-1

Type 2 diabetes (T2D) is a progressive metabolic disease primarily characterised by abnormal glucose metabolism. The pathogenesis is heterogeneous, and characterised by chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver³.

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^{4,5}. Subjects with T2D have a decreased incretin effect⁶⁻⁹. 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 supra physiological levels¹⁰. In addition, supra physiological levels of GLP-1 lower body weight due to decreased energy intake induced by reduced appetite¹¹. These mechanisms of action make GLP-1 an attractive pharmacological treatment for T2D¹²⁻¹⁴.

3.1.2 Oral semaglutide

Semaglutide is a long-acting GLP-1 receptor agonist (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 T2D. Compared to human native GLP-1, which has a very short half-life, the semaglutide molecule has three minor but important modifications ensuring protraction of its action: amino acid substitutions at position 8 (alanine to alfa-aminoisobutyric acid, a synthetic amino acid) and position 34 (lysine to arginine), and acylation of the peptide backbone with a spacer and C-18 fatty di-acid chain to lysine in position 26¹⁵. 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 T2D. As the bioavailability of GLP-1 RAs is very low when administered orally, semaglutide has been co-formulated with the absorption enhancing excipient sodium N-(8-(2-hydroxybenzoyl) amino) caprylate (SNAC) based on the [REDACTED] concept developed by [REDACTED] in order to increase

bioavailability. When semaglutide is co-formulated with SNAC, SNAC has the capacity to augment the absorption of semaglutide across the gastrointestinal epithelium. The absorption enhancement by SNAC is dose, size and time-dependent and is believed to take place in close proximity of the tablet in the stomach. The absorption process is hampered if dosed with food, liquid or in the presence of significant stomach content. Throughout this document oral semaglutide will refer to the drug product, that is, semaglutide co-formulated with 300 mg SNAC.

Novo Nordisk is currently also developing semaglutide for once-weekly subcutaneous (s.c.) administration in subjects with T2D.

3.1.3 Non-clinical data

3.1.3.1 Semaglutide

The non-clinical programme for semaglutide was designed according to the ICH M3 guideline 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 low¹⁶.

Embryo–foetal development toxicity

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

potential of semaglutide in this species. These data suggest an important species-dependent mechanism, whereby semaglutide is teratogenic in rats but not in primates.

A review of results from the non-clinical studies can be found in the current edition of the investigator's brochure (IB) for s.c. semaglutide (NN9535)¹⁷, and the current edition of the IB for oral administration of semaglutide (NN9924)¹⁸ or any updates to these documents.

3.1.3.2 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.

The most common observations related to oral dosing of SNAC were, depending on species, salivation, emesis and other clinical signs such as hypoactivity, lethargy, somnolence and ataxia. When SNAC is administered at high doses (200 mg/kg/day or more, depending on species) mortality has been observed in all toxicology species. The mortality is considered to be due to inhibition of cellular respiration, mainly via an inhibition of complex 1 in the electron transport chain. The mortality was found to be related to high doses and very high initial plasma concentration levels in animals. Similar plasma concentrations have not been observed in humans and are not achievable following administration of oral semaglutide.

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

A review of results from the non-clinical studies can be found in the current edition of the IB for oral administration of semaglutide (NN9924)¹⁸, or any updates thereto.

3.1.4 Clinical data 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 T2D.

For details on the individual trials, please see the current edition of the IB for oral administration of semaglutide (NN9924)¹⁸, or any updates thereto.

3.1.4.1 Pharmacokinetics

In single dose trials, oral semaglutide has demonstrated a long mean terminal half-life ($t_{1/2}$) 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 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 T2D.

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

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. The tablet should be taken with up to half a glass of water (i.e. 120mL/4 fluid oz).

Drug-drug interaction investigations have explored the effect of oral semaglutide on the exposure to lisinopril, warfarin, metformin and digoxin as well as the effect of omeprazole on oral semaglutide and SNAC. It was demonstrated that oral semaglutide did not change the exposure to lisinopril, warfarin or digoxin, but increased the exposure to metformin when taken simultaneously. The increase in exposure to metformin may be related to delayed gastric emptying caused by semaglutide as observed for other GLP-1 RAs. Based on the wide therapeutic index of metformin, the increased exposure to metformin was however not considered clinically relevant. Further, it was demonstrated that the exposure to semaglutide appeared to be slightly higher when administered with omeprazole in comparison to semaglutide alone, but the effect was not statistically significant or considered clinically relevant. In subjects with mild to end-stage renal impairment, the exposure to semaglutide appeared similar in subjects with normal and impaired renal function, whereas the AUC for SNAC was greater in subjects with impaired renal function than in subjects with normal renal function. The C_{max} of SNAC appeared similar in subjects with normal and impaired renal function. The renal clearance of all SNAC metabolites was decreased in subjects with renal impairment.

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. 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 T2D. It is extensively metabolized and no accumulation of SNAC has been observed in clinical trials.

3.1.4.2 Efficacy

The efficacy of oral semaglutide in adult subjects with T2D 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 to -6.98 kg).

3.1.4.3 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, common adverse events (AEs) included nausea and vomiting, most of them of mild to moderate 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 administered 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 studies 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) were 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 current edition of the IB for oral administration of semaglutide (NN9924)¹⁸, or any updates thereto.

3.1.5 Oral semaglutide and cardiovascular risk

Based on the nonclinical and clinical data obtained with semaglutide dosed either orally or subcutaneously to date, no adverse safety signals have been identified that indicate an increased risk of cardiovascular events. In addition, although an increase in heart rate has been observed as a class effect for GLP-1 RAs, the extensive amount of clinical data from marketed products have not indicated that this drug class increases risk of cardiovascular events. In support, results from the LEADER[®] (EX2211-3748) trial showed that treatment with once-daily s.c. liraglutide does not increase the risk of MACE as compared to placebo. In fact, treatment with liraglutide reduced the

risk of the primary composite endpoint consisting of death from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke by 13% versus placebo¹⁹. Also, the SUSTAIN™ 6 trial (NN9535-3744) achieved its primary objective by showing non-inferiority of once-weekly s.c. semaglutide versus placebo on cardiovascular outcomes; moreover, s.c. semaglutide statistically significantly reduced cardiovascular risk versus placebo²⁰.

The absorption enhancer SNAC used in the formulation of oral semaglutide is an excipient with no discernable systemic or pharmacodynamic effects. Accordingly, the potential for adverse effects on the cardiovascular system is considered low. The collective nonclinical and clinical evidence on SNAC from [REDACTED] and Novo Nordisk has not identified safety signals related to cardiovascular disease. However, information on potential long-term cardiovascular effects of SNAC is not yet available.

For an assessment of benefits and risks of the trial, see section [18.1](#).

3.2 Rationale for the trial

The purpose of this trial is to assess the cardiovascular safety of oral semaglutide in subjects with T2D at high risk of cardiovascular events. This trial has been designed to address the requirements contained in the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance documents^{21,22} which specify how to demonstrate that a new antidiabetic therapy is not associated with an unacceptable increase in cardiovascular risk.

4 Objectives and endpoints

4.1 Objectives

The primary objective is to confirm that treatment with oral semaglutide does not result in an unacceptable increase in cardiovascular risk compared to placebo (rule out 80% excess risk) in subjects with type 2 diabetes at high risk of cardiovascular events.

The secondary objectives are to compare the efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes at high risk of cardiovascular events.

4.2 Endpoints

The primary endpoint is time from randomisation to first occurrence of a MACE composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The confirmatory secondary endpoint is time from randomisation to first occurrence of an expanded composite cardiovascular endpoint consisting of: cardiovascular death, non-fatal

myocardial infarction, non-fatal stroke, unstable angina requiring hospitalisation or hospitalisation for heart failure*

The secondary endpoints are:

- Time from randomisation to first occurrence of each of the individual components in the expanded composite cardiovascular endpoint*
- Time from randomisation to first occurrence of a composite endpoint consisting of: all-cause death, non-fatal myocardial infarction or non-fatal stroke*
- Time from randomisation to all-cause death
- Time to permanent discontinuation of trial product due to AE(s)
- Number of serious adverse events (SAEs)

Change from baseline to last assessment of:

- Biochemistry
- Haematology
- Calcitonin
- Eye examination category
- Pulse
- Systolic and diastolic blood pressure
- Glycosylated haemoglobin (HbA_{1c})
- Body weight
- Lipids

* Key supportive secondary endpoint prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT)

5 Trial design

5.1 Type of trial

This trial is a randomised, double-blind, placebo-controlled trial to assess the cardiovascular safety of oral semaglutide versus placebo when added to standard of care in subjects with T2D at high risk of cardiovascular events. Subjects will be randomised 1:1 to receive either oral semaglutide or placebo. Randomisation will be stratified according to evidence of cardiovascular disease at screening (presence of cardiovascular disease or risk factors only) to ensure even distribution of the two treatment arms within strata. The stratum ‘presence of cardiovascular disease’ consists of subjects at least 50 years of age and recognised as fulfilling **at least one** item of inclusion criterion no. **3a-h** at screening, whereas the stratum ‘presence of cardiovascular risk factors only’ consists of subjects at least 60 years of age and recognised as fulfilling **at least one** item of inclusion criterion no. **3i-l** and **not** fulfilling **any** of the items of inclusion criterion no. **3a-h** at screening (see section [6.2](#)).

All tablets containing oral semaglutide or placebo are identical with regards to visual appearance to maintain the blinding of the trial.

The trial will be event-driven and will be continued until at least 122 first MACEs confirmed by adjudication have accrued. Throughout the remainder of this protocol, MACE will be defined as MACE confirmed by adjudication.

The recruitment period is expected to last 7 months. The treatment period for each subject is estimated to be between 12 and 19 months, depending on the time-point of recruitment and the accrual of first MACEs. The follow-up period is 5 weeks to allow for wash-out of trial drug. A schematic diagram of the trial design is shown in [Figure 5-1](#).

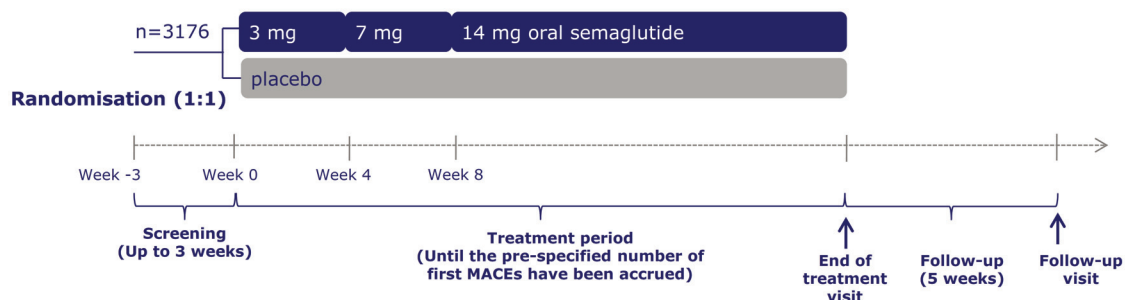


Figure 5-1 Trial design

The trial is designed to evaluate cardiovascular outcomes and will apply a targeted approach to collection of safety data focusing on SAEs, AEs leading to discontinuation of trial product and other selected AEs. An adequate characterisation of the less serious and more common AEs will be evaluated in the other phase 3a trials conducted with oral semaglutide comprising more than 4000 subjects with T2D.

An external event adjudication committee (EAC) will perform ongoing adjudication of predefined cardiovascular events and other selected AEs in an independent and blinded manner.

An independent external data monitoring committee (DMC) will have unblinded access to data from the trial and perform review of accumulating data on an ongoing basis. The DMC will provide recommendation on trial continuation, modification or termination.

5.2 Rationale for trial design

A randomised, double-blind, placebo-controlled trial has been chosen in accordance with the trial objectives and to avoid bias of the results. The planned duration of the trial has been estimated based on the number of subjects randomised and the expected first MACE rate. The treatment period is expected to be between 12 and 19 months. This duration should be adequate to provide data to assess the cardiovascular safety of oral semaglutide.

5.3 Treatment of subjects

Subjects will be randomised in a 1:1 ratio to receive either oral semaglutide or placebo. Randomised subjects will initiate treatment with 3 mg oral semaglutide/placebo once daily and follow a fixed 4-week dose escalation regimen until reaching the maximum dose of 14 mg oral semaglutide/placebo as illustrated in [Table 5–1](#). The 4-week dose escalation intervals are applied in order to mitigate the risk of gastrointestinal adverse events (AEs). Subjects should remain on the 14 mg dose level throughout the maintenance period; however, if treatment with the trial product is associated with unacceptable AEs (as judged by the investigator), dose reductions and extensions of dose escalation periods are allowed. In case the dose is reduced due to unacceptable AEs, the investigator should consider escalating the dose of oral semaglutide once the subject has recovered. Trial product dose and date of change or discontinuation should be recorded in the electronic case report form (eCRF) throughout the trial.

Table 5–1 Treatment of subjects

Trial periods		Screening	Trial period 1	Trial period 2	Trial period 3	Follow-up
Alias for trial period		Screening	Dose escalation	Dose escalation	Maintenance	Follow-up
First visit in each period		V1	V2	V4	V5	V17
Duration of each period		Up to 3 weeks	4 weeks	4 weeks	Up to 75 weeks	5 weeks
Treatment arm	N					
Oral semaglutide	1588	Screening	3 mg	7 mg	14 mg	Follow-up
Placebo	1588	Screening	Placebo	Placebo	Placebo	Follow-up

5.3.1 Missed doses

The trial product should be administered once daily; however, if one or more doses of trial product are missed due to circumstances not related to the safety of the trial product (as judged by the investigator) and treatment with trial product is resumed, the below recommendations for dose adjustment apply:

- If ≤ 21 consecutive doses of 14 mg oral semaglutide/placebo are missed, the once-daily regimen can be resumed as prescribed without dose reduction.

- If 22-35 consecutive doses of 14 mg oral semaglutide/placebo are missed, it is recommended to resume treatment at 7 mg oral semaglutide/placebo and subsequently, escalate to the higher dose after 4 weeks of treatment.
- If ≥ 36 consecutive doses of 14 mg oral semaglutide/placebo are missed, it is recommended to resume treatment at 3 mg oral semaglutide/placebo and subsequently, escalate to the higher doses with 4-week dose escalation steps.

Please refer to section [10](#) for instructions on how to use the interactive voice/web response system (IV/WRS) in relation to subjects discontinuing and resuming trial product treatment.

5.3.2 Dosing instructions

Absorption of oral semaglutide is significantly affected by food and fluid in the stomach, hence subjects should take the oral semaglutide/placebo tablets in the morning in a fasting state and at least 30 minutes before the first meal of the day. The tablets should be taken with up to half a glass of water (approximately 120 mL/4 fluid oz). The tablets must be swallowed whole and must not be broken or chewed. Other oral medication can be taken 30 minutes after the trial product. The tablets should be taken immediately after removal from the blister.

5.3.3 Background medication

The investigator will assume responsibility for the management of glycaemic control in each subject enrolled in the trial. The investigator is responsible for ensuring that glycaemic control is maintained and optimised in each subject while maintaining a low risk of hypoglycaemic episodes. If deemed necessary to achieve glycaemic target, antidiabetic medication (excluding GLP-1 RAs, DPP-4 inhibitors and pramlintide from visit 1 to 17) may be adjusted or added, at the investigator's discretion. The background medication should be used in accordance with standard of care and the current local label.

If episodes of hypoglycaemia require reduction of antidiabetic medication, investigators should reduce or modify the dosing of background medication. In particular, dose reduction of insulin should be done already at randomisation (e.g. 10-20% reduction of the insulin dose) to reduce the risk of hypoglycaemia when introducing an additional glucose lowering agent. Similar considerations should be made for subjects treated with sulphonylureas.

All subjects will be provided with a BG meter at randomisation and glycaemic management will be guided by review of fasting plasma glucose (FPG) and HbA_{1c} results measured at the site as well as self-measured plasma glucose (SMPG) results measured at home by the subject. In addition, it is important that other information such as symptoms of hypo/hyperglycaemia, previous response to dose adjustments and other indicators of the subject's level glycaemic control is taken into consideration when decisions on dose adjustments of the background antidiabetic medication are made. In subjects treated with insulins, close contact should be ensured in the initial 12 weeks after

randomisation to allow for adequate adjustment of insulin dose, at the investigator's discretion. Additional phone contacts in the weeks where no site visit is planned should be considered for subjects treated with insulins.

Please note that due to the long half-life of oral semaglutide and the gradual dose escalation, the full effect of the investigational product on glycaemic parameters may not be apparent until several weeks into the maintenance period.

The investigator is responsible for ensuring ongoing management of cardiovascular diseases and risk factors as well as potential microvascular complications such as diabetic kidney disease and diabetic retinopathy according to local standard of care at the investigator's discretion.

5.4 Treatment after discontinuation of trial product

When discontinuing trial product at the end of the treatment period, the subject should be switched to a suitable marketed product at the discretion of the investigator. Oral semaglutide will not be available for prescription until marketing authorisation is issued.

For Brazil only: At the end of the trial, subjects will be assured access to the best proved prophylactic, diagnostic and therapeutic methods identified during the trial.

5.5 Rationale for treatment

Three treatment doses of oral semaglutide will be investigated in the phase 3a development programme: 3 mg, 7 mg and 14 mg. The selected doses are based on the data derived from the NN9924-3790 dose-finding trial. This dose range is expected to have the optimal benefit-risk profile for further development of oral semaglutide. In addition, the increments between the three doses are expected to provide clinically meaningful differentiation between the effects on glycaemic control while ensuring mitigation of gastrointestinal AEs through gradual dose escalation. For further details regarding the results obtained in the phase 2 dose-finding trial (NN9924-3790), please refer to the current edition of the IB for oral administration of semaglutide (NN9924)¹⁸, or any updates thereto.

Similar to other cardiovascular outcomes trials, the maximum treatment dose (14 mg oral semaglutide) will be investigated and compared to placebo in the present trial. Blinded treatment with oral semaglutide or placebo offers a robust method for assessment of oral semaglutide's effect on trial endpoints. Treatment intensification of the background medication is allowed throughout the course of the trial to ensure adequate glycaemic control in all participating subjects. Use of other GLP-1 RAs and DPP-4 inhibitors and pramlintide is not allowed, because these drugs, similarly to oral semaglutide, affect the incretin pathway.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be randomised: 3,176

For Mexico only: Approximately 150 subjects are planned to be randomised 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 diagnosed with type 2 diabetes.
3. Age \geq 50 years at screening and at least one of the below conditions:
 - a. prior myocardial infarction
 - b. prior stroke or transient ischaemic attack (TIA)
 - c. prior coronary, carotid or peripheral arterial revascularisation
 - d. $>$ 50% stenosis on angiography or imaging of coronary, carotid or lower extremity arteries
 - e. history of symptomatic coronary heart disease documented by e.g. positive exercise stress test or any cardiac imaging or unstable angina pectoris with ECG changes
 - f. asymptomatic cardiac ischaemia documented by positive nuclear imaging test or exercise test or stress echo or any cardiac imaging
 - g. chronic heart failure New York Heart Association (NYHA) class II-III
 - h. moderate renal impairment (corresponding to an estimated glomerular filtration rate (eGFR) between 30-59 mL/min/1.73 m²)

or

- Age \geq 60 years at screening and at least one of the below risk factors:
- i. microalbuminuria or proteinuria
 - j. hypertension and left ventricular hypertrophy by ECG or imaging
 - k. left ventricular systolic or diastolic dysfunction by imaging
 - l. ankle/brachial index $<$ 0.9

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to the trial product 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 childbearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice. Local country regulations or practices are specified in section 8 of the protocol).
4. Receipt of any investigational medicinal product within 90 days before screening.
For Brazil only: Participation in other clinical trials within one year prior to screening unless there is a direct benefit to the research subject at the investigator's discretion.
5. Participation in another clinical trial of an investigational medicinal product. Participation in a clinical trial which evaluate stent(s) is allowed.
6. Current or previous (within 90 days prior to screening) treatment with any GLP-1 receptor agonist, DPP-4 inhibitor or pramlintide.
7. Any disorder, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
8. Family or personal history of multiple endocrine neoplasia type 2 (MEN 2) or medullary thyroid carcinoma (MTC).
9. History of pancreatitis (acute or chronic).
10. 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).
11. Subjects presently classified as being in New York Heart Association (NYHA) Class IV heart failure.
12. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
13. Any of the following: myocardial infarction, stroke or hospitalisation for unstable angina or transient ischaemic attack within the past 60 days prior to screening.
14. Chronic or intermittent hemodialysis or peritoneal dialysis or severe renal impairment (corresponding to eGFR <30 mL/min/1.73 m²).
15. History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and carcinoma in situ).
16. History of diabetic ketoacidosis.
17. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to screening or within the period between screening and randomisation.

6.4 Composition of overall trial population

In order to secure sufficient overall cardiovascular risk within the trial population, randomisation of subjects with risk factors only (inclusion criterion no. 3, i-l) will be stopped when 650 of these subjects have been randomised.

6.5 Premature discontinuation of trial product

All efforts should be made to keep the subject on trial product throughout the trial. The subject may, however, decide to discontinue trial product for any reason, or they may be discontinued from trial product due to safety concerns at the discretion of the investigator. In case the trial product is interrupted due to suspicion of acute pancreatitis or a hypersensitivity reaction to the trial product, please see sections [8.2.1](#) and [8.2.2](#).

Furthermore, the subject must discontinue treatment with trial product if any of the following applies:

- pregnancy
- intention of becoming pregnant
- participation in another clinical trial with an investigational medicinal product
- calcitonin ≥ 100 ng/L

Discontinuation of treatment with trial product, whether temporary or permanent, must not prompt the investigator to withdraw the subject from the trial. Instead, the subject should maintain adherence to trial visits and procedures to the extent possible. In each separate case, the primary reason for discontinuation of trial product must be specified in the eCRF. The subject should be encouraged to resume treatment with trial product once they are willing or when the safety concern has ceased, respectively.

A subject who does not fulfil the eligibility criteria (inclusion/exclusion criteria) must not be randomised. If a subject is randomised in error, this will be handled as an important protocol deviation, and the IEC/IRB and regulatory authorities must be notified according to local requirements. If there are no safety concerns, trial treatment may be continued or resumed at the discretion of the investigator following a discussion with the sponsor's global medical expert.

See section [5.3.1](#) for instructions about resuming trial product treatment after a treatment pause.

6.6 Withdrawal of consent

The subject may withdraw at will at any time. If a subject has withdrawn their consent, the investigator must make every effort to establish the subject's vital status at the end of the trial. See section [8.4](#) for further instructions about withdrawals.

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 have withdrawn their consent will not be replaced.

6.8 Rationale for trial population

This trial will include subjects with T2D at high risk of cardiovascular events. This includes subjects with previous cardiovascular disease or well-established risk factors for cardiovascular disease and advanced age, as based on their medical records. The inclusion of subjects with established risk for cardiovascular disease will ensure that the primary objective of the trial can be obtained within a reasonable timeframe.

Subjects with a recent event of myocardial infarction, stroke or hospitalisation for unstable angina or TIA prior to screening are excluded, aiming to avoid any effect of cardiovascular events that are likely to be secondary to another cardiovascular event or intervention.

6.8.1 Determining subject's eligibility

It is the responsibility of the investigator to ensure unequivocal evidence for a subject's eligibility. When determining a subject's eligibility based on medical history, it is at the investigator's discretion on a case by case basis to decide if further medical records are needed or if the available documentation is adequate. Any laboratory values used to assess eligibility must reflect the subject's current health status.

6.8.2 Microalbuminuria and proteinuria

For the diagnosis of microalbuminuria and proteinuria, local guidelines, if such exist, can be used. Otherwise, commonly accepted guidelines should be used²³. [Table 6-1](#) shows examples of how albuminuria can be assessed²⁴.

Table 6–1 Measurement of albuminuria

	Normal	Microalbuminuria	Macroalbuminuria	Advantages	Disadvantages
Urine dipstick for protein	-	-	+	Convenience	Dependent on level of hydration
Urine 24-hour protein (mg)	< 150	< 500	≥ 500	Overcomes problem of diurnal variation in excretion	Subject to collection errors
Urine 24-hour albumin (mg)	< 30	30-300	> 300	Overcomes problem of diurnal variation in excretion	Subject to collection errors
Timed urine collection (µg/min)	< 20	20-200	> 200	Overcomes problem of diurnal variation in excretion	Subject to collection errors
Spot urine collection (µg albumin/mg creatinine)	< 30	30-300	> 300	Convenience Not dependent on hydration level Most reproducible	Ratios vary based on gender

6.8.3 Glomerular filtration rate, estimated (eGFR)

To evaluate whether a subject meets inclusion criterion no. [3](#) and exclusion criterion no. [14](#), the creatinine level that best reflects the current status of the subject in the medical records should be used to calculate eGFR. The equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi)²³ including variables for age, sex, and race should be used to calculate eGFR.

7 Milestones

Planned duration of recruitment period (i.e. FSFV – LSFV): 7 months.

End of trial is defined as Last Subject Last Visit (LSLV).

Novo Nordisk will follow the screening and randomisation rates closely via IV/WRS in order to estimate when to stop screening. Investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened, and IV/WRS will be closed for further screening.

The treatment period for the last randomised subject is expected to be 12 months. The trial duration is, however, decided by the first MACE rate (see section [5.1](#)), and the trial duration will be adjusted

as needed. When the trial comes to an end, investigators will be notified and instructed by Novo Nordisk regarding the visit schedules for their subjects.

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure²⁵, it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors²⁶, the Food and Drug Administration Amendment Act²⁷, European Commission Requirements^{28,29} 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 duration of this trial is decided by the observed first MACE rate (see section 5.1). It is expected that each subject will be asked to attend maximum eighteen visits. Eleven of these are regular clinic visits, two visits can be performed over the telephone, and five visits are dispensing visits. Dispensing visits are a combination of dispensing trial product and collecting relevant information over the telephone (see section 2). If the subject provides the required information to site staff when collecting trial product, the telephone contact can be omitted.

Depending on when a subject entered the trial and the accrual of first MACEs, subject's visit schedule may be shortened. This will imply omission of visit(s) in the treatment period, as, when the trial comes to an end, all subjects should be asked to attend visit 17 and 18. For a subject who discontinued trial product prematurely (i.e. more than 5 weeks prior to the anticipated visit 17), visit 17 can be postponed to the point when visit 18 is otherwise due.

The timing and content of visits and the visit windows are outlined in section 2, while procedures and assessments to be carried out at the visits are described in this section.

8.1.1 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP¹ and the requirements in the Declaration of Helsinki².

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. This includes the use of an impartial witness, where required according to local regulations. The subject 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 product.

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.

8.1.2 In/exclusion criteria

Subjects should be assessed for eligibility according to sections [6.2](#) and [6.3](#) at visit 1. For further instructions about determining the eligibility of a subject, see sections [6.8.1](#), [6.8.2](#) and [6.8.3](#).

For inclusion criterion no. [3](#) (section [6.2](#)), the investigator must provide just one answer (yes or no) on the inclusion criteria form in the eCRF for each subject.

For exclusion criterion no. [3](#) (section [6.3](#)), each female of childbearing potential must have a negative pregnancy test in order to be randomised.

For exclusion criterion no. [17](#) (section [6.3](#)), each subject must have a fundus photography or dilated funduscopy performed and evaluated before randomisation, in accordance with the instructions in section [8.1.7](#).

8.1.3 Screening

At visit 1, the investigator must perform a screening session in IV/WRS (see section [10](#)), and each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined into one list.

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.

Screening failures: If a subject is screened, but for some reason never randomised, the subject is a screening failure. For screening failures, the screening failure form in eCRF must be completed with the reason for not continuing in the trial. SAEs from screening failures must be transcribed by the investigator into the eCRF. Follow-up of SAEs must be carried out according to section [12](#). A screening failure session must be made in the IV/WRS. The case book must be signed electronically. Re-screening is not allowed.

8.1.4 Demography

Demography (date of birth or age, sex, race and ethnicity) will be recorded at visit 1, unless prohibited according to local regulations.

8.1.5 Tobacco use

Details of tobacco use must be recorded at visit 1. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked. If the subject has smoked, record approximately when the subject stopped smoking.

8.1.6 Physical examination

Physical examinations should be performed according to local procedures, when indicated in section [2](#), and will as a minimum include examination of:

- head, ears, eyes, nose, throat, neck
- respiratory system
- cardiovascular system
- gastrointestinal system, incl. mouth
- musculoskeletal system
- central and peripheral nervous system
- skin
- lymph node palpation
- general appearance
- thyroid gland

For each assessment, the investigator should indicate whether the outcome was normal or abnormal, and, if abnormal, indicate whether clinically significant. Relevant findings as a result of screening procedures conducted at visit 1 must be recorded as concomitant illness/medical history in accordance with section [8.1.9](#).

Please note that the diagnostic evaluation of thyroid nodules should be in accordance with the American Thyroid Association Management Guidelines or any updates hereof³⁰, adapted to local treatment guidelines.

8.1.7 Eye examination

Results of a fundus photography or dilated fundoscopy must be available and evaluated by the investigator before randomisation. If the subject had a fundus photography or dilated fundoscopy performed within 90 days prior to screening, the investigator may base their evaluation upon the results of that examination. However, the examination must be repeated before randomisation if the subject experienced worsening of visual function since the last examination. If the applicable fundus photography or dilated fundoscopy was performed before the subject signed the informed consent form, it must be documented in the medical records that the reason for performing the examination was not related to this trial.

If the subject did not have a fundus photography or dilated fundoscopy performed within 90 days prior to screening, such examination must be performed by the investigator or other qualified health care professional prior to randomisation.

In addition to the eye examination performed at screening, fundus photography or dilated fundoscopy should be performed at visit 12 and visit 17 as per the flow chart in section 2.

Fundoscopy requires pharmacological dilation of both pupils. The investigator should indicate whether the outcome of each eye examination was normal or abnormal, and, if abnormal, indicate whether clinically significant. Relevant findings as a result of the screening procedure must be recorded as concomitant illness/medical history in accordance with section [8.1.9](#), and relevant findings occurring after randomisation should be reported as an AE if applicable according to section [12.2](#).

8.1.8 Pregnancy test

Female subjects of childbearing potential will have pregnancy tests (urine dipsticks) performed as per the flow chart in section [2](#). In addition, urine pregnancy test should be performed at any time during the trial if a menstrual period is missed, or if pregnancy is suspected, or as required by local law.

Pregnancy testing will not be required (unless required by local law) for women of non-childbearing potential defined as, but not limited to, women who have undergone hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or who are postmenopausal (i.e. women above the age of 50 with no menstrual periods for at least 1 year). This has to be documented in the medical records.

Contraceptive methods

Female subjects of childbearing potential must use adequate contraceptive methods until 5 weeks after the last date on trial product. Throughout the protocol, last date on trial product is defined as date of the subject's last dosage of trial product.

For Argentina only: Adequate contraceptive measures are: Barrier methods (condom or diaphragm) with spermicide; contraceptive pills or intrauterine devices. Contraceptive methods will be reimbursed by Novo Nordisk Pharma Argentina S.A.

For Brazil only: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.

For Germany only: Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or sexual abstinence or vasectomised partner..

For Thailand only: Adequate contraceptive measures are: Diaphragm, condom (by the partner), intrauterine device in place for last three months before trial starts, sponge, cap with spermicide, contraceptive patch, approved hormonal implant (i.e. Norplant), oral contraceptives taken without difficulty for the last three months before trial starts, post-menopausal state or sterilisation.

For United Kingdom only: Adequate contraceptive measures are defined as established use of oral, intravaginal, transdermal, combined estrogen and progestogen hormonal methods of contraception; oral, injected or implanted progestogen only hormonal methods of contraception; placement of an intrauterine device or intrauterine hormone releasing system, bilateral tubal occlusion, barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository), female sterilisation, vasectomised partner (where partner is sole partner of subject), or true abstinence (when in line with preferred and usual lifestyle).

8.1.9 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at visit 1) or found as a result of a screening procedure.

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 transcribed to the eCRF.

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 assessed at visit 1 and transcribed to disease-specific forms, i.e. not to the medical history/concomitant illness form:

- Diabetes history/diabetes complications (e.g. date of diagnosis, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy)
- History of cardiovascular disease (e.g. ischaemic heart disease, myocardial infarction, heart failure incl. NYHA class³¹, hypertension, stroke, peripheral arterial disease) including answering yes or no/unknown for each cardiovascular condition/risk factor mentioned in inclusion criterion no. 3 a-1 (see section 6.2)
- 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 assessed according to section 12.1 and reported if applicable as per section 12.2.

8.1.10 Concomitant medication

A **concomitant medication** is any medication, other than the trial product, which is taken during the trial, i.e. as of visit 1 until the time point of visit 18.

Details of any concomitant medication must be recorded at visit 1. Changes in concomitant medication must be recorded at each subsequent visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, indication, total daily dose (only applicable for medication taken to treat diabetes and cardiovascular related disease), start date and stop date or continuation.

For subjects treated with insulin(s), total daily dose administered on the day preceding each trial visit (if available) should be recorded in the eCRF.

8.1.11 Body measurements (height and body weight)

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

Body weight is measured wearing light clothes and no shoes and recorded in the eCRF in kilogram or pound (kg or lb) with one decimal. If possible, the same calibrated weighing scale equipment should be used throughout the trial.

8.1.12 Vital signs

Pulse and systolic and diastolic blood pressure should be assessed 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 measured values should be recorded without rounding. If possible, the same equipment should be used throughout the trial.

8.1.13 Electrocardiogram

12-lead ECGs will be performed at selected visits (see the flow chart in section [2](#)). Investigator's interpretation of each ECG must be documented on the document or in the subject's medical records and abnormalities assessed according to section [12.1](#), and reported if applicable as per section [12.2](#). However, for abnormal clinically significant findings revealing baseline conditions at visit 2 the investigator must record these as concomitant illness/medical history, and, if applicable, update answer(s) related to inclusion criterion [3](#) (see section [8.1.9](#)).

The ECGs will also undergo central assessment and the investigator must forward the ECGs to the central ECG readers as soon as possible. If the central evaluation of a baseline ECG is suggestive of a prior myocardial infarction, the investigator will be notified. Unless already done, the investigator should consider recording the condition as cardiovascular history and update the answer(s) related to inclusion criterion [3](#) (see section [8.1.9](#)). If the central ECG evaluation of a post-baseline ECG is suggestive of new myocardial infarction, the investigator will be notified and a confirmatory ECG should be submitted to central ECG readers. Unless already done, and at the investigator's discretion, the investigator should assess the finding according to section [12.1](#), and if applicable report it as per section [12.2](#).

If additional ECG recordings are performed at the investigator's discretion at other visits than the planned ECG visits, such ECGs should also be submitted to the central ECG readers. The reason for recording an additional ECG should be documented.

Findings suggestive of new myocardial infarction detected by the central ECG readers will be adjudicated by the EAC (see section [12.7.3](#)).

8.1.14 Randomisation, dispensing of trial product and drug accountability

At visit 2, subjects are randomised into one of the two treatment arms. The randomisation session must be performed in IV/WRS and will include allocation of dispensing unit numbers (DUNs) to be dispensed to the subject.

All assessments pertaining to visit 2 must be performed before first dose of trial product is taken. Date of first administration of trial product must be captured in the eCRF.

At each visit where dispensing of trial product is indicated (see section [2](#)), IV/WRS must be used to allocate DUNs according to the subject's assigned treatment group (assigned at randomisation). The allocated DUNs should be dispensed by the site, hospital pharmacy or equivalent.

The investigator must ensure that the subject is reminded about dosing instructions (see section [5.3.2](#)) at every dispensing visit, as needed.

At each visit where the subject returns used, partially used or unused trial product, the investigator will account for the returned trial products in IV/WRS (see section [9.4](#)).

8.1.15 Blood sampling

Laboratory kits and laboratory manual will be provided to each site. The manual will include instructions for handling, storage and shipment of blood samples, and contact information for the central laboratory, including a link to their website where current laboratory certificates can be obtained. Blood samples should be collected according to the flow chart in section [2](#) and the laboratory parameters listed below will be assessed at a central laboratory (see Attachment I).

Glucose metabolism:

- HbA_{1c}
- FPG

Lipids:

- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides

Biochemistry:

- Alanine aminotransferase (ALT)
- Albumin
- Alkaline phosphatase (ALP)
- Amylase
- Aspartate aminotransferase (AST)
- Bicarbonate
- Bilirubin, total
- Calcium
- Creatinine
 - eGFR will be calculated by the central laboratory
- Lipase
- Potassium
- Sodium
- Urea
- Creatine kinase

Haematology:

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

Hormones:

- Calcitonin

The laboratory results will be made available for the investigator on an ongoing basis. The investigator must sign and date each laboratory report or ensure review is documented in the subject's medical records. For laboratory results outside the reference range, the investigator must indicate as either clinically significant or not clinically significant. Concomitant illnesses and AEs must be assessed and reported according to this protocol, as applicable.

If a calcitonin assessment results in a value ≥ 10 ng/L, the investigator must follow the algorithm in Protocol [Appendix A](#).

FPG levels are monitored to aid investigators in glycaemic management through adjustment of background medication, but will not be included as an endpoint.

Subjects must attend visits fasting when FPG and lipids are assessed (see section [2](#)). Fasting is defined as having consumed only water within the last 8 hours. Administration of trial product is allowed prior to the visit. If a subject attends the visit in a non-fasting state, the visit procedures should be performed, excluding blood sampling, and subjects must be asked to visit the site once more within the visit window to have blood sampling performed.

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. *For Brazil only: All laboratory results will be communicated to the investigators.* The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

Blood samples will be destroyed at completion of the clinical trial report at the latest, except samples obtained for anti-semaglutide antibody analysis in relation to suspicion of hypersensitivity reaction (see section [8.2.2](#) and [24.2](#)).

8.1.16 Hand out and instruct in BG meter use

At visit 2, the subject should be provided with a BG meter including auxiliaries. The subject should be instructed in how to use the device. The instructions should be repeated as necessary during the trial.

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.

The investigator should instruct and encourage the subject to measure and record fasting SMPG according to individual recommendation from the investigator. The SMPG measurements may be recorded anywhere as per the subject's own choice or the investigator's recommendation. The measurements will not be transcribed into the eCRF, i.e. these measurements are only encouraged in order to facilitate good diabetes management at the discretion of the investigator.

8.1.17 Adverse events and technical complaints

AEs and technical complaints must be reported in accordance with the procedures outlined in section [12](#).

8.1.17.1 Hypoglycaemic episodes

All severe hypoglycaemic episodes defined according to the ADA classification³² must be reported as an AE with additional data collection, see section [12.1.4](#), [12.2](#) and [Appendix B](#). The investigator is not required to report a hypoglycaemic episode if the episode is both non-serious and non-severe.

A severe hypoglycaemic episode is defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

If the hypoglycaemic episode fulfils the criteria for an SAE then a safety information form must also be filled in, see section [12](#).

8.1.17.2 Medication errors

If a medication error concerning trial product (see definition in section [12.1.4](#)) is observed during the trial, the following information is required:

- Trial product(s) involved
- Classification of medication error
 - Wrong drug(s) administered
 - Wrong route of administration
 - Wrong dose administered
- Whether the subject experienced any AE(s) as a result of the medication error
- Suspected primary reason for the medication error

8.1.18 End of trial

When a subject completes visit 18, the investigator should fill in the end-of-trial forms in the eCRF.

If a subject proves difficult to reach for visit 18, and vital status is collected via sources other than the subject him/herself (see section [8.4](#)), the investigator should fill in the end-of-trial forms after collecting the vital status. If, before the database lock, the investigator establishes contact with the subject, the investigator will update the end-of-trial forms.

8.2 Other assessments

8.2.1 Assessments in case of suspicion of acute pancreatitis

Most patients with acute pancreatitis experience 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 relief³³. 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 pancreatitis³³. 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, trial product treatment should be promptly interrupted. Appropriate additional examinations must be performed, including measurement of amylase and lipase.

The diagnosis of acute pancreatitis requires two of the following three features³⁴:

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

If acute pancreatitis is ruled out, the subject should resume trial product treatment, at the investigator's discretion.

If acute pancreatitis is confirmed, the investigator should initiate careful monitoring of the subject. The subject must be discontinued from trial product, but should remain in the trial (see section [6.5](#) and [8.4](#)).

The event must be assessed according to section [12.1](#) and reported if applicable as per section [12.2](#).

8.2.2 Assessments in case of suspicion of hypersensitivity reactions to the trial product

In case of suspicion of a severe immediate systemic hypersensitivity reaction³⁵ to the trial product, the subject must be discontinued from trial product but should remain in the trial (see sections [6.5](#) and [8.4](#)).

To assist in diagnosis it is recommended to draw a blood sample for measurement of tryptase (total and/or mature tryptase, to be assessed at a local laboratory) within 3 hours of the hypersensitivity reaction, and, if this is achieved, a tryptase sample should also be collected at next site visit. Furthermore, a blood sample for assessment of anti-semaglutide IgE antibodies and anti-semaglutide antibodies should be drawn as soon as possible after the event and at next site visit and sent to central laboratory for analysis.

In case of suspicion of immune complex disease³⁵, the subject must be discontinued from trial product but should remain in the trial (see sections [6.5](#) and [8.4](#)). It is recommended to collect a

blood sample for assessment of complement levels (C3 and C4) to assist the diagnostic evaluation (to be assessed at a local laboratory).

The event must be assessed according to section [12.1](#) and reported if applicable as per section [12.2](#).

8.2.3 Assessments in case of increased levels of aminotransferases

In case of

1. ALT or AST > 3x UNL **and** total bilirubin > 2x UNL,
2. ALT or AST > 5x UNL **and** total bilirubin ≤ 2x UNL,

the event must be reported as an AE requiring additional data collection (see section [12](#) and [Appendix B](#)).

For both events, prompt repeat testing (at central laboratory) including ALT, AST, ALP and total bilirubin should be done and discontinuation of trial product 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.

8.3 Treatment compliance

Treatment compliance will be assessed by monitoring of drug accountability. Subjects will be asked to bring along all used, partly used and unused trial products including empty packaging at each visit where drug accountability is performed (see sections [2](#) and [9.4](#)). The investigator must assess the amounts of trial product used compared to expected usage since 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 them of the importance of following the instructions given including taking the trial products as prescribed.

8.4 Trial adherence

Throughout the trial, the investigator will remind the subject to follow the trial procedures and requirements. It is the responsibility of the investigator to ensure that the subject's visits occur according to schedule.

If a clinic visit is missed and it is not possible to reschedule, the investigator should ensure that relevant information is collected for example over the telephone. The subject should be asked to attend the next scheduled visit according to the visit schedule.

If extra trial product is needed, the investigator can perform an additional dispensing session in IV/WRS (see section [10](#)).

The subject can remain in the trial regardless of lack of compliance with trial treatment, lack of adherence to the visit schedule, missed assessments, discontinuation of trial treatment for any reason or development of comorbidities or clinical outcomes.

Premature discontinuation of trial product: Subjects who discontinue treatment with trial product should still be followed according to the visit schedule in section [2](#). For subjects who are off trial product, a reduced visit schedule and conversion of site visits to telephone visits may be considered if this becomes a prerequisite for their continued participation in the trial. Reasons for not adhering to the standard visit schedule must be documented in medical records. Premature trial product discontinuation should be registered in the eCRF (see section [5.3](#)) and in IV/WRS (see section [10](#)).

Withdrawals: A subject who explicitly wants to withdraw their consent must be formally 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/willing to come to the trial site. Although a subject is not obliged to give his/her reason(s) for withdrawing from a trial, 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 not completing the trial must be specified on the end-of-trial form in the eCRF.

A subject who agrees to provide information concerning relevant morbidities at the planned end of trial should not be considered withdrawn from the trial.

Regarding subjects who are withdrawn when the trial comes to an end, the investigator must scrutinise publicly available registries for relevant safety information, unless prohibited by local regulations. Vital status must be determined as a minimum, wherever possible.

Lost to follow-ups: If a subject proves difficult to reach for their visit 18, extensive attempts must be made to locate the subject and obtain relevant safety information, in particular related to MACE. This may include consulting contacts provided by the subject (e.g. relatives or emergency contacts), relevant health care professionals/clinics, medical records, local registries and locator agencies. A subject cannot be deemed lost to follow-up until at least the following contacts have been attempted and documented in medical records:

- to subjects: two phone calls and one written contact
- to primary physician and/or other health care professionals: calls until contact is established
- to relatives or other contacts provided by the subject: two phone calls and one written contact
- to relevant publicly available registries

A subject will only be considered lost to follow-up in case vital status cannot be determined at the time of visit 18, or at least before the trial database lock is initiated.

9 Trial supplies

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

Each trial site will be supplied with sufficient trial products for the trial on an ongoing basis controlled by IV/WRS. Trial products will be distributed to trial sites in accordance with subject enrolment rates at the individual site.

Trial product should only be dispensed to persons participating in the trial. If a subject is unable to attend the site for a dispensing visit (see flowchart in section 2), a non-participating person may, however, collect the allocated trial product on behalf of the subject. If trial product is collected by a non-participant, this must be agreed with the subject on beforehand and thoroughly documented at the site e.g. by means of a letter of authorisation issued by the subject, and, on each occasion, the investigator must follow up by contacting the subject.

9.1 Trial products

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

Table 9–1 Investigational medicinal products

Trial product	Strength	Dosage form	Route of administration	Container
Semaglutide 3 mg tablet	3 mg	Tablet	Oral	Dose pack with 1 blister card each containing 7 tablets
Semaglutide 7 mg tablet	7 mg			
Semaglutide 14 mg tablet	14 mg			
Placebo tablet	N/A			

Semaglutide and placebo tablets are white to light yellow oval-shaped tablets, embossed with “M8” on one side. All tablets are visually identical, irrespective of strength.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13³⁶, local regulations and trial requirements.

9.3 Storage

Storage conditions for the trial products are outlined in [Table 9-2](#) and on the trial product labels.

Table 9-2 Storage conditions for trial products

Trial product	Storage conditions	In-use conditions
Semaglutide 3 mg tablet	Do not store above 30°C (86°F) Do not freeze Do not refrigerate Store in the original package	Take the tablet immediately after dispensation from blister card
Semaglutide 7 mg tablet		
Semaglutide 14 mg tablet		Take the tablets whole: Do not break or chew
Placebo tablet		

The investigator must ensure the availability of proper storage conditions, and also record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. stored in a refrigerator).

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

9.4 Drug accountability and destruction

Subjects must be instructed to bring along all used, partly used and unused trial products including empty packaging material on an ongoing basis. Returned trial product must be stored separately from non-allocated trial product.

Drug accountability is the responsibility of the investigator and should be done at tablet level by means of IV/WRS. All trial products received at site should be accounted for. Non-allocated trial product (expired, damaged and available) should be accounted as unused at closure of the trial site at the latest.

Destruction of expired stock and damaged or returned trial product may be done on an ongoing basis throughout the trial, in accordance with local procedures, after accountability is finalised and reconciled by the monitor. Remaining stock can be destroyed after last end-of-treatment visit has been carried out at the site. On-site destruction may be arranged if local procedures allow. Destruction of trial products must be documented in IV/WRS.

9.5 Auxiliary supplies

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

- BG meters and BG meter auxiliaries

10 Interactive voice/web response system

A trial-specific IV/WRS will be set up which can be accessed at any time via the internet or telephone. Access to the IV/WRS must be restricted to and controlled by authorised persons. IV/WRS user manuals will be provided to each trial site.

IV/WRS is used for:

- Screening
- Screening failure
- Randomisation
- Data change
- Medication arrival
- Dispensing
 - Semaglutide 3 mg / placebo tablets
 - Semaglutide 7 mg / placebo tablets
 - Semaglutide 14 mg / placebo tablets
- Subject treatment status change (treatment pause / treatment resume)
- Code break
- Drug accountability

At the screening session in IV/WRS, the investigator may need to indicate whether the subject fulfils one or more of the criteria a-h in inclusion criterion no. [3](#) (see section [6.2](#)).

In case a subject discontinues trial treatment, or resumes trial treatment after a treatment pause, this should be registered in IV/WRS by means of the ‘subject treatment status change’ session.

When using the ‘subject treatment status change’ session to resume treatment, the investigator will need to decide which trial product dose to prescribe (cf. section [5.3.1](#)). If trial product treatment is resumed at 3 or 7 mg oral semaglutide/placebo, IV/WRS will per default dispense trial product to support the dose escalation steps outlined in section [5.3.1](#), and extraordinary dispensing visits may be needed in order to get the subject back into the ordinary dispensing visit schedule outlined in the flow chart in section [2](#).

At all times during the trial, investigators must have robust procedures in place to ensure they only dispense the DUNs allocated to the particular subject by IV/WRS. This will ensure that:

- The subject receives the trial treatment they are randomised to
- Adequate stock is available at site
- Dispensed trial products can be accounted for

If a subject needs trial product between dispensing visits, the investigator should make an additional dispensing session in IV/WRS. For subjects who withdraw from the trial or pass away during the

trial, final drug accountability will need to be performed. The system will then be updated by Novo Nordisk and the site will no longer be supplied with trial product for the particular subject.

11 Randomisation procedure and breaking of blinded codes

Only eligible subjects are allowed to be randomised. The investigator must use IV/WRS for randomisation of subjects. IV/WRS will ensure random assignment to the two treatment arms in a 1:1 ratio and ensure even distribution of the two treatment arms within the strata described in section [5.1](#).

11.1 Breaking of blinded codes

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 IV/WRS, record the reason, and sign and date the document. The IV/WRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IV/WRS is not accessible at the time of code break the IV/WRS helpdesk should be contacted. Contact details are listed in Attachment I.

The subject may resume or continue trial product treatment although their code was broken.

12 Adverse events, technical complaints and pregnancies

This trial is designed to evaluate cardiovascular outcomes and will apply a targeted approach for collection of safety data focusing on SAEs, AEs leading to discontinuation of trial product and other selected events.

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a 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: 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 considered as AEs:

- Pre-existing conditions, including those found as a result of screening procedures (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.

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 serious adverse event (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 dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

The following events must always be reported as SAEs using the important medical event criterion if no other seriousness criterion is applicable:

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

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 Adverse events requiring additional data collection

Adverse events requiring additional data collection are events which, in the evaluation of safety, have a special focus (e.g. required by the health authorities).

If any of the following AEs are applicable for reporting according to section [12.2](#), additional data collection is required:

- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or TIA)
- Heart failure requiring hospitalisation
- Pancreatitis
- Neoplasm (excluding thyroid neoplasm)
- Thyroid disease (including thyroid neoplasm)
- Renal event
- Hypersensitivity reaction to the trial product
- Lactic acidosis
- Medication error concerning trial product:
 - Administration of wrong drug.
 - Note: Use of wrong DUN is not considered a medication error per se.
 - Wrong route of administration
 - Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
 - Accidental administration of a higher dose than intended. That is a dose of 1 tablet or 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.

If a subject missed one or more doses of trial product, this should not be reported as a medication error.

- Severe hypoglycaemic episode (see section [8.1.17.1](#))
- Hepatic event:
 - 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

Additional assessments should be made for hepatic events (see section [8.2.3](#)).

- Diabetic retinopathy and related complications

12.1.5 Technical complaint

A technical complaint is any written, electronic, or oral communication that alleges product 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)
- The packaging material (e.g. cracks or errors in labelling text)

12.2 Reporting of adverse events

In this trial the following events must be collected and reported:

- SAEs
- AEs leading to discontinuation of trial product
- Medication errors
- Severe hypoglycaemic episodes
- Hepatic events
- Diabetic retinopathy and related complications
- Pregnancies

Medication errors, severe hypoglycaemic episodes, hepatic events and diabetic retinopathy and related complications must be reported regardless of seriousness and whether trial product is discontinued.

Events occurring as of the first trial-related activity after the subject signed the informed consent until the end of the follow-up period are in scope for collection and reporting. The events must be recorded in the applicable CRFs 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, for example by asking: "Have you experienced any problems since the last contact?"

All SAEs, AEs leading to discontinuation of trial product, medication errors, severe hypoglycaemic episodes, hepatic events and diabetic retinopathy and related complications, either observed by the investigator or subject, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents: IB for oral administration of semaglutide (NN9924), current edition¹⁸ or any updates thereto.

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

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

AEs requiring additional data collection must be reported using both the AE form and the specific event form. A specific event form is a form tailored to collect specific information related to the individual event (see [Appendix B](#) for details about the specific event forms and the additional information to report).

Certain events will undergo event adjudication by the Event Adjudication Committee (EAC), please refer to section [12.7.3](#). For such events, the Event Adjudication Form will also have to be completed in the eCRF. The Event Adjudication Form is a checklist of clinical data to be provided from the site.

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the eCRF within the specified timelines:

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

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

- **SAEs fulfilling criteria for additional data collection:** In addition to above, the corresponding specific event form **within 14 calendar days** of investigators knowledge of the event.

- **Events for adjudication:** Event Adjudication Form **within 14 calendar days** of the investigator's first knowledge of the AE.

The investigator should preferably provide the medical documentation within 4 weeks of event identification.

If the eCRF is unavailable, the concerned AE information must be reported on paper forms 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 appropriate forms in the eCRF.

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

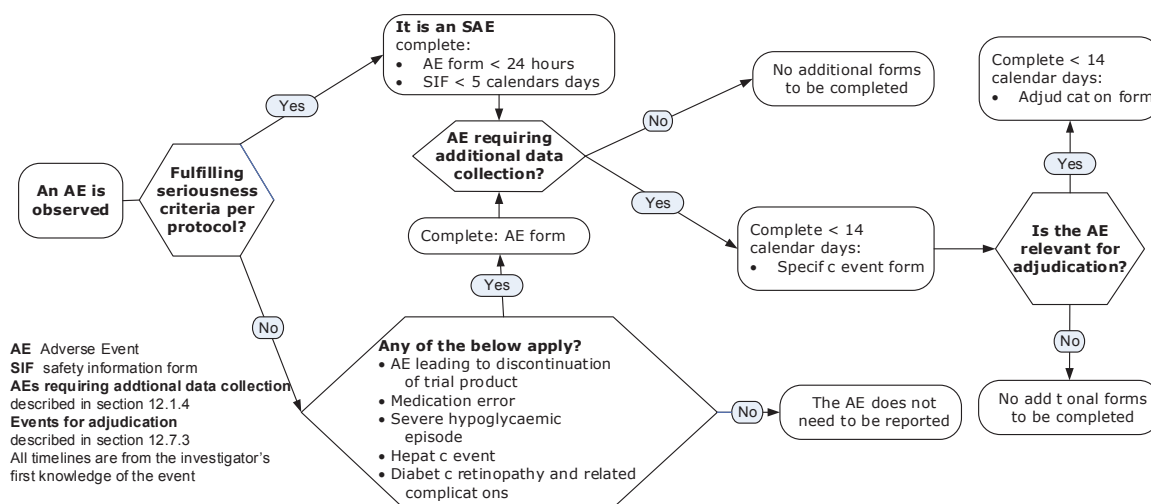


Figure 12–1 Initial reporting of AEs

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 GCP¹. 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 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 GCP¹, unless locally this is an obligation of the investigator.

To avoid introducing bias and to maintain the integrity of the primary analysis, Novo Nordisk will exempt SAEs that are part of the primary endpoint evaluation from unblinding during regulatory reporting, even though the cases fulfil the definition of SUSARs. The DMC (see section [12.7.2](#)) receives unblinded data and makes recommendations to the Novo Nordisk safety committee. This ensures adequate monitoring of safety while maintaining SAE reports related to the primary endpoint blinded for Novo Nordisk.

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

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

Novo Nordisk products used as concomitant medication:

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

12.3 Follow-up of adverse events

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

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

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

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

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

The investigator must ensure that the 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.

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 / placebo tablets
- Semaglutide 7 mg / placebo tablets
- Semaglutide 14 mg / 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. A technical complaint form for each code number or for each DUN 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 sent with the sample.

The investigator must ensure that the technical complaint sample contains the code number and, if available, the DUN.

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. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (see section [9](#)).

12.5 Pregnancies

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

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

The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and newborn infant. When needed, Novo Nordisk will provide paper forms for collection of the relevant information. The investigator must report the requested information to Novo Nordisk - electronically (e.g. in PDF format), or by fax or courier.

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 (mild/moderate) include: hunger, slight headache, nausea, light-headedness, palpitations, and sweating. Severe hypoglycaemia may produce loss of

consciousness. Symptoms of non-severe hypoglycaemia should be treated by ingestion of carbohydrates. Severe hypoglycaemia resulting in loss of consciousness should be treated at the investigator's discretion according to best available medical practise.

One case of accidental overdose of oral semaglutide was reported in the NN9924-3692 trial in a subject treated with 20 mg oral semaglutide once daily. The subject accidentally took the trial product [REDACTED] of the trial. No AEs were reported at the same time. The medication error was discovered [REDACTED]. The subject did not report any symptoms and treatment was continued without any change.

One case of accidental overdose has been reported in s.c. semaglutide once weekly treated subjects. The case was classified as moderate in severity and considered probably related to semaglutide and was reported by a subject enrolled in the trial NN9535-1821. No hospitalisation was needed. 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. Plasma glucose levels, blood pressure and pulse were monitored during the following 5 days, and no symptoms of hypoglycaemia or any other symptoms or signs were noted. The subject was withdrawn from the trial after 19 days of treatment due to an AE (diarrhoea).

For further details please see the IB for oral administration of semaglutide (NN9924), current edition¹⁸, or any updates thereto.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

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

12.7.2 Data monitoring committee

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

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

12.7.3 Event adjudication committee

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

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

The events are reviewed by the EAC in a blinded manner. The EAC will have no authorisation to impact 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 12-1](#) have been selected for adjudication in order to obtain an external independent validation of the diagnosis. In addition, cardiovascular events are being adjudicated in accordance with FDA requirements³⁷.

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication packages (e.g. x-rays, 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.

AEs for adjudication can be identified in four different manners:

- AEs reported by the investigator for adjudication
- Screening of AEs reported by the investigator as not relevant for adjudication
- Unreported AEs detected by the EAC while reviewing source data for other AEs reported by the investigator
- ECGs suggestive of new myocardial infarction (see section [8.1.13](#))

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 independence and in-depth 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.

Table 12–1 Adverse events for adjudication

Events	Description	Adjudication outcomes
Death	<ul style="list-style-type: none"> All-cause death 	<ul style="list-style-type: none"> Cardiovascular death (including undetermined cause of death) Non-cardiovascular death
Acute Coronary Syndrome	<ul style="list-style-type: none"> ST-elevation acute myocardial infarction (STEMI) Non-ST elevation acute myocardial infarction (NSTEMI) Silent myocardial infarction Unstable angina pectoris (UAP) requiring hospitalisation 	<ul style="list-style-type: none"> Acute myocardial infarction (STEMI or NSTEMI), silent myocardial infarction Unstable angina pectoris requiring hospitalisation
Cerebrovascular events	<ul style="list-style-type: none"> 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 (TIA) is defined as a transient episode (<24 hours) of focal neurological dysfunction caused by brain, spinal cord, or retinal ischaemia, without acute infarction 	<ul style="list-style-type: none"> Ischaemic stroke Haemorrhagic stroke Undetermined stroke TIA
Heart failure requiring hospitalisation	<ul style="list-style-type: none"> Hospitalisation with a primary diagnosis of heart failure (new episode or worsening of existing heart failure) 	<ul style="list-style-type: none"> Heart failure requiring hospitalisation
Acute pancreatitis	<p>The diagnosis of acute pancreatitis requires two of the following three features:</p> <ul style="list-style-type: none"> Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) Serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal Characteristic findings of acute pancreatitis on imaging 	<ul style="list-style-type: none"> Acute pancreatitis <ul style="list-style-type: none"> Mild Moderate Severe
Malignant neoplasm	<p>Malignant neoplasms are defined as:</p> <ul style="list-style-type: none"> 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 <p>Thyroid neoplasms are excluded in this event category</p>	<ul style="list-style-type: none"> Malignant neoplasm
Thyroid disease, if malignant thyroid neoplasm or C-cell hyperplasia	<p>Malignant thyroid neoplasms are defined as</p> <ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Malignant thyroid neoplasm C-cell hyperplasia
Acute kidney injury	<p>Acute kidney injury²³ is defined as any of the following (not graded):</p> <ul style="list-style-type: none"> 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 < .5 mL/kg/h for 6 hours 	<ul style="list-style-type: none"> Acute kidney injury

Events	Description	Adjudication outcomes
Lactic acidosis	Lactic acidosis is characterized by increased blood lactate level in association with metabolic acidosis	• Lactic acidosis

The safety data accumulating during the trial will be screened 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.

The event adjudication vendor or 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 or subjects never randomised for whatever reason.

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

13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRFs). 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 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.

The following will be provided as paper CRFs:

- Pregnancy forms (distributed to site if a pregnancy occurs)

In addition, paper AE forms, safety information forms and technical complaint forms will be provided. These must be used when access to the eCRF is revoked or if the eCRF is unavailable.

On the paper CRFs, 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. Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

Corrections to data on paper CRFs may only be made by drawing a straight line through the incorrect data and then writing the correct data next to the original entry. Each correction must be initialled, dated and explained (if necessary).

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

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.

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 for trial sites with subjects in screening, treatment or follow-up.

The monitor must be given direct access to 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).

The eCRF must not be used for capturing source data, i.e. all data recorded in the eCRF must be verifiable in source documentation. 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.

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

Monitor will review the subject's medical records and other source data to ensure consistency and/or identify omissions compared to the CRF. If discrepancies are found, the investigator will be questioned about these.

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

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a data management unit within Novo Nordisk or a CRO.

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 may use their own electronic systems to capture source data.

17 Statistical considerations

The blinding of the randomised treatments will be maintained until the database has been released for statistical analysis. No interim analyses or other analyses of unblinded or between group data will be performed before the database is locked, with the exception of those highly confidential analyses performed by an external independent statistician to support the deliberations of the DMC (see section [12.7.2](#)) or in direct response to a recommendation by the DMC.

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

Data from all sites will be analysed and reported together.

In statistical analyses where stratification is included, the evidence of cardiovascular disease at screening (presence of cardiovascular disease or risk factors only) will be included based on the actual information collected through the eCRF. In case of missing eCRF information the information collected in IV/WRS will be used.

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

Laboratory values below the lower limit of quantification (LLoQ) will be set to $\frac{1}{2}$ LLoQ. Number of values below LLoQ by treatment and visit will be summarised if deemed relevant.

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

Primary estimand

The trial aims to confirm that treatment with oral semaglutide does not result in an unacceptable increase (80% excess risk) in cardiovascular risk compared to placebo in subjects with T2D at high risk of cardiovascular events. Time from randomisation to first MACE will be the primary endpoint and treatment arms will be compared using the hazard ratio. This is an event-driven trial and information is planned to be collected on all randomised subjects until at least 122 first MACEs have accumulated during the planned trial duration of 19 months.

Primary estimand:

- de-facto estimand comparing oral semaglutide and placebo for all randomised subjects. Subjects who discontinue treatment with trial product should be followed according to the planned visit schedule. Estimation of the primary estimand will include all first MACEs

collected during the trial as defined by the in-trial observation period (see section [17.2](#)) regardless of adherence to randomised treatment.

17.1 Sample size calculation

Firstly, the primary endpoint; time from randomisation to first occurrence of a MACE composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, will be tested for non-inferiority using a 1.8 non-inferiority margin. If the hypothesis is confirmed, the confirmatory secondary endpoint; time from randomisation to first occurrence of an expanded composite cardiovascular endpoint consisting of: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina requiring hospitalisation or hospitalisation for heart failure, will be tested for non-inferiority using a 1.8 non-inferiority margin. The type-I-error will be preserved in the strong sense at 5% (two-sided) when using the hierarchical testing strategy.

The sample size is made to ensure a power of 90% for testing the confirmatory hypothesis for the primary endpoint. Based on a logrank test, a total of 122 first MACEs will provide 90% power to rule out hazard ratios exceeding 1.8, assuming a true hazard ratio of 1.0.

In order to have a total of 122 first MACEs with trial duration of 19 months and 1,588 subjects randomised to each treatment group (1:1 randomisation), in total 3,176 subjects, the following is assumed based on the trials EX2211-3748 (LEADER[®]) and NN9535-3744 (SUSTAIN[™] 6):

- First MACEs occur at a rate of 3 per 100 patient years of observation time (PYO) in both treatment groups throughout the trial
- Recruitment into the trial occurs uniformly during 7 months
- The lost-to-follow-up rate is 1% per year throughout the trial
- LSLV occurs 19 months after first subject was randomised

[Table 17-1](#) shows expected trial duration for different event rates under the same assumptions as described above for the other parameters.

Table 17-1 Expected trial duration according to event rates

Event rate per 100 PYO in both treatment arms	2.5	2.75	3.0	3.25	3.5
Expected trial duration from randomisation of subject to LSLV (months)	22.2	20.4	19	17.8	16.7

17.2 Definition of analysis sets

The following analysis set is defined:

- Full analysis set (FAS): includes all randomised subjects. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation “as randomised”.

In this trial, two observation periods will be defined. Definition of the observation periods:

- **In-trial observation period:** This observation period will include information assessed from randomisation to the date of the last subject-site contact regardless of adherence to treatment, which is scheduled to take place 5 weeks (with a +3 days visit window) after last planned dose of the trial product. The 5 weeks follow-up period corresponds to approximately five half-lives of oral semaglutide. For subjects lost to follow-up the end-date will be the date of the last contact with the subject (site visit or by telephone). If a subject dies during the trial, the date of death will be the end-date of the in-trial observation period regardless of the above defined end-dates.
- **On-treatment observation period:** This observation period is a subset of the in-trial observation period and will include information assessed on or after the first date of trial product up to and including the first date of (i) last date on trial product +38 days or (ii) 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. In addition, the ascertainment window includes the follow-up visit window of +3 days after last date on trial product.

Subjects not having a MACE within the observation period will be censored at the end of the observation period in the primary analysis assuming independent censoring for subjects lost to follow-up. Hence, a subject censored at a given time should be representative of those still at risk at that time point. For EAC confirmed events the onset date will be the onset date assessed by the EAC. EAC confirmed events with adjudicated onset date prior to randomisation will be described in listings. EAC confirmed events with adjudicated onset date after in-trial observation period but prior to database lock will be evaluated and summarised descriptively. For events not subjected to adjudication or negatively adjudicated, the onset date for the adverse event reported by the investigator will be used.

17.3 Primary endpoint

- Time from randomisation to first occurrence of a MACE composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

The primary estimand will be estimated based on the FAS and the in-trial observation period. The primary statistical analysis of the primary endpoint will be a stratified Cox proportional hazards model with treatment group (oral semaglutide, placebo) as fixed factor. The model will be stratified

by evidence of cardiovascular disease at screening (presence of cardiovascular disease or risk factors only). From this model the estimated hazard ratio (HR) (oral semaglutide/placebo) together with the 2-sided 95% confidence interval will be presented. Non-inferiority of oral semaglutide versus placebo will be considered confirmed if the upper limit of the two-sided 95% confidence interval for the HR is below 1.8 or equivalent if the p-value for the one-sided test of

$$H_0: HR \geq 1.8 \text{ against } H_a: HR < 1.8$$

is less than 2.5% (or equivalent to 5% for a two-sided test).

A Kaplan-Meier plot with number of subjects at risk at specific time points will be presented and used graphically to assess the validity of the assumption of proportional hazards. This will be supported by the use of Schoenfeld residuals.

17.3.1 Sensitivity analysis

To explore the robustness of the primary analysis results the following sensitivity analyses will be performed. The sensitivity analyses will evaluate different de-jure estimands and, thus, will focus on events occurring while subjects to a greater extent compared to the primary estimand are treatment adherent. Different observation periods will be defined considering treatment adherence and different follow-up periods after last date on trial product. All sensitivity analyses will be based on FAS and analysed using the same model as the primary analysis including the censoring rules and the assumption of independent censoring for subjects with shorter observation period than the trial duration.

Sensitivity analysis 1: Including additional covariates

This sensitivity analysis will explore the primary analysis by fitting a stratified Cox regression analysis and estimate of the treatment hazard ratio (oral semaglutide/placebo) with a 2-sided 95% confidence interval while including the additional covariates sex, region, baseline age, diabetes duration, smoking history, and eGFR at baseline. The model will be stratified by evidence of cardiovascular disease at screening (presence of cardiovascular disease or risk factors only). The analysis will be based on the FAS and the in-trial observation period.

Sensitivity analysis 2: Ascertainment window of 38 days after last date on trial product

This sensitivity analysis will include all first MACEs that are collected in the on-treatment observation period.

Sensitivity analysis 3: Ascertainment window of 7 days after last date on trial product

This sensitivity analysis will include all first MACEs that are collected on or after the first date on trial product up to and including the last date on trial product +7 days.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoint

- Time from randomisation to first occurrence of an expanded composite cardiovascular endpoint consisting of: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina requiring hospitalisation or hospitalisation for heart failure

The confirmatory secondary endpoint will be analysed using the same analysis including sensitivity analyses as for the primary endpoint.

17.4.2 Safety endpoints

Time to event endpoints

- Time from randomisation to first occurrence of each of the individual components in the expanded composite cardiovascular endpoint
- Time from randomisation to first occurrence of a composite endpoint consisting of: all-cause death, non-fatal myocardial infarction or non-fatal stroke
- Time from randomisation to all-cause death
- Time to permanent discontinuation of trial product due to AE(s)

The analyses of the above time-to-event composite endpoints (except for the last endpoint) will be the same as the primary analysis. The analysis of time to permanent discontinuation of trial product due to AE(s) will be adjusted for the competing risk of other predefined reasons for discontinuing trial product prematurely. The above analyses will be based on the FAS and performed for both the in-trial and on-treatment observation periods. Cumulative incidence functions will be plotted for all of the endpoints.

Adverse events

- Number of SAEs

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

SAEs 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). The summaries will be based on FAS and performed for both the in-trial and the on-treatment observation periods. Furthermore, events confirmed by adjudication and AEs leading to discontinuation of trial product will be summarised as above.

Continuous safety endpoints

Change from baseline to last assessment of:

- Pulse
- Systolic and diastolic blood pressure

The last available measurement for the above endpoints will be analysed separately in an analysis of covariance (ANCOVA) with treatment group as fixed factors and the corresponding baseline value as a covariate. From the ANCOVAs the estimated treatment differences for oral semaglutide versus placebo together with the corresponding 2-sided 95% confidence intervals will be presented. The analyses will be based on FAS and performed for both the in-trial and the on-treatment observation periods.

Other safety endpoints

- Biochemistry
- Haematology
- Calcitonin
- Eye examination category

The above assessments will be summarised using descriptive statistics by treatment group for all scheduled visits and for last available assessment based on FAS and performed for both the in-trial and the on-treatment observation periods. Categorical safety endpoints will be summarised as counts and relative frequencies. Calcitonin will also be presented by sex.

17.4.3 Efficacy endpoints

Change from baseline to last assessment of:

- HbA_{1c}
- Body weight
- Lipids

The last available measurement for the above endpoints will be analysed separately in an ANCOVA with treatment group as fixed factors and the corresponding baseline value as a covariate. From the ANCOVAs the estimated treatment differences for oral semaglutide versus placebo together with the corresponding 2-sided 95% confidence intervals will be presented. The analyses will be based on FAS and performed for both the in-trial and the on-treatment observation periods.

18 Ethics

The trial will be conducted in compliance with ICH GCP¹ and applicable regulatory requirements, and in accordance with the Declaration of Helsinki². When treatment with trial product ends, the subject and investigator will decide on the best available treatment for each subject.

18.1 Benefit–risk assessment of the trial

Risks and precautions

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

The sections below describe identified and potential risks and precautions associated with oral semaglutide treatment. These are based on findings in nonclinical 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. In addition, in case a subject experiences unacceptable tolerability issues, dose reduction to a lower treatment dose is allowed.

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 of 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 T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from nonclinical- or clinical trials or postmarketing 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.

Severe 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. In this trial, it is recommended to reduce the dose of insulin and sulphonylurea at randomisation to reduce the risk of hypoglycaemia when introducing an additional glucose lowering agent.

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.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, an allowed background treatment, have also been associated with volume depletion. It is recommended to monitor for signs and symptoms of fluid loss during therapy. Severe dehydration may be a risk factor for diabetic ketoacidosis.

Impaired renal function may increase the risk of metformin associated lactic acidosis when GLP-1 RAs are co-administered with metformin. As a precaution serum creatinine will be measured regularly.

Other

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 intends 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 the site at screening, follow-up and at any time during the trial if a menstrual period is missed, or is required by local law.

Diabetic retinopathy complications

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive antidiabetic treatment³⁸⁻⁴⁰. 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^{41,42} even in intensively treated patients who experienced early worsening³⁹. 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. As a precaution in this trial, all subjects are required to have a fundus photography or dilated funduscopy performed before enrolment into the trial; moreover, subjects with proliferative retinopathy or maculopathy requiring acute treatment will be excluded.

General precautions

All subjects will be included after a thorough evaluation in regards to in- and exclusion criteria defined in order to ensure that subjects are eligible for trial treatment. It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2014 Standards of Medical Care in Diabetes⁴³.

Further details with regards to safety of trial product are described in the current edition of the IB for oral semaglutide (NN9924)¹⁸, or any updates thereto.

Benefits

For all participating subjects, the anticipated benefits include a close monitoring of their T2D and an optimised antidiabetic treatment. All subjects will be treated within an antidiabetic regimen anticipated to be better than or equal to the treatment that they receive at the time of entry into the trial. The investigator is responsible for adjusting or adding antidiabetic medication throughout the course of the trial to maintain an adequate level of glycaemic control in each subject. In addition, it

is expected that all subjects will benefit from participation through close contact with the trial site including thorough medical examinations and close follow-up of their T2D. Finally, data from two cardiovascular outcomes trials investigating treatment with GLP-1 RAs compared to placebo have indicated that there might be a potential beneficial effect of these drugs on cardiovascular outcomes when added to standard of care in subjects with T2D at high risk of cardiovascular events (see section [3.1.5](#)).

Risk and benefit conclusion

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile for the investigational medicinal product generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of oral semaglutide in accordance with the planned clinical trial.

18.2 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 data collected at follow-up will be retained by Novo Nordisk, entered into the database and used for the 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.

18.3 Information to subject during trial

The site will be offered a communication package to the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subject at the discretion of the investigator. The subject may e.g. receive a "patient newsletter" during trial participation and a "thank you for your participation letter" after the trial has ended.

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.

18.4 Premature termination of the trial and/or trial site

The DMC may recommend premature termination of the trial (cf. section [12.7.2](#)).

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

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 clinical database.

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

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*

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

For US only:

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

FDA form 1572:

For US sites:

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

For sites outside the US:

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

By signing the protocol, each investigator agrees to comply fully with ICH GCP¹, applicable regulatory requirements and the Declaration of Helsinki².

By signing the protocol, 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. 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 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 must ensure adequate supervision of the conduct of the trial at the trial site.

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 should be kept in a secure locked facility, so no unauthorised persons can get access to the data.

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

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

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

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

23 Reports and publications

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

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

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

One or more investigator(s) will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator(s)) on behalf of all participating investigators. The signatory investigator(s) will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications⁴⁴.

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 Disclosure²⁵.

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 Editors⁴⁵ (sometimes referred to as the Vancouver Criteria).

At the end of the trial, one or more publications (abstracts, posters, manuscripts) will be prepared for submission to scientific congresses and peer-reviewed journals in collaboration between Novo

Nordisk and investigator(s) appointed by Novo Nordisk. These investigator(s) must meet the International Committee of Medical Journal Editors authorship criteria to be named authors on publications.

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 trial subjects' data available, and will be provided with the randomisation codes after the end of the trial.

24 Retention of clinical trial documentation and human biospecimens

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 as long as the product is on the market plus 20 years.

The files from the trial site/institution must be retained for 15 years after the completion of the trial, 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 biospecimens

In order to comply with any future requests from health authorities to further characterise the antibody response, antibody samples collected in relation to suspicion of hypersensitivity reactions during the trial may be stored at Novo Nordisk until no further marketing authorisations are pending or maximum 15 years after the trial ended, whichever comes first. Stored antibody samples will be identified only by a subject number, a visit number and a trial identification number. The investigator is responsible for maintaining a list which links each subject number to a subject name. This list must be kept for at least 15 years after the trial ended. The list may be reviewed by Novo Nordisk staff including auditors or representatives from regulatory authorities.

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

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

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

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to IB, SUSARs, 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 Argentina only: Novo Nordisk Pharma Argentina S.A. has contracted insurance as required by local law.

For Germany only: German Drug Law dated August 24, 1976, last amended by article 3 of the law dated December 17, 2014 (Federal Law Gazette I p. 2222).

For Mexico only: Novo Nordisk carries product liability for its products and liability as assumed under the special laws, acts/and/or guidelines for conducting trials in any country, including those applicable provisions on the Mexican United States. If the subject feels that something goes wrong during the course of this trial, the subject should contact the trial staff in the first instance.

If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the 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.

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.

For the Netherlands only: Wetgeving betreffende geneesmiddelen; geneesmiddelenwet 1 juli 2007 (Medicines Law, 1 July 2007). De Wet Medisch-wetenschappelijk Onderzoek met mensen (WMO), 1 maart 2006 (Medical Research Involving Human Subjects Act, 1 March 2006). Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015, 24 november 2014 (Decree compulsory insurance in medical research involving human subjects 2015, 24 November 2014).

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

27 References

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