Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02607865
Sponsor trial ID:	NN9924-4222
Official title of study:	Efficacy and long-term safety of oral semaglutide versus sitagliptin in subjects with type 2 diabetes
Document date:	21-November-2018

16.1.1 Protocol and protocol amendments

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Protocol amendment 3 - FR ..... Link

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

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Protocol

Trial ID: NN9924-4222

PIONEER 3 - vs. DPP-4 inhibitor

Efficacy and long-term safety of oral semaglutide versus sitagliptin in subjects with type 2 diabetes

Trial phase: 3a

Protocol originator

[redacted]

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List of abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BG	blood glucose
BMI	body mass index
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLAE	clinical laboratory adverse event
CoEQ	Control of Eating questionnaire
CRF	case report form
CTR	clinical trial report
CVD	cardiovascular disease
DDI	drug-drug interaction
DPP-4i	dipeptidyl peptidase 4 inhibitor
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate (CDISC term is GFR, 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
FU	follow-up
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like-peptide-1 receptor agonist
HbA_{1c}	glycosylated haemoglobin
HDL	high density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IWQoL-Lite	Impact of Weight on Quality of Life questionnaire
IRB	institutional review board
IWRS	interactive web response system
LDL	low density lipoprotein
LSFV	last subject first visit
LSLV	last subject last visit
MAR	missing at random
MEN 2	Multiple Endocrine Neoplasia Type 2
MI	myocardial infarction
MTC	Medullary Thyroid Carcinoma
MMRM	Mixed Model for Repeated Measurements
NIMP	non-investigational medicinal product
NYHA	New York Heart Association
OAD	oral antidiabetic drug
P	phone contact

PG	plasma glucose
PK	pharmacokinetics
PP	per protocol
PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous(ly)
SF-36v2™	Short Form-36 version 2 health survey
SIF	Safety information form
SMPG	self-measured plasma glucose
SmPC	summary of product characteristics
SNAC	sodium N-(8-(2-hydroxybenzoyl) amino) caprylate
SU	sulfonylurea
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse events
TIA	transient ischemic attack
TMM	Trial Materials Manual
UNL	upper normal level
UTN	Universal Trial Number
V	visit
VLDL	very low density lipoprotein

1 Summary

Objectives and endpoints:

Primary objective

To compare the effect of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without sulfonylurea (SU), on glycaemic control in subjects with type 2 diabetes mellitus (T2DM).

Secondary objectives

To compare the effect of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without SU, on body weight in subjects with T2DM.

To compare the long-term safety and tolerability of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without SU, in subjects with T2DM.

Primary endpoint

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

Key secondary endpoints

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

Subjects who after 26 weeks of treatment achieve (yes/no):
- $HbA_{1c} < 7.0\%$ (53 mmol/mol), American Diabetes Association (ADA) target
  This endpoint will also be evaluated after week 52 and after week 78.

Change from baseline to week 52 and to week 78 in:
- HbA_{1c}
- Body weight (kg)
- FPG

Number of treatment emergent adverse events (TEAEs) during exposure to trial product, assessed up to approximately 83 weeks

Number of treatment emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 83 weeks

Trial design:

The trial is a 78 week, randomised, double-blind, double-dummy, active-controlled, parallel-group, multi-centre, multi-national, four-armed trial.

Subjects with T2DM inadequately controlled with metformin or metformin + sulfonylurea (SU) will be randomised in a 1:1:1:1 manner to receive either a dose of 3 mg, 7 mg or 14 mg of oral semaglutide once-daily or a dose of 100 mg sitagliptin once-daily.

Total trial duration for the individual subject will be approximately 85 weeks. The trial includes a 2 week screening period, followed by a 78 week randomised treatment period and a follow-up period of 5 weeks.

Trial population:

It is planned to randomise 1860 subjects.

Key inclusion criteria

- Male or female, age ≥ 18 years at the time of signing informed consent.
  For Japan only: Male or female, age ≥ 20 years at the time of signing informed consent.
- Diagnosed with T2DM ≥ 90 days prior to day of screening.
- HbA_{1c} 7.0-10.5 % (53-91 mmol/mol) (both inclusive).
- Stable daily dose of metformin (≥ 1500 mg or maximum tolerated dose as documented in subject medical record) alone or in combination with SU (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record) within 90 days prior to the day of screening.

Key exclusion criteria

- Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).
  For certain specific countries: Additional specific requirements apply.
- 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).
- Any of the following: myocardial infarction, stroke or hospitalization for unstable angina and/or transient ischaemic attack within the past 180 days prior to the day of screening.
- Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
- Renal impairment defined as estimated Glomerular Filtration Rate (eGFR) < 60 mL/min/1.73 m^2 as per Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).
- History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas).

Key assessments:

Efficacy:

- HbA_{1c}
- FPG
- Body weight

Safety:

- Adverse events
- Hypoglycaemic episodes

Trial products:

The following trial products will be supplied by Novo Nordisk A/S, Denmark:

- Semaglutide, 3 mg tablet
- Semaglutide, 7 mg tablet
- Semaglutide, 14 mg tablet
- Semaglutide placebo tablet (Placebo I)
- Sitagliptin (Januvia®), 100 mg tablet
- Sitagliptin placebo tablet (Placebo II)

2 Flow chart

Trial Periods	Screening[1]	Randomisation	Treatment													End-of-treatment (EoT)	Follow-up[2]	EoT premature discontinuation[3]	Follow-up premature discontinuation[3]
Visit (V), Phone (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V16A	V17A
Timing of visit (weeks)	Up to -2 wks	0	2	4	8	14	20	26	32	38	45	52	59	66	72	78	83	Shortly after discontinua-tion of trial product	5 weeks after discontinua-tion of trial product (last dose)
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3		+3
SUBJECT RELATED INFO/ASSESSMENTS																			
Informed consent	x																		
In/exclusion criteria	x	x																	
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography	x																		
Tobacco use	x																		
Concomitant illness and medical history	x																		
History of diabetes	x																		
History of cardiovascular disease	x																		
History of gallbladder disease	x																		
History of gastrointestinal disease	x																		
Randomisation		x																	
Withdrawal criteria			x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	

Trial Periods	Screening[1]	Randomisation	Treatment													End-of-treatment (EoT)	Follow-up[2]	EoT premature discontinuation[3]	Follow-up premature discontinuation[3]
Visit (V), Phone (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V16A	V17A
Timing of visit (weeks)	Up to -2 wks	0	2	4	8	14	20	26	32	38	45	52	59	66	72	78	83	Shortly after discontinua-tion of trial product	5 weeks after discontinua-tion of trial product (last dose)
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3		+3
EFFICACY																			
HbA_{1c}	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x		x	
Fasting plasma glucose		x		x	x	x	x	x		x		x		x		x		x	
PK Sampling[4]		x		x	x	x		x		x		x				x	x	x	x
Lipids		x						x				x				x		x	
Body height		x																	
Body weight, BMI		x		x	x	x	x	x	x	x	x	x	x	x	x	x		x	
Waist circumference		x				x		x		x		x		x		x		x	
7-point profile		x						x				x				x		x	
PRO questionnaires		x						x				x				x		x	
SAFETY																			
Eye examination[5]	x																		
Physical examination	x											x				x		x	
Electrocardiogram		x						x				x				x	x	x	x
Vital signs		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test[6]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Calcitonin		x				x		x		x		x		x		x	x	x	x
Biochemistry[7]	x	x		x	x	x		x		x		x		x		x	x	x	x
Haematology		x		x	x	x		x		x		x		x		x	x	x	x

Trial Periods	Screening[1]	Randomisation	Treatment													End-of-treatment (EoT)	Follow-up[2]	EoT premature discontinuation[3]	Follow-up premature discontinuation[3]
Visit (V), Phone (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V16A	V17A
Timing of visit (weeks)	Up to -2 wks	0	2	4	8	14	20	26	32	38	45	52	59	66	72	78	83	Shortly after discontinua-tion of trial product	5 weeks after discontinua-tion of trial product (last dose)
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3		+3
Antibodies[8]		x		x	x	x		x		x		x				x	x	x	x
Adverse events[9]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Technical complaints			x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
TRIAL MATERIAL																			
IWRS call	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x		x	
Dispensing of trial product		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																			
Hand out ID card	x																		
Hand out and instruct in BG meter use	x																		
Dispense and/or collect diary	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Attend visit fasting[10]		x		x	x	x	x	x		x		x		x		x		x	

Footer	Description
X[1]	Subject can be randomised as soon as all inclusion and exclusion criteria are confirmed. The screening assessments must not exceed 2 weeks prior to randomisation (V2).
X[2]	Subjects, who have discontinued trial product prematurely, are not required to attend V17 (Follow-up).
X[3]	V16A and V17A are only applicable for subjects who have discontinued trial product prematurely.
X[4]	PK sampling is only applicable for a subset of the subjects. No PK sampling should be done for visits occurring after V17A (subjects who have discontinued trial product prematurely).
X[5]	Dilated fundoscopy/fundus photography performed within 90 days prior to randomisation is acceptable if results are available for evaluation at V2, unless worsening of visual function since last examination.
X[6]	For women of child bearing potential: Urine pregnancy test should also be performed at any time during the trial if a menstrual period is missed and/or according to local regulations/law.
X[7]	At V1 only Creatinine and eGFR will be assessed as part of Biochemistry.
X[8]	At randomisation, the antibody sampling must be done pre-dose. No antibody sampling should be done for visits occurring after V17A (subjects who have discontinued trial product prematurely).
X[9]	Adverse events reporting, includes adverse events from the first trial-related activity after the subject has signed the informed consent at V1.
X[10]	Fasting for blood sampling is defined as having consumed only water within the last 8 hours prior to visit.

3 Background information and rationale for the trial

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

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.

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

3.1 Background information

3.1.1 Type 2 diabetes mellitus

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

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

3.1.2 Glucagon-like peptide-1

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

inhibitory effect on gastric emptying; however this effect seems to diminish upon chronic exposure [14-16]. These mechanisms of action make GLP-1 an attractive pharmacological treatment for T2DM.[17-19]

3.1.3 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 T2DM. 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-aminoisobuztyric acid, a synthetic amino acid) and position 34 (lysine to arginine) and acylation of the peptide backbone with a spacer and C-18 fatty di-acid chain to lysine in position 26.[20]The fatty di-acid side chain and the spacer mediate strong binding to albumin, thereby reducing renal clearance. The amino acid substitution at position 8 makes semaglutide less susceptible to degradation by dipeptidyl peptidase-4 (DPP-4). The change in position 34 from a lysine to an arginine is included to have only one lysine in the sequence where to a spacer can be attached.

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

3.1.4 Non-clinical data

3.1.4.1 Semaglutide

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

Thyroid C-cell tumours in rodents
Treatment-related non-genotoxic proliferative changes in the thyroid C-cells of mice and rats were observed in 2-year carcinogenicity studies with semaglutide; thyroid hyperplasia was preceded by an increase in serum calcitonin. C-cell changes have not been observed in long-term studies in non-human primate. The observed pattern of effects in mice and rats and lack of these effects in the non-human primate and in man suggest that the mechanism by which semaglutide acts on the thyroid C-cells in rodents is the same as has been demonstrated for other GLP-1 RAs, including liraglutide. According to this mechanism, C-cell hyperplasia is mediated by the GLP-1 receptor and is not associated with RET (re-arranged during transfection) gene activation and rodents appear to be particularly sensitive, whereas humans are not. The relevance for human subjects is currently unknown, but considered to be low[21].

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 investigator's brochure (IB) for Semaglutide (subcutaneous administration), edition 10[22] and the IB for Oral administration of semaglutide (NN9924), edition 6[23], or any updates of these documents.

3.1.4.2 SNAC

SNAC was developed as an absorption enhancing excipient for the oral route of administration. The non-clinical programme to support clinical phase 3 development and marketing authorisation application (MAA) 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 (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 IB for Oral administration of semaglutide (NN9924), edition 6[23], or any updates hereof.

3.1.5 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 T2DM.

For details on the individual trials, please see the IB for Oral administration of semaglutide (NN9924) edition 6[23], or any updates hereof.

3.1.5.1 Pharmacokinetics

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

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

Exposure of semaglutide exhibits a substantially greater dose-to-dose variation following oral administration compared to s.c. administration. However, when administered orally once-daily the PK properties of semaglutide, i.e. low clearance and long half-life, will limit the variation in 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 can be taken with up to half a glass of water (approximately 120mL/4 fluid oz).

Drug-drug interaction (DDI) 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 T2DM. It is extensively metabolized and no accumulation of SNAC has been observed in clinical trials.

3.1.5.2 Efficacy

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

Results from the trial showed that oral semaglutide effectively lowered 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).

3.1.5.3 Safety

In the clinical trials completed so far, no unexpected safety findings have been identified for oral semaglutide administered up to 40 mg once daily. Consistent with other GLP-1 RAs, 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 administrated heparin in combination with SNAC (heparin/SNAC). The heparin/SNAC programme ([redacted].) included 29 phase 1 trials (SNAC doses ranged from 0.172-10.5 g). In three of these trials SNAC alone was investigated (to a maximum

dose of 10.5 g). The 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) was investigated. The overall safety profile of oral semaglutide and heparin/SNAC indicates that SNAC is safe and well-tolerated.

For further details please see the IB for Oral administration of semaglutide (NN9924) edition 6[23], or any updates hereof.

3.1.6 Sitagliptin

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

Further information can be obtained in the locally approved Januvia® label[24].

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

3.2 Rationale for the trial

The rationale for the present trial is to compare the efficacy and safety of once-daily dosing with three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide with sitagliptin 100 mg once-daily in subjects with T2DM. Furthermore, the trial will ensure that long-term safety data are collected from subjects with T2DM exposed to oral semaglutide for a minimum of 18 months, as recommended by U.S. Food and Drug Administration (FDA)[24].

4 Objective(s) and endpoint(s)

4.1 Objective(s)

4.1.1 Primary objective

To compare the effect of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without SU, on glycaemic control in subjects with T2DM.

4.1.2 Secondary objectives

To compare the effect of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without SU, on body weight in subjects with T2DM.

To compare the long-term safety and tolerability of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without SU, in subjects with T2DM.

4.2 Endpoint(s)

4.2.1 Primary endpoint

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

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

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

4.2.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

Change from baseline to week 52 and to week 78 in:

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

Change from baseline to week 26, to week 52 and to week 78 in:

- Body weight (%)
- FPG*
- Self-measured plasma glucose (SMPG), 7 point profile
    - Mean 7 point profile
    - Mean post prandial increment (over all meals)
- Body mass index (BMI)
- Waist circumference
- Fasting lipid profile (total cholesterol, low density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, free fatty acids)
- Patient reported outcomes
    - Short Form-36 version 2 (SF-36v2™) (acute version) health survey
    - Impact of Weight on Quality of Life (IWQoL-Lite) Clinical Trial Version
    - Control of Eating questionnaire (CoEQ)

Subjects who after 26 weeks of treatment achieve (yes/no):

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

The above eight endpoints will be evaluated after week 52 and after week 78 as well.

Time to event endpoint

- Time to rescue medication

This endpoint will be evaluated after week 26, after week 52 and after week 78.

Supportive secondary safety endpoints

- Number of TEAEs during exposure to trial product, assessed up to approximately 83 weeks*
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 83 weeks*
- Treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 83 weeks (yes/no)

Change from baseline to week 78 in:

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

Occurrence of anti-semaglutide antibodies (yes/no):

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

Anti-semaglutide binding antibody levels

Endpoints to be included in PK meta-analyses across phase 3a trials with oral semaglutide

PK-concentrations

- Semaglutide plasma concentration in a subset of the subjects (approximately 50%) for population PK analyses

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

5 Trial design

5.1 Type of trial

The trial is a 78 week, randomised, double-blind, double-dummy, active-controlled, parallel-group, multi-centre, multi-national trial with four arms comparing efficacy and safety of oral semaglutide 3 mg, 7 mg and 14 mg once-daily with sitagliptin 100 mg once-daily. Subjects with T2DM inadequately controlled on metformin alone or in combination with SU will be randomised in a 1:1:1:1-manner to receive either:

- oral semaglutide 3 mg and sitagliptin placebo
- oral semaglutide 7 mg and sitagliptin placebo
- oral semaglutide 14 mg and sitagliptin placebo
- sitagliptin 100 mg and oral semaglutide placebo

Randomisation will be stratified according to anti-diabetic pre-trial background medication (metformin or metformin + SU) to ensure even distribution of the four treatment arms within strata.

To maintain the blinding of the trial, the treatment will consist of two tablets daily as the sitagliptin tablet is not visually identical to the oral semaglutide tablets (see Section 9.1).

Total trial duration for the individual subject will be approximately 85 weeks. The trial includes a 2 week screening period, followed by a 78 week randomised treatment period and a follow-up period of 5 weeks.

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

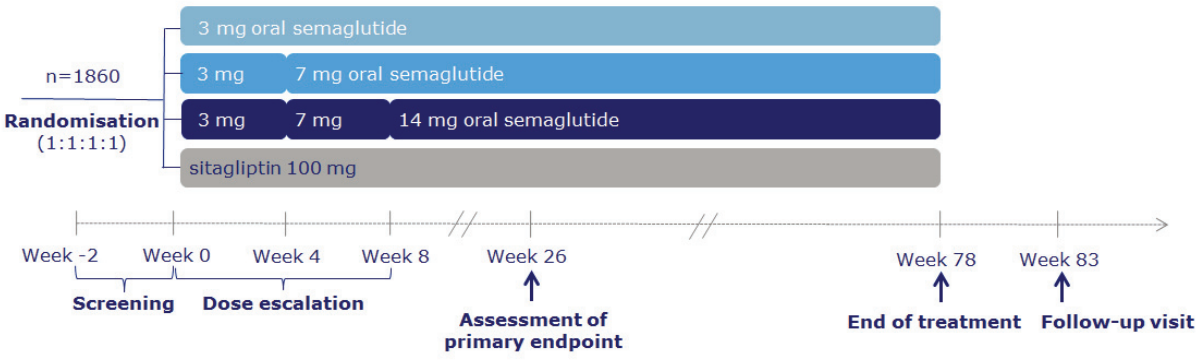


Figure 5–1 Trial design

5.2 Rationale for trial design

Parallel treatment arms and a randomised double-blind double-dummy active controlled design have been chosen in accordance with trial objectives and to avoid bias in the trial. The primary

efficacy endpoint will be evaluated at week 26 (see Section 17). No interim analysis will be done and the blinding will remain throughout the trial in order to assess long-term safety and tolerability in an un-biased manner (see Section 17). Supportive secondary efficacy endpoints are also included at week 52 and week 78.

5.3 Treatment of subjects

Treatment of subjects is summarised in Table 5–1.

Oral semaglutide treatment arms

All subjects randomised to semaglutide will initiate treatment with 3 mg once daily. Subjects randomised to maintenance doses of 7 mg or 14 mg will follow a fixed dose-escalation regimen with 4 weeks between the dose escalation steps. The maintenance dose of 7 mg once daily will be reached after 4 weeks on 3 mg once daily. The maintenance dose of 14 mg once daily will be reached after 4 weeks on 3 mg once daily, followed by 4 weeks on 7 mg once daily. In addition, all subjects randomised to oral semaglutide will receive sitagliptin placebo once daily.

Sitagliptin treatment arm

Subjects randomised to sitagliptin will receive 100 mg once daily without dose escalation. In addition, all subjects randomised to sitagliptin will receive oral semaglutide placebo once daily.

Table 5–1 Treatment of subjects

	Screening	Treatment period 1	Treatment period 2	Treatment period 3	Follow-up
First visit in each period	V1	V2	V4	V5	V16
Duration of each period[a]	2 weeks	4 weeks	4 weeks	70 weeks	5 weeks
Treatment arm					
oral semaglutide 3 mg + sitagliptin placebo	Screening	3 mg + placebo	3 mg + placebo	3 mg + placebo	Follow-up
oral semaglutide 7 mg + sitagliptin placebo	Screening	3 mg + placebo	7 mg + placebo	7 mg + placebo	Follow-up
oral semaglutide 14 mg + sitagliptin placebo	Screening	3 mg + placebo	7 mg + placebo	14 mg + placebo	Follow-up
sitagliptin 100 mg + oral semaglutide placebo	Screening	100 mg + placebo	100 mg + placebo	100 mg + placebo	Follow-up

[a] Please see Section 2 for visit windows.

5.3.1 Dosing instructions

Absorption of oral semaglutide is significantly affected by food and fluid in the stomach, hence dosing should be in the morning in fasting state and at least 30 minutes before the first meal of the day. Trial products can be taken with up to half a glass of water (approximately 120 ml/4 fluid oz). The tablets must be taken whole: do not break or chew (see Table 9–2). Furthermore, other oral medication can be taken 30 minutes after trial products.

5.3.2 Background medication

After inclusion (V1), subjects must continue anti-diabetic pre-trial background medication (i.e. metformin alone or in combination with SU) throughout the entire trial. The background medication must be maintained at the stable, pre-trial dose and at the same frequency during the whole treatment period unless rescue medication is needed (see Section 6.4) or if the subject has unacceptable hypoglycaemia on a background of SU in which case the dose of SU can be reduced.

In addition, all background medication:

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

[redacted]

5.4 Treatment after discontinuation of trial product

When discontinuing trial products the subject should be switched to a suitable marketed product at the discretion of the investigator *(for Brazil only: or it will be made available according to local regulations*). After discontinuation of trial product, GLP-1 RAs are not allowed before completion of the follow-up visit (see Section 8.1.4 and 8.1.5) which is to take place 5 weeks after the last date on trial product (to avoid interference with the antibody analysis).

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

5.5 Rationale for treatment

The doses of oral semaglutide have been chosen based on the data from the phase 2 dose-finding trial. The selected doses are expected to have the optimal benefit risk profile for further development for treatment of T2DM. The duration and doses of randomised treatments are considered adequate to collect sufficient data on efficacy and safety in accordance with the trial objectives.

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

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 3100

Number of subjects planned to be randomised: 1860

Number of subjects expected to complete the trial on or off randomised trial product: 1674

For Japan only: 200 Japanese subjects planned to be randomised with an approximate equal distribution across the 4 treatment arms.

For Mexico only: 98 Mexican subjects planned to be randomised.

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age ≥ 18 years at the time of signing informed consent.
   For Japan only: Male or female, age ≥ 20 years at the time of signing informed consent.
3. Diagnosed with type 2 diabetes mellitus ≥ 90 days prior to day of screening.
4. HbA_{1c} 7.0-10.5% (53-91 mmol/mol) (both inclusive).
5. Stable daily dose of metformin (≥ 1500 mg or maximum tolerated dose as documented in the subject medical record) alone or in combination with SU (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in the subject medical record) within 90 days prior to the day of screening.

6.3 Exclusion criteria

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

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

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

4. Receipt of any investigational medicinal product within 90 days before screening.
   For Brazil only: Participation in other trials within one year prior to screening visit (visit 1) unless there is a direct benefit to the research subject at the investigator´s discretion
5. Any disorder, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
6. Family or personal history of Multiple Endocrine Neoplasia Type 2 (MEN 2) or Medullary Thyroid Carcinoma (MTC).
7. History of pancreatitis (acute or chronic).
8. History of major surgical procedures involving the stomach potentially affecting absorption of trial product (e.g. subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery).
9. Any of the following: myocardial infarction, stroke or hospitalization for unstable angina and/or transient ischaemic attack within the past 180 days prior to the day of screening.
10. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
11. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.

12. Renal impairment defined as estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73 m^2 as per Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).

13. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before the day of screening. An exception is short-term insulin treatment for acute illness for a total of ≤ 14 days.

14. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomisation.

15. History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas).

6.4 Rescue criteria

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification. To allow time for dose escalation and to observe the expected effect of treatment on glycaemic parameters, rescue criteria will be applied from week 8 and onwards. If any of the FPG values (including fasting SMPG) exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified, a confirmatory FPG (at central laboratory) should be obtained by calling the subject for a re-test:

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

If the confirmatory FPG also exceeds the values described above, the subject should be offered rescue medication (i.e. intensification of existing anti-diabetic background medication and/or initiation of new anti-diabetic medication).

In addition, subject should be offered rescue medication if:

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

It is important for trial integrity that only subjects actually needing treatment intensification (as defined above) are started on rescue medication. Subjects that are started on rescue medication should continue to follow the protocol-specified visit schedule. Rescue medication should be prescribed as add-on to randomised treatment and according to ADA/European Association for the Study of Diabetes guidelines[25,26](excluding GLP-RAs, DPP-4 inhibitors and amylin analogues). Rescue medication and any changes hereto should be captured on the concomitant medication form in the electronic case report form (eCRF), see Section 8.2.4. Rescue medication is considered to be NIMP and will not be provided by Novo Nordisk.

6.5 Premature discontinuation of trial product

All efforts should be made to keep the subject on trial product.

However, if necessary for safety concerns related to trial product, or unacceptable intolerability, as judged by the investigator, treatment with trial product must be discontinued (i.e. a treatment discontinuation call must be made in the interactive web response system (IWRS)) and in these cases trial product should not be re-initiated. In case the trial product is interrupted due to suspicion of acute pancreatitis, please see Section 8.7.1.

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

- pregnancy
- intention of becoming pregnant
- included in the trial in violation of the inclusion and/or exclusion criteria
- participation in another clinical trial with an investigational medicinal product (IMP)
- calcitonin ≥ 100 ng/L

Subjects discontinuing treatment with trial product will not be withdrawn from trial and will be followed as described in Section 8.1.5.

The primary reason for discontinuation of trial product must be specified in the eCRF.

6.6 Withdrawal criteria

This section refers to withdrawal from the trial.

The subject may withdraw at will at any time. The subject's request to withdraw from trial must always be respected.

Subjects who agree to attend or provide health status at the planned V16 should not be considered withdrawn from the trial.

Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule, missing assessments or trial product discontinuation for any reason. Only subjects who decline any further contact with the site in relation to the trial should be considered as withdrawn from the trial.

Subjects who consider withdrawing informed consent should be encouraged to have procedures performed according to the V16A and V17A visits.

See Section 8.1.6 for procedures to be undertaken in case of withdrawal from trial.

A subject included in the trial in violation of the inclusion and/or exclusion criteria must discontinue treatment with trial product, but will not be withdrawn from the trial. The subject will be followed as described in Section 8.1.5.

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 are withdrawn will not be replaced

6.8 Rationale for trial population

Subjects with T2DM inadequately controlled on metformin alone or in combination with SUs will be included in the trial. The eligibility criteria allow for enrolment of a relatively broad trial population. This will ensure that the trial population will resemble the target population in common practice. However, concomitant conditions which could jeopardise the safety of the subjects or compliance with the protocol will preclude subjects from participating (see Section 6.3).

7 Milestones

Planned duration of recruitment period FSFV-LSFV 20 weeks

Planned FSFV: 15-Feb-2016

Planned LSLV: 23-Feb-2018

End of trial is defined as LSLV

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

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

8 Methods and assessments

8.1 Visit procedures

Each subject will attend 16 site visits and 1 phone visit. Subjects who prematurely discontinue trial product will also be asked to attend V16A and V17A, but will not be asked to attend V17.

For visit numbers, timing of site and phone visits and visit windows during the trial period, please refer to the flow chart, Section 2. Planned visits can be re-scheduled within the allowed visit window. It is the responsibility of the investigator to ensure that all site visits occur according to the flow chart.

If a visit is missed and it is not possible to re-schedule, every effort should be made to ensure information is collected at a telephone contact. Subjects will be invited for the next scheduled visit according to the visit schedule.

If a subject is unable or unwilling to attend all subsequent visit(s) the investigator should at least aim to have the subject attend the V8, V12 and the End-of-treatment visit (V16) as these visits should be performed for all subjects (except subjects who withdraw informed consent, see Section 8.1.6).

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

8.1.1 Screening, visit 1

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 in one list.

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

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

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

Once all data relating to visit 1 have been obtained, these must be reviewed, dated and signed by the investigator and/or documented in medical records to assess that the subject is eligible to continue in the trial.

Screening failures: For screening failures the screening failure form in the CRF must be completed with the reason for not continuing in the trial. Serious adverse events (SAEs) from screening failures must be transcribed by the investigator into the CRF. Follow-up of SAEs must be carried out according to Section 12.

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

Re-screening is NOT allowed. However, in case any laboratory samples are not available (e.g. haemolysed/lost), re-sampling is allowed.

8.1.2 Fasting visits

The subjects must attend several visits in a fasting state (see Section 2). Fasting for blood sampling is defined as having consumed only water within the last 8 hours prior to the visit. Trial product must be taken after blood sampling and other oral medication can be taken 30 minutes after trial products.

Glucose lowering agents and trial product should not be taken until after blood sampling has been performed.

If subjects do not attend the visit in a fasting state they must be asked to attend a re-scheduled visit within the visit window to have all planned visit assessments performed. Only AEs should be captured in the eCRF at the original visit.

8.1.3 Randomisation and trial product administration

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

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

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

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

8.1.4 End-of-treatment (visit 16) and Follow-up (visit 17)

Subjects who stay on trial product throughout the trial, must attend the End-of-treatment visit (V16) 78 weeks after randomisation and the Follow-up visit (V17) 5 weeks after the last date on trial product (+3 days visit window). A completion call must be performed in the IWRS after completion of visit 16 (see Section 10).

In case the subject cannot be reached (by clinic visit or phone contact) at the scheduled visit 17 and the subject has consented to it, the site should consult the contacts provided by the subject (e.g. close relatives), relevant physicians, medical records and locator agencies (if allowed according to local law) to collect health status. If no health status can be collected, the subject should be considered lost to follow up.

8.1.5 Premature discontinuation of trial product and Follow-up (visits 16A and 17A)

Subjects who discontinue trial product prematurely should attend visit 16A, scheduled to take place shortly after discontinuation of trial product. Visit 17A should be scheduled 5 weeks (+3 days visit window) after the last date on trial product. A treatment discontinuation session must be performed in the IWRS at visit 16A (see Section 10).

Subjects should continue with the originally scheduled site contacts after visit 17A and up to visit 16. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after V17A. However, as a minimum, these subjects should be asked to attend the scheduled V8 at week 26, V12 at week 52 and End-of-treatment (V16) at week 78.

In case the subject cannot be reached (by clinic visit or phone contact) at the scheduled visit 16 and the subject has consented to it, the site should consult the contacts provided by the subject (e.g. close relatives), relevant physicians, medical records and locator agencies (if allowed according to local law) to collect health status. If no health status can be collected, the subject should be considered lost to follow up.

8.1.6 Withdrawals

If a subject considers withdrawing from the trial, the investigator must aim to undertake procedures similar to those for visit 16A as soon as possible and visit 17A should be scheduled 5 weeks (+3 days visit window) after the last date on trial product, if the subject agrees to it.

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

Although a subject is not obliged to give his/her reason(s) for withdrawing 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.

8.1.7 Investigator assessments

Review of diaries, PROs, laboratory reports, ECGs and fundoscopy/fundus photography must be documented either on the documents and/or in the subject's medical record.

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

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

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

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

The evaluation should be based on investigators judgement.

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

In case of abnormal clinically significant findings found as a result of screening procedures conducted at visit 1 or assessments revealing baseline conditions at visit 2 the investigator must state a comment in the subject's medical record and record this in the medical history/concomitant illness form in the eCRF.

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

8.2 Subject related information

8.2.1 Demography

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

- date of birth or age (according to local regulation)
- sex
- race (according to local regulation)
- ethnicity (according to local regulation)

8.2.2 Tobacco use

Details of smoking status 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.

8.2.3 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (V1) or found as a result of a screening procedure.

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

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

The following must be recorded in the eCRF (at visit 1) on the disease specific forms only i.e. not on the medical history/concomitant illness form:

- **Diabetes history/diabetes complications** (e.g. date of diagnosis, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy)
- **History of cardiovascular disease** (CVD) (e.g. ischaemic heart disease, myocardial infarction, heart failure incl. NYHA class, hypertension, stroke, peripheral arterial disease)
- **History of gallbladder disease** (e.g. gallstone, cholecystitis, cholecystectomy)
- **History of gastrointestinal disease** (e.g. gastroesophageal reflux disease, ulcer disease, chronic gastritis)

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

8.2.4 Concomitant medication

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

Details of any concomitant medication must be recorded at the first visit. For antidiabetic medication, the start date of current dose must be recorded at visit 1. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes
- trade name or generic name
- indication
- start date and stop date or continuation
- total daily dose (only applicable for antidiabetic medication).

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

8.3 Assessments for efficacy

8.3.1 Blood samples

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

Glucose metabolism:
- HbA_{1c}
- FPG

Lipids (fasting see Section 8.1.2):
- Total cholesterol
- LDL-cholesterol
- HDL-cholesterol
- VLDL-cholesterol
- Free fatty acids
- Triglycerides

8.3.2 7 -point self-measured plasma glucose profile

At visit 1, subjects will be provided with a blood glucose meter (BG meter) including lancets, plasma-calibrated test strips and control solutions as well as instructions for use. The subjects will be instructed in how to use the device, the instruction will 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 subject will be instructed to perform a 7-point SMPG profile four times during the trial period (see Section 2) using the BG meter provided for the trial. The 7-point SMPG profile should be performed on a day where the subject does not anticipate unusual strenuous exercise. The 7-point profile should preferably be taken within a week prior to the visit.

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

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

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

8.3.3 Body weight, height and BMI

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

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

BMI will be calculated for the investigators convenience at visit 1 in the eCRF but will not be saved in the clinical database. The equation used in the eCRF is listed below:

BMI kg/m2 = body weight (kg)/(Height (m) x Height (m)) or (kg/m2 = [lb/in2 x 703])

All BMI calculations will subsequently take place in the clinical database using measurements of height and weight according to flowchart 2.

8.3.4 Waist circumference

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

The measurement of waist circumference must be performed and recorded in the eCRF. Waist circumference is measured in the horizontal plane and rounded up or down to the nearest 0.5 cm or 0.2 inches using a non-stretchable measuring tape. The same measuring tape should be used throughout the trial (measuring tape will be provided to the sites).

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

8.3.5 Patient reported outcomes questionnaires

PRO will be assessed using the questionnaires:

- SF-36v2™ (acute version) health survey[37-39]
- IWQoL-Lite Clinical Trial Version[40,41]
- CoEQ[42-45]

The questionnaires must be completed by the subject as specified in the flow chart, see Section 2, preferably before any other trial-related activities for that visit. It takes approximately fifteen minutes to complete the three questionnaires. Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. All results from the PRO questionnaires must be transferred into the eCRF.

The questionnaires SF-36v2™ and IQWoL-Lite Clinical Trial Version are commonly used PRO instruments, also in the T2DM area. The Control of Eating questionnaire has not been developed to be used in clinical trials. However, it has previously been included in clinical trials on an item per item basis, among others in a T2DM population.

All the questionnaires will be translated to local language before being handed out to the subjects participating in the trial.

SF-36 acute version

SF-36v2™ acute version measures the individual overall health related quality of life on 8 domains; Physical functioning, Role functioning, Bodily pain, General health, Vitality, Social functioning,

Role emotional and Mental health. The acute version's questions are based on a recall period of one week. SF-36v2™ contains 36 items.

Impact of Weight on Quality of Life questionnaire (IWQoL-Lite) Clinical Trial Version

The IWQoL-Lite for Clinical Trials was adapted from the IWQOL-Lite and measures the health related quality of life. The IQWoL- Lite Clinical Trial Version contains 23 items.

Control of Eating Questionnaire (CoEQ)

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

8.4 Assessments for safety

8.4.1 Physical examination

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

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

8.4.2 Vital signs

Systolic and diastolic blood pressure

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

Pulse

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

8.4.3 Eye examination

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

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

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

8.4.4 Electrocardiogram – 12 –lead

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

If the central ECG evaluation of a post-baseline ECG is suggestive of new myocardial infarction (MI), the investigator will be notified and, unless already done, the investigator should report this as AE or SAE at investigator's discretion (see Section 12.1).

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

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

8.4.5 Blood samples

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

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

Biochemistry:
- Alanine aminotransferase (ALT)
- Albumin
- Alkaline phosphatase (ALP)
- Amylase
- Aspartate aminotransferase (AST)
- Bilirubin, total
- Calcium, total
- Creatinine
- eGFR per CKD-EPI[32]
- Creatine kinase (CK)
- Lipase
- Potassium
- Sodium
- Urea

Hormones:
- Calcitonin

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

8.4.6 Pregnancy test

Females of childbearing potential will have a urine dip-stick pregnancy test performed at site as specified in Section 2 or as required by local law.

In case a menstrual period is missed or if pregnancy is suspected between the scheduled visits a urine pregnancy test should be performed.

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 a hysterectomy, bilateral oophorectomy or bilateral tubal ligation or who are postmenopausal (i.e. women above the age of

50, who have been without menstrual period for at least 1 year). The basis for non-bearing potential should be documented in medical records.

Contraceptive methods

Female subjects of childbearing potential must ensure using adequate contraceptive methods until 5 weeks after the last date on trial product.

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 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).

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

For Argentina only: Birth control methods will be reimbursed by Novo Nordisk Pharma Argentina S.A.

8.4.7 Antibodies

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

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

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

8.4.8 Hypoglycaemic episodes

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

All PG values:

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

should be reported in the diary according to the instructions below throughout the trial from visit 1 to end of trial.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the SMPG value is > 3.9 mmol/L (70 mg/dL) or symptoms have been resolved in accordance to current guidelines[33].

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

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

The record should include the following information:

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

The answer to the question: "Was subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration[33].

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

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

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)
- Where the treatment was administered (in clinic/emergency room/ hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet changed, medication error (i.e. overdose, mix-up between products), other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[34] (layman term used in the diary is specified in brackets if different from the protocol term)?
    - Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
    - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
    - General malaise: headache or malaise (feeling discomfort/unease)
    - Other symptoms?

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

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data [35,36].

The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies low SMPG values not reported as hypoglycaemic episodes.
If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form (SIF) must also be filled in, see Section 12.

8.5 Laboratory assessments

The laboratory analyses will mainly be performed by a central laboratory. Anti-semaglutide antibodies, *in vitro* neutralising effect, IgE anti-semaglutide antibodies and PK samples will be analysed by a special laboratory and Novo Nordisk A/S (see Sections 8.4.7, 8.6.1 and 8.7.2. For some of the analyses described in Section 8.7.1 and 8.7.1 a local laboratory must be used.

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

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

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

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

The central laboratory will provide laboratory results to the investigator on an on-going basis and the investigator must review all laboratory results for signs of concomitant illness and AEs and report these according to Section 8.7 and 12). However, anti-semaglutide antibody and semaglutide plasma concentration results will not be available to the investigator during the trial. These results will be provided to the investigator upon request after the completion of the clinical trial report (CTR).

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

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator.

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

All laboratory samples will be destroyed at the latest at the completion of the CTR, except samples obtained for anti-semaglutide antibody analysis. Antibody samples may be retained until drug approval by FDA and/or European Medicines Agency (EMA). The retained antibody samples may be used for further characterisation of antibody responses towards drug if required by health authorities or for safety reasons, see Section 24.2.

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

8.5.1 Fasting plasma glucose

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

Low FPGs reported by a laboratory in connection to trial related visits, i.e. FPG results ≤ 3.9 mmol/L (70 mg/dL), should not be reported as hypoglycaemic episodes but as an AE (e.g. a FPG result of 2.9 mmol/L (52 mg/dL) should be reported as "low plasma glucose of 2.9 mmol/L (52 mg/dL)"). See Section 12 for reporting of AEs.

8.6 Other assessments

8.6.1 Pharmacokinetics

The blood samples for the population PK will be drawn in a sub population for bioanalysis of semaglutide plasma concentrations (see Section 2). The sub population will include approximately 50% of all randomised subjects and the selection of sites to participate will be done in collaboration with local Novo Nordisk affiliate. The investigator must record the exact date and time for sampling the blood for PK analysis in the eCRF. The date and time of the latest trial product administration prior to the visit must be recorded by the subject in the subject diary and transcribed to the eCRF by the investigator.

8.6.2 Subject diary

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

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

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

- date and time of first trial product administration
- date and time of last trial product administration prior to visits with PK sampling
- hypoglycaemic episodes
- changes in concomitant medication
- AEs
- SMPG 7-point profile

8.7 Additional safety assessments

All AEs must be collected and reported according to the procedures described in Section 12.

8.7.1 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 relief.[46] The pain is often associated with nausea and vomiting. Physical examination usually reveals severe upper abdominal tenderness at times associated with guarding.

In general, both amylase and lipase are elevated during the course of acute pancreatitis. The serum lipase may remain elevated slightly longer than amylase. The level of the serum amylase and/or lipase does not correlate with the severity of acute pancreatitis.[46] In general, serum lipase is thought to be more sensitive and specific than serum amylase in the diagnosis of acute pancreatitis.

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

The diagnosis of acute pancreatitis requires two of the following three features[47]:

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

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

If acute pancreatitis is confirmed, appropriate treatment and careful monitoring of the subject should be initiated. The subject must be discontinued from trial product (treatment discontinuation call), but should remain in the trial (see Section 6.5 and 8.1.5). The event should be reported as an AE requiring additional data collection (see Section 12.1) and Appendix B) and will undergo assessment by the EAC (see Section 12.7.2).

8.7.2 Assessments in case of suspicion of hypersensitivity reactions

In case of suspicion of a severe immediate systemic hypersensitivity reaction[48] to the trial product, the subject must be discontinued from trial product but should remain in the trial (see Section 6.5 and 8.1.5).

To assist in the diagnostic evaluation it is recommended to draw a blood sample for measurement of tryptase (total and/or mature tryptase, local assessment) within 3 hours of onset of the hypersensitivity reaction, and if this is achieved, a tryptase sample should also be drawn at V17A.

Furthermore, a blood sample for assessment of anti-semaglutide IgE antibodies should be drawn as soon as possible after the event and at V17A and sent to central laboratory for analysis. Tryptase concentrations, if available, should be included in the specific event form when reporting the AE.

In case of suspicion of immune complex disease[48], the subject must be discontinued from trial product but should remain in the trial (see Section 6.5 and 8.1.5). It is recommended to draw a blood sample for local assessment of complement levels (C3 and C4) to assist in the diagnostic evaluation. Complement level results should be included in the specific event form when reporting the AE.

The event should be reported as an AE requiring additional data collection (see Section 12.1 and Appendix B).

8.7.3 Assessments in case of increased levels of creatine kinase

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

The event should be reported as an AE requiring additional data collection (see Section 12.1 and Appendix B).

8.7.4 Assessments in case of increased levels of aminotransferases

In case of

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

the event must be reported as an SAE (see Section 12.1).

2. ALT or AST >10x UNL **and** total bilirubin ≤2x UNL,

the event should be reported as an AE requiring additional data collection(see Section 12.1 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 should be gathered to seek a possible cause of the observed laboratory test abnormalities.

8.8 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. Treatment compliance will be assessed by monitoring of drug accountability. Prior to visits where drug accountability is performed the subject will be asked to return all used, partly used and unused trial products and dose packs. The investigator must assess the amount of trial products returned compared to what was dispensed at the last dispensing visit and, in case of discrepancies, question the subject.

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

9 Trial supplies

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

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

9.1 Trial products

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

Table 9–1 Investigational medicinal products

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Semaglutide 3 mg tablet	3 mg	Tablet	Oral	Dose pack[a]
Semaglutide 7 mg tablet	7 mg			
Semaglutide 14 mg tablet	14 mg			
Placebo I tablet	N/A			
Sitagliptin (Januvia®) tablet	100 mg	Tablet	Oral	Dose pack[a]
Placebo II tablet	N/A			

[a]One dose pack contains one blister pack.

Metformin and SU and rescue medication are considered NIMPs and will not be supplied by Novo Nordisk. However, metformin and SU will be reimbursed if required by the country's regulatory authority or IRB/IEC.

[redacted]

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

Oral semaglutide and the corresponding placebo tablets are white to light yellow oval shaped tablets embossed with "M8" on one side. The comparator sitagliptin and the corresponding placebo tablets are beige, round, convex tablets engraved with "277" on one side. For both semaglutide and sitagliptin, respectively, the active drug and the corresponding placebo tablets are identical with regard to visual appearance and all semaglutide tablets are visually identical to each other, irrespective of dose levels.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[49], local regulations and trial requirements.

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

9.3 Storage

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

Table 9–2 Storage conditions for investigational medicinal products

Trial product	Storage conditions (not-in-use)	In-use conditions
Semaglutide 3 mg tablet	Do not store above 30ºC (86ºF) Do not freeze Do not refrigerate Store in the original package	Take the tablet immediately after dispensation from blister card Take the tablets whole: Do not break or chew
Semaglutide 7 mg tablet		
Semaglutide 14 mg tablet		
Placebo I tablet		
Sitagliptin (Januvia®) 100 mg tablet	Do not store above 30ºC (86ºF) Do not freeze Do not refrigerate Store in the original package	Must not be used if tablets appear damaged, if the blister pack is broken or unsealed before use
Placebo II 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. outside temperature range).

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

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

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator.

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

Returned trial product (used/partly used or unused including empty packaging material) can be stored at room temperature and must be stored separately from non-allocated trial product.

Drug accountability is performed by using the IWRS. Only dispensed DUNs returned by the subject (used/partly used or unused) are accounted for. Drug accountability should be done on tablet level.

Destruction will be done according to local procedures after accountability is finalised and verified by the monitor. Destruction of products must be documented and recorded in IWRS including destruction confirmation.

9.5 Auxiliary supplies

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

- BG meters and BG meter auxiliaries

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

10 Interactive web response system

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

IWRS is used for:

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

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

11 Randomisation procedure and breaking of blinded codes

The trial is a double-blinded trial. A randomisation session will be carried out for all subjects using IWRS.

At the randomisation visit (visit 2) subjects meeting all eligibility criteria will be randomised to one of four parallel treatment arms as described in Section 5.1.

11.1 Breaking of blinded codes

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

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

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

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

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

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

- Pre-existing conditions, including those found as a result of screening 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.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see Section 8.4.8.

The following three definitions are used when assessing an AE:

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

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

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

Serious adverse event

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

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

[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 dyscrasiasis or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Trial specific serious adverse event

The following laboratory abnormalities must be reported as an SAE:

- ALT or AST >3x UNL **and** total bilirubin >2x UNL

Additional assessments should be made for events meeting the above criterion (see Section 8.7.4).

Non-serious adverse event

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

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). The AEs requiring additional data collection are:

- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or transient ischaemic attack (TIA))
- Heart failure requiring hospitalisation
- Pancreatitis
- Neoplasm (excluding thyroid neoplasm)
- Thyroid disease (including thyroid neoplasm)
- Renal event
- Hypersensitivity reactions
- Acute gallstone disease
- Medication error (concerning trial products):
    - Administration of wrong drug.
      Note: Use of wrong DUN is not considered a medication error.
    - Wrong route of administration.
    - Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
    - Accidental administration of a higher dose than intended. A higher dose is a dose of at least one tablet more than the intended dose; however the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.
- Lactic acidosis
- Creatine kinase (CK) > 10x UNL
- Hepatotoxicity events:
    - ALT or AST > 10x UNL and total bilirubin ≤ 2x UNL
    - Hepatotoxicity leading to trial product discontinuation

Technical complaint

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

Examples of technical complaints:

- The physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- The packaging material (e.g. cracks or errors in labelling text)

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (V17) for subjects on trial product OR until the end of trial (V16 or V17A, whichever comes last) for the subjects who have discontinued trial product prematurely. The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

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

All AEs, either observed by the investigator or subject, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents:

- IB for Oral administration of semaglutide (NN9924), edition 6[23] and any updates hereof.
- Summary of Product Characteristics (SmPC) for Januvia® (sitagliptin)[50] and any updates hereof.

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

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

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

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

Some events will undergo event adjudication by the Event Adjudication Committee (EAC), please refer to Section 12.7.2. For AEs qualifying for event adjudication, 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.

For an overview of AEs requiring additional data collection and AEs that will undergo event adjudication, please see Table 12–1.

Table 12–1 Overview of AEs requiring additional data collection and AEs subject to event adjudication

Event	AEs requiring additional data collection	Event adjudication
Death	No	Yes
Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)	Yes	Yes
Cerebrovascular event (stroke or transient ischaemic attack)	Yes	Yes
Heart failure requiring hospitalisation	Yes	Yes
Pancreatitis	Yes	Yes (only if acute pancreatitis)
Neoplasm (excluding thyroid neoplasm)	Yes	Yes (only if malignant)
Thyroid disease (including thyroid neoplasm)	Yes	Yes (only if malignant thyroid neoplasm or C-cell hyperplasia)
Renal event	Yes	Yes (only if acute kidney injury)
Hypersensitivity reactions	Yes	No
Acute gallstone disease	Yes	No
Medication error	Yes	No
Lactic acidosis	Yes	Yes
Creatine kinase (CK) > 10x UNL	Yes	No
Hepatotoxicity events	Yes	No

Timelines for initial reporting of AEs:

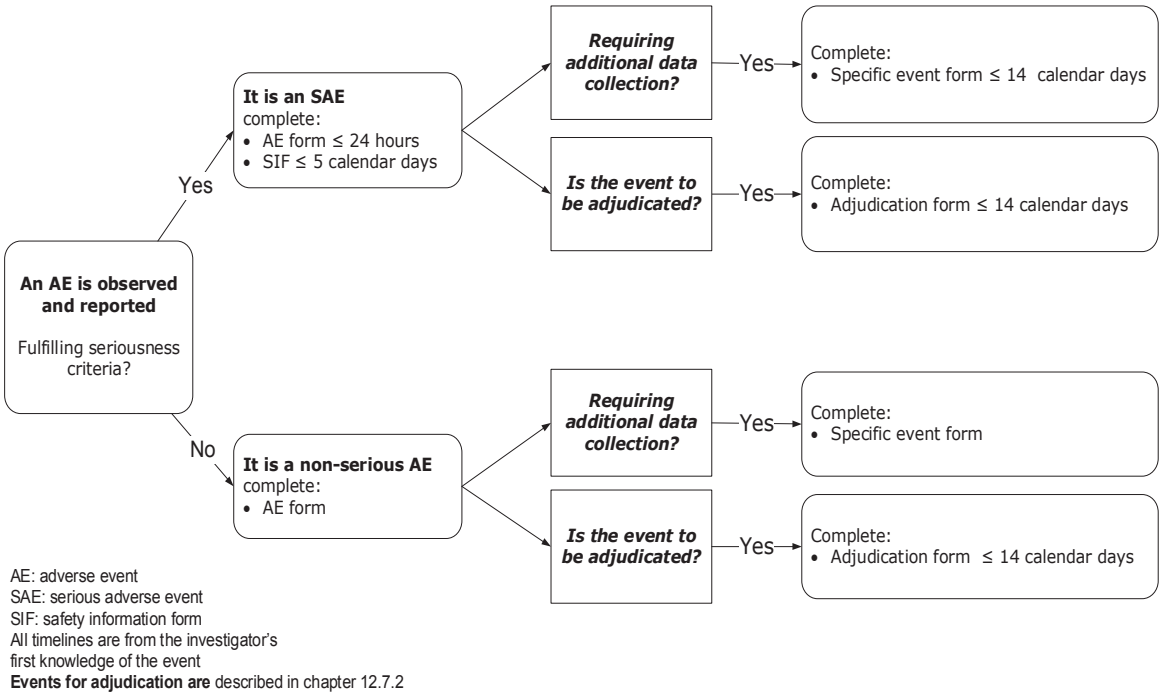
The investigator must complete the following forms in the eCRF within the specified timelines:

- **SAEs**: The AE form **within 24 hours** and the SIF **within 5 calendar** days of the investigator's first knowledge of the SAE.
  Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.
- **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:** Specific Event Adjudication Form must be completed **within 14 calendar days**. 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.

The AE form for a non-serious AE should be signed when the event is resolved or at the end of the trial.

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



AE: adverse event
SAE: serious adverse event
SIF: safety information form
All timelines are from the investigator's first knowledge of the event
Events for adjudication are described in chapter 12.7.2

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 GCP.[1] In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including 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 GCP[1], unless locally this is an obligation of the investigator.

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 SIF. Novo Nordisk may need to report this AE to relevant regulatory authorities.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the medical records and the forms in the eCRF.
Follow up information must be reported to Novo Nordisk according to the following:

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

  The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.
- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

The investigator must ensure that the 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/7 mg/14 mg or placebo I tablets
- Sitagliptin 100 mg or placebo II 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 print or 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 in female subjects

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

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

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

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

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

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

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

Reporting of AE information

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

Forms and timelines for reporting AEs:

Non-serious AEs:

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

SAEs:

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

* It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or newborn infant.

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

12.6 Precautions and/or overdose

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

There is a potential risk of hypoglycaemia during dosing with semaglutide. The typical signs and symptoms of a non-severe hypoglycaemia (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 [redacted] mg oral semaglutide once daily. The subject accidentally took the trial product [redacted]. 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 classified as moderate in severity and considered to be probably related to semaglutide 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] the subject wished to continue in the trial. PG levels, blood pressure and pulse were monitored during the following [redacted] days and no symptoms of hypoglycaemia or any other symptoms or signs were noted. The subject was withdrawn from the trial after [redacted] days of treatment due to an AE (diarrhoea).

For further details please see the current edition of the IB for Oral administration of semaglutide (NN9924), edition 6[23], and any updates hereof.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal oral semaglutide safety committee to perform ongoing safety surveillance. The oral semaglutide safety committee may recommend unblinding of any data for further analysis and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

12.7.2 Event adjudication committee

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

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

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

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

The events outlined in Table 12–2 have been selected for adjudication in order to obtain an external independent validation of the diagnosis. In addition, cardiovascular events are being adjudicated according to FDA requirements[51].

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication packages (e.g. x-ray, ECGs, ultrasound images, discharge summaries, pathology

reports and death certificates). The investigator must provide medical documentation as soon as possible, when they receive the request from Novo Nordisk or the event adjudication vendor.

The 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.

The following AEs will be adjudicated in this trial:

Table 12–2 Adverse events for adjudication

Events	Description	Adjudication outcome
Death	• All-cause death	• Cardiovascular death (including undetermined cause of death) • Non-Cardiovascular death
Acute Coronary Syndrome	Acute Coronary Syndrome conditions include: • ST-elevation acute myocardial infarction (STEMI) • Non-ST elevation acute myocardial infarction (NSTEMI) • Silent MI • Unstable angina pectoris (UAP)	• Acute myocardial infarction (STEMI or NSTEMI), silent MI • Unstable angina pectoris requiring hospitalisation
Cerebrovascular events	• 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	• Ischaemic stroke • Haemorrhagic stroke • Undetermined stroke • TIA
Heart failure requiring hospitalisation	• Hospitalisation with a primary diagnosis of heart failure (new episode or worsening of existing heart failure)	• Heart failure requiring hospitalisation
Acute pancreatitis	The diagnosis of acute pancreatitis requires two of the following three features: • 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	Acute pancreatitis • Mild • Moderate • Severe
Malignant neoplasm	Malignant neoplasms are defined as • neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or	• Malignant neoplasm

	spread to other parts of the body through the blood and lymph systems Thyroid neoplasms are excluded in this event category	
Thyroid disease, if malignant thyroid neoplasm or C-cell hyperplasia	Malignant thyroid neoplasms are defined as • thyroid neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body through the blood and lymph systems • C-cell hyperplasia, defined as hyperplasia of the parafollicular C-cells of the thyroid gland	• Malignant thyroid neoplasm • C-cell hyperplasia
Acute kidney injury	Acute kidney injury[52] is defined as any of the following (not graded): • Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours, or • Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, or • Urine volume < 0.5 mL/kg/h for 6 hours	• Acute kidney injury
Lactic acidosis	• Lactic acidosis is characterized by increased blood lactate level in association with metabolic acidosis	• Lactic acidosis

All AEs 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.

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 eCRF. This system and support services to the system will be provided by an external supplier.

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

The following will be provided as paper case report forms (CRF):

- Pregnancy forms

In addition paper AE forms and paper SIFs will be provided. These must be used when access to the eCRF is revoked or if the eCRF is unavailable. The paper technical complaint form must also be used for complaints that are not subject specific.

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

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

13.1 Corrections to case report forms

Corrections to the 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.

13.2 Case report form flow

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

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

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

14 Monitoring procedures

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 CRFs, 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 active subjects (defined as 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).

All data must be verifiable in source documentation other than the CRF (BMI and age are not source data verified as they are calculated in EDC).

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

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

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

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

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

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

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

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

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to another data management unit within Novo Nordisk or an external Contract Research Organisation.

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

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

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

16 Computerised systems

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

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

17 Statistical considerations

General considerations

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 data will be performed before the database is locked.

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

Data from all sites will be analysed and reported together.

In statistical analyses where stratification is included, the two combinations (metformin; metformin+SU) will be included based on the actual information collected through the eCRF. In case of missing eCRF information the information collected from IWRS system will be used.

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

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

The primary and confirmatory efficacy endpoints will be confirmed at week 26. This approach will result in a lower proportion of missing data compared to the expected proportion of missing data at week 52 and week 78 and therefore a more reliable estimate of efficacy.

Results from a statistical analysis will as a minimum be presented by the estimated treatment contrasts for the below three comparisons at week 26, week 52 and week 78 with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference:

- oral semaglutide 14 mg vs. sitagliptin 100 mg
- oral semaglutide 7 mg vs. sitagliptin 100 mg
- oral semaglutide 3 mg vs. sitagliptin 100 mg

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

Primary and secondary estimands

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

- Primary estimand
    - de-facto treatment difference at week 26 for all randomised subjects
- Secondary estimand
    - de-jure treatment difference at week 26 for all randomised subjects if all subjects adhered to treatment and did not initiate rescue medication

The primary de-facto estimand assesses the average effect in a future population that results from initiating treatment with oral semaglutide including potential rescue medication(s) as compared to initiating treatment with sitagliptin 100 mg including potential rescue medication(s). Generalisation of this estimand depends among other things on the extent to which the use of rescue medication and treatment adherence in this trial reflects clinical practice. All post-baseline scheduled visit data will be included in the analysis, including data collected after discontinuation of trial product or initiation of rescue medication(s).

The secondary de-jure estimand assesses the glycaemic benefit a future subject is expected to achieve if initiating and continuing treatment with oral semaglutide as compared to sitagliptin 100 mg. It is considered a clinically relevant estimand as it provides information to treating clinicians about the expected glycaemic efficacy of oral semaglutide compared to sitagliptin 100 mg for purposes of treating individual subjects. Generalisation of this estimand depends among other things on the extent to which the compliance to trial product administration in this trial reflects clinical practice. Only post-baseline scheduled visit data collected prior to discontinuation of trial product or initiation of rescue medication will be included in the analysis. This will avoid confounding from rescue medication.

Missing data considerations at week 26

The proportion of missing data i.e. data that do not exist even though subjects are intended to stay in the trial regardless of treatment status and initiation of rescue medication(s), when estimating the primary estimand , is expected to be maximum 10% based on the oral semaglutide phase 2 trial (NN9924-3790). Thus, missing data will be due to withdrawal from trial or lost to follow-up.

The proportion of missing data when estimating the secondary estimand is expected to be higher (20%) since data collected after discontinuation of trial product or initiation of rescue medication(s) will be set to missing. The 20% of missing data is based on the sitagliptin phase 3 trials[50] the oral semaglutide phase 2 trial (NN9924-3790) and the indication that a low starting dose with gradual dose escalation diminishes GI AEs compared with more aggressive dosing regimens. Across treatment arms the main reasons for missing data are expected to be early treatment discontinuation due to GI AEs and eventually initiation of rescue medication. Initiation of rescue medication is expected to be more frequent in the sitagliptin 100 mg arm and in the oral semaglutide 3 mg arm

than for the two highest dose levels of oral semaglutide. A higher proportion of subjects are expected to discontinue treatment due to AEs in the oral semaglutide 14 mg arm, compared to the other treatment arms. So overall the frequency of missing data is expected to be similar across treatment arms.

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

17.1 Sample size calculation

The primary endpoint is change from baseline to week 26 in HbA_{1c}. For HbA_{1c} both non-inferiority and superiority versus sitagliptin 100 mg are planned to be tested at each dose level. The confirmatory secondary endpoint is change from baseline to week 26 in body weight (kg). For body weight, superiority versus sitagliptin 100 mg is planned to be tested at each dose level. The sample size calculation is based on jointly meeting the below three out of the nine pre-specified confirmatory hypotheses shown in Figure 17–1. The closed testing procedure described in Bretz et al 2011[53] is used to control the overall type-1 error at a nominal two-sided 5% level. The three hypotheses are

- HbA_{1c} superiority of oral semaglutide 14 mg vs. sitagliptin 100 mg
- HbA_{1c} superiority of oral semaglutide 7 mg vs. sitagliptin 100 mg
- HbA_{1c} non-inferiority of oral semaglutide 3 mg vs. sitagliptin 100 mg (margin 0.3%)

The statistical testing strategy is based on the following two principles:

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

The sample size is calculated using the calcPower function in the R package, gMCP[54] using 10000 simulations. All of the nine pre-specified confirmatory tests are assumed to be independent. Since positive correlations among the tests are expected, the assumption of independence is viewed as conservative.

The sample size assumptions for treatment effects (TE), adjusted treatment effects and the common standard deviation (SD) used across dose levels are given in Table 17–1. These are based on the oral semaglutide phase 2 results (NN9924-3790), sitagliptin phase 3a trial results[50] and supported by results from the s.c. semaglutide phase 2 trial (NN9535-1821).

Since the equalising effect of rescue medication will be included in the primary analysis as well as a conservative approach for handling of missing data will be performed, an adjustment in treatment effect will be implemented for the 10% of subjects who discontinue trial product or initiate rescue medication and for the 10% of subjects with missing data. The treatment effects used in the sample

size calculation will be adjusted according to a 75% smaller effect in these subjects. In addition, the non-inferiority margin of 0.3 % for HbA_{1c} is used, when testing for non-inferiority. The adjusted treatment effects for testing non-inferiority (HbA_{1c} only) and superiority are as described below:

- Non-inferiority
    - 0.8*TE + 0.2*TE*0.25 + non-inferiority margin*0.1
- Superiority
    - 0.8*TE + 0.2*TE*0.25

Table 17–1 Assumptions for sample size calculation

Semaglutide vs. sitagliptin	HbA_{1c}			Body weight		
Treatment dose	14 mg	7 mg	3 mg	14 mg	7 mg	3 mg
Treatment effect (TE)	-0.5%	-0.3%	-0.1%	-3.0 kg	-2.0 kg	-1.0 kg
Adjusted TE, non-inferiority	-0.395%	-0.225%	-0.055%	-2.52 kg	-1.67 kg	-0.82 kg
Adjusted TE, superiority	-0.425%	-0.255%	-0.085%	-2.55 kg	-1.70 %	-0.85%
Standard deviation	1.1%	1.1%	1.1%	4.0 kg	4.0 kg	4.0 kg

With the above assumptions, allocating 465 subjects to each of the semaglutide treatment arms and sitagliptin 100 mg provides 90 % power to jointly confirm HbA_{1c} superiority of semaglutide 14 mg vs. sitagliptin 100 mg, HbA_{1c} superiority of semaglutide 7 mg vs. sitagliptin 100 mg and HbA_{1c} non-inferiority of semaglutide 3 mg vs. sitagliptin 100 mg. Calculated powers for selected individual hypotheses are presented in Table 17–2. In total 4×465 = 1860 subjects are planned to be randomised.

Table 17–2 Powers for individual hypotheses

Statistical test	HbA_{1c} superiority			Body weight superiority			HbA_{1c} non-inferiority (margin = 0.3 %)
Treatment dose	14 mg	7 mg	3 mg	14 mg	7 mg	3 mg	3 mg
Power (%)	> 99	90	19	> 99	> 99	89	> 99

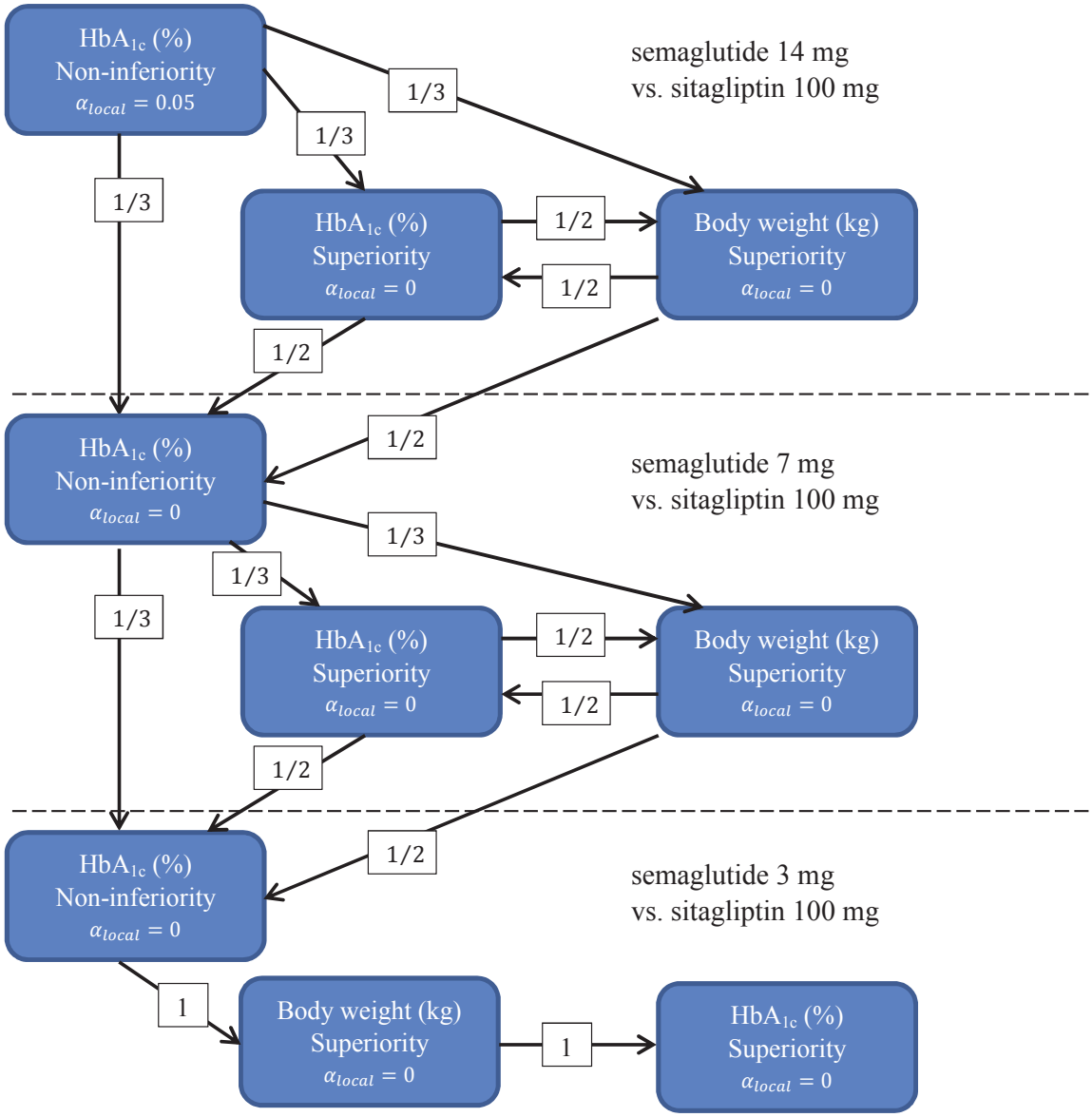


Figure 17–1 Graphical illustration of the closed testing procedure

The overall significance level of α = 0.05 (two-sided) is initially allocated to the HbA_{1c} non-inferiority test of semaglutide 14 mg vs. sitagliptin 100 mg. The local significance level (α-local) will be reallocated if a hypothesis is confirmed according to the weight given by the directed edges between nodes (hypotheses).

17.2 Definition of analysis sets

The following analysis sets will be defined:
Full analysis set (FAS): includes all randomised subjects. Subjects in the FAS will contribute to evaluation "as randomised".

Safety analysis set (SAS): includes all subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation based on the trial product received for the majority of the period where they were on treatment. This will be referred to as contributing to the evaluation "as treated".

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

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

Subjects in the PP analysis set will contribute to the analysis "as treated".

Before data are locked for statistical analysis and the randomisation code is broken, a review of all data will take place. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group. Exclusion of data from analyses will be used restrictively and normally no subjects will be excluded from the FAS. If any subjects or observations are to be excluded from the analysis sets or the observation periods defined below, this, together with the reasons for their exclusion, will be documented and signed by those responsible before database lock. A description of these exclusions will be included in the clinical trial report.

Data selections and observation periods
Unless subjects withdraw their informed consent, data collection will continue for the full duration of the trial. The full duration of the trial is defined as

- up to and including the follow-up visit (V17) for subjects on trial product
- the End-of-treatment visit (V16) or the follow-up premature discontinuation visit (V17A), whichever comes last, for subjects who have discontinued trial product prematurely.

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

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

In this trial, three observation periods will be defined, as described below. Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period. For adjudicated events, onset date will be the EAC adjudicated onset date.

Definition of the observation periods:

- **In-trial:** This observation period will include information assessed at or after date of randomisation (as registered in the IWRS system) and up to and including the last direct subject-site contact, which is scheduled to take place 5 weeks (+3 days visit window) after the planned last dose on trial product at a follow-up visit. For subjects who withdraw their informed consent, the in-trial observation period ends at their date of withdrawal. If a subject is lost to follow-up, the end of the in-trial period is defined as the date of the last subject-investigator contact (site or phone visit). In the case 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. This observation period will be the primary observation period for estimating the primary estimand used for evaluating safety.
- **On-treatment:** This observation period is a subset of the in-trial observation period and represents the time period in which a subject is considered exposed to trial product. For adjudicated events, ECGs, anti-semaglutide antibodies and AEs including hypoglycaemic episodes information collected on or after the first date of trial product up to and including the first date of (i) the follow-up visit V17, (ii) the follow-up prematurely discontinuation visit V17A, (iii) the last date on trial product +38 days or (iv) the end-date for the in-trial observation period will be used. 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. For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) information collected on or after the first date of trial product up to and including the last date on trial product +3 days will be used in order to ensure specificity to reversible effects of treatment. The end-date for all assessments in the on-treatment observation period will be before or the same date as the end-date for the in-trial observation period. This observation period will be considered supportive for evaluating efficacy and used for evaluating safety.
- **On-treatment without rescue medication:** This observation period is a subset of the on-treatment observation period. To avoid potential confounding from rescue medications, information that is collected after initiation of rescue medication will be excluded from this observation period. Specifically, it includes information collected at or after date of first dose on trial product up to and including the first date of; (i) last date on trial product +3 days or (ii) initiation of rescue medication. Thus, an ascertainment window of 3 days for subjects not initiating rescue medication. This observation period will be the primary observation period for estimating the secondary estimand.

17.3 Primary endpoint

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

17.3.1 Primary analysis for the primary estimand

The primary estimand will be estimated based on the FAS using week 26 measurements from the in-trial observation period. The primary statistical analysis will be a pattern mixture model using multiple imputation to handle missing data assuming that the missing data mechanism is missing at random (MAR). Imputation of missing data at week 26 will be done within 16 groups of subjects defined by randomised treatment arm, stratification factor and whether subjects at week 26; (i) have discontinued treatment or initiated rescue medication or (ii) still on treatment and have not initiated rescue medication. It is hereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who at week 26 are similar in terms of randomised treatment arm and treatment adherence/rescue status.

Missing values for each group will be imputed as follows:

- An analysis of covariance (ANCOVA) with region as a categorical fixed effect and baseline HbA_{1c} measurement as a covariate will be fitted to observed values of the change from baseline in HbA_{1c} at week 26.
- The estimated parameters for location and dispersion will be used to impute 100 values for each subject with missing week 26 data based on region and baseline HbA_{1c}. Thus, 100 complete data sets will be generated including observed and imputed values.

Analysis used for confirming superiority versus sitagliptin at week 26:
For each of the 100 (now complete) imputed data sets the change from baseline to week 26 will be analysed using an ANCOVA with treatment, stratification factor and region as categorical fixed effects and baseline HbA_{1c} as covariate. The results obtained from analysing the datasets will be combined using Rubin's rule[55] to draw inference.

From this analysis the estimated treatment differences between each of the oral semaglutide dose levels and sitagliptin 100 mg together with associated two-sided 95 % CIs and unadjusted two-sided p-values for testing no difference from zero will be presented.

Analysis used for confirming non-inferiority versus sitagliptin at week 26:
Prior to analysing the data using the same model and approach as used for confirming superiority (see above) a value of 0.3 % (the non-inferiority margin) will be added to imputed values at week 26 for the oral semaglutide treatment arms only (Koch 2008)[56]. For evaluating non-inferiority versus sitagliptin 100 mg unadjusted two sided p-values for testing no difference from the non-inferiority margin will be presented.

17.3.2 Primary analysis for the secondary estimand

The secondary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 26 from the on-treatment without rescue observation period. The primary analysis for the secondary estimand will be a Mixed Model for Repeated Measurements (MMRM). A restricted maximum likelihood (REML) will be used. The model will include all post baseline HbA_{1c} measurements collected at scheduled visits up to and including week 26 as dependent variables. The independent effects included in the model will be treatment, stratification factor and region as categorical fixed effects and baseline HbA_{1c} as a covariate, all nested within visit. An unstructured covariance matrix for HbA_{1c} measurements within the same subject will be employed, assuming measurements from different subjects are independent. For subjects who have no post-baseline scheduled assessments available, the baseline value will be carried forward to the first scheduled visit to ensure that all randomised subjects will contribute to the statistical analysis.

The MMRM is a well-established method that accounts for the uncertainty pertaining to missing data. This analysis assumes that the missing data mechanism is MAR. Under this assumption the statistical behaviour of the missing data (given the observed responses and model fixed effects and covariates) is assumed to be same as the observed data. Even if the assumption of MAR is not satisfied, this analysis is not expected to bias the estimated HbA_{1c} treatment effect for the secondary estimand in favour of oral semaglutide to any important degree. This is supported by the oral semaglutide phase 2 results (NN9924-3790) that showed that subjects who discontinue oral semaglutide do not have better outcome on average than those who remain on treatment.

Primary hypotheses

For the primary HbA_{1c} endpoint the following two confirmatory one-sided hypotheses are planned to be tested at each dose level of oral semaglutide versus sitagliptin 100 mg. Let the mean treatment difference be defined as μ = (oral semaglutide minus sitagliptin 100 mg):

- Non-inferiority, using a non-inferiority margin of 0.3 %
    - H_0: $\mu \geq 0.3$ % against Ha: $\mu < 0.3$ %
- Superiority
    - H_0: $\mu \geq 0.0$ % against Ha: $\mu < 0.0$ %

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

Multiplicity and criteria for confirming hypotheses

The Type-I error for testing the nine confirmatory hypotheses related to the HbA_{1c} and body weight endpoints (see Section 17.1) will be preserved in the strong sense at 5 % (two-sided) using the weighted Bonferroni-based closed testing procedure described in Bretz et al 2011[53] and outlined in Figure 17–1. The first hypothesis to be tested is non-inferiority of HbA_{1c} at the highest dose level. It will be tested at the overall significance level (5 %) while allocating 0 % local significance level to the remaining of the hypotheses. For this hypothesis, and in general, if a hypothesis is confirmed the

significance level will be reallocated according to the weight and the direction of the edges going from the confirmed hypothesis to the next hypotheses as specified in Figure 17–1. Each of the following hypotheses will be tested at their local significance level (α-local). This process will be repeated until no further hypotheses can be confirmed.

Non-inferiority and/or superiority will be considered confirmed if the mean treatment difference is supporting the corresponding alternative hypothesis and the two-sided p-value from the primary analysis of the primary estimand is strictly below its local two-sided significance level as defined by the closed testing procedure in Figure 17–1. This is equivalent to using a one-sided p-value (nominal alpha = 0.025) and a one-sided 2.5 % overall significance level in the closed testing procedure.

17.3.3 Sensitivity analyses

To investigate the sensitivity of the primary analysis results, complementary and separate analyses will be performed for the primary and secondary estimand. In line with EMA recommendations[57] and with a report from the US National Research Council[58], these analysis will primary evaluate the sensitivity of the results due to the impact of missing data. Since conservatism, i.e. avoiding bias in favour of semaglutide, depends on the context, separate sensitivity analyses will be made for non-inferiority and superiority testing.

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

Sensitivity analyses for the primary estimand

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

- A comparator multiple imputation analysis based on FAS using the in-trial observation period (superiority).
- A comparator multiple imputation analysis based on FAS using the on-treatment observation period (superiority). This sensitivity analysis aims to compare oral semaglutide versus sitagliptin 100 mg for subjects who adhere to treatment regardless of whether or not rescue medication has been initiated.
- A comparator multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely based on FAS using the in-trial observation period (superiority).
- A tipping-point multiple imputation analysis based on FAS using the in-trial observation period (non-inferiority and superiority).
- A MMRM analysis (the primary for the secondary estimand) based on FAS using the in-trial observation period (non-inferiority and superiority).

Sensitivity analyses for the secondary estimand

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

- A comparator multiple imputation analysis based on FAS using the on-treatment without rescue medication observation period (superiority).
- A comparator multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely based on FAS using the on-treatment without rescue medication observation period (superiority).
- A tipping-point multiple imputation analysis based on FAS using the on-treatment without rescue medication observation period (non-inferiority and superiority).

17.3.3.1 Pattern mixture models

Common for the three pattern mixture model sensitivity analyses is that they all aim to stress-test the primary HbA_{1c} results by changing the assumptions for part or all missing data in the oral semaglutide treatment arms, while maintaining the missing data assumption for the sitagliptin 100 mg arm. The analyses will all be implemented using multiple imputation as described for the primary analysis of the primary estimand:

- *Comparator multiple imputation analysis:* In this sensitivity analysis missing data at week 26 for all subjects will be imputed to resemble in distribution the week 26 values observed in the sitagliptin 100 mg treatment arm. In effect this imputation approach removes the treatment difference between oral semaglutide and sitagliptin 100 mg for all subjects randomised to oral semaglutide, given that oral semaglutide is better than sitagliptin 100 mg. Due to the potential lack of sensitivity for testing non-inferiority this sensitivity analysis will only be used to evaluate the robustness of HbA_{1c} superiority conclusions.
- *Comparator multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely:* In this sensitivity analysis missing data at week 26 for subjects who discontinue oral semaglutide treatment due to treatment related AE(s) will be imputed to resemble in distribution the week 26 values observed in the sitagliptin 100 mg treatment arm. Treatment related AEs are defined as AEs classified as possible or probable related to trial product as reported by the investigator. In effect this imputation approach removes the treatment difference between oral semaglutide and sitagliptin 100 mg for this selected group of subjects randomised to oral semaglutide. This sensitivity analysis is less conservative as compared to the first sensitivity analysis. Due to the potential lack of sensitivity for testing non-inferiority this sensitivity analysis will only be used to evaluate the robustness of HbA_{1c} superiority conclusions.
- *Tipping-point multiple imputation analysis:* In this sensitivity analysis, missing data will first be imputed according to the primary analysis. Second, for all oral semaglutide treatment arms a penalty will be added to the imputed values at week 26. The approach is to gradually increase this penalty until all confirmed HbA_{1c} conclusions from the primary analysis are reversed. For each hypothesis tested the specific value of the penalty that reverses the conclusion will be used

to evaluate the robustness of the primary analysis results. This sensitivity analysis will be used for evaluating the robustness of the HbA_{1c} non-inferiority and superiority conclusions.

17.3.3.2 Other sensitivity analysis

The following additional sensitivity analysis will be specified

- *Per-protocol analysis*: This sensitivity will be based on the per-protocol analysis set. Data from the in-trial observation period will be analysed using the primary analysis approach for the primary estimand. This sensitivity analysis will be used to evaluate the robustness of the HbA_{1c} non-inferiority conclusions.
- *Complete case analysis:* This sensitivity analysis will be based on the on-treatment without rescue medication observation period and include subjects in the FAS who have a valid HbA_{1c} measurement at week 26. The change from baseline to week 26 in HbA_{1c} will be analysed by a linear normal model (ANCOVA) with treatment, stratification factor and region as categorical fixed effects and baseline HbA_{1c} as a covariate. This sensitivity analysis will be used to evaluate the robustness of the HbA_{1c} non-inferiority conclusions.
- *Last observation carried forward (LOCF) analysis:* This sensitivity analysis will be based on the FAS using the on-treatment without rescue medication observation period. The change from baseline to week 26 in HbA_{1c} will be analysed by a linear normal model (ANCOVA) with treatment, stratification factor and region as categorical fixed effects and baseline HbA_{1c} as a covariate. This sensitivity analysis will be used for evaluating the robustness of the HbA_{1c} non-inferiority and superiority conclusions.

17.3.3.3 Assessment of sensitivity analyses

The results from the sensitivity analyses will be collectively used to interpret the robustness of the trial results for HbA_{1c} and body weight. Due to the large number of sensitivity analyses and their inherent conservative nature, it will not be a requirement that all confirmatory hypotheses are consistently confirmed across the sensitivity analyses. Thus, no absolute success criteria will be pre-defined for each sensitivity analysis. The sensitivity results in totality will be used to substantiate the credibility of the trial results.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoints

Change from baseline to week 26 in body weight (kg) will be a confirmatory secondary endpoint.

The primary and secondary estimands will be estimated using the same approaches as described for the primary HbA_{1c} endpoint. Body weight will only be tested for superiority. Baseline body weight will be used as a covariate instead of baseline HbA_{1c} in both the imputation and analysis model.

From the analyses the three estimated treatment differences between each of the oral semaglutide dose levels and sitagliptin 100 mg will be presented together with associated two-sided 95 % CIs and unadjusted two-sided p-values for testing no difference from zero.

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

Sensitivity analyses similar to the ones pre-specified for testing superiority for the primary HbA_{1c} endpoint will be made to evaluate the robustness of the body weight results.

17.4.2 Supportive secondary endpoints

17.4.2.1 Efficacy endpoints

The below supportive secondary efficacy endpoints will be evaluated for

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

Continuous efficacy endpoints

Change from baseline to week 52 and 78 in:

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

Change from baseline to week 26, 52 and 78 in:

- Body weight (%)
- FPG
- BMI
- Waist circumference
- Fasting lipid profiles (total cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol, triglycerides, free fatty acids)

Change from baseline to week 26, 52 and 78 in the below derived endpoints from the 7-point profile:

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

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

endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

For evaluation of the primary estimand the analysis will be performed separately for week 26, 52 and 78. For the analysis at week 52 and at week 78, the imputation of missing data will be further differentiated by whether subjects have discontinued trial product or initiated rescue medication prior to week 26 or at or after week 26. This will result in imputation of missing data within 32 groups of subjects instead of the 16 groups as described for the week 26 evaluation in Section 17.3.1. The frequency of missing data is expected to be slightly larger at week 52 and week 78 compared to week 26. The rate of missing data is expected to decline over time.

For evaluation of the secondary estimand the MMRM based primary analysis will include all scheduled post-baseline measurement up to and including week 78. From this model the estimated treatment differences (ratios) will be presented at week 26 (except for HbA_{1c} and body weight), 52 and 78 with 95 % confidence intervals and two-sided p-values for test of no difference.

Binary efficacy endpoints
Subjects who after 26 weeks of treatment achieve (yes/no):

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

The above eight endpoints will be evaluated after week 52 and after week 78 as well.

Handling of missing data for the response status of the above categorical endpoints will be determined from the imputed continuous responses. A total of 100 imputed data sets will be created based on the same models as used to analyse HbA_{1c} and body weight. For the secondary estimand the MMRM based analysis will be implemented in a MI setting. The imputed complete data sets will be analysed using a logistic regression model with treatment, stratification factor and region as categorical fixed effects and baseline response as covariate (i.e. baseline HbA_{1c} for binary HbA_{1c} endpoints, baseline weight for binary weight endpoints and both baseline HbA_{1c} and body weight for the binary endpoint that combines both parameters). Inference comparing treatments will be drawn using Rubin's rule[55].

Time to event endpoint

- Time to rescue medication

Subjects completing the study without need for rescue medication will be censored at the time point of actual date of last trial product. Start time is date of first trial product. Time to rescue medication will be described and compared for each of the oral semaglutide dose level versus sitagliptin 100 mg using likelihood ratio tests obtained from a proportional Cox hazards model. From this analysis the estimated Hazard ratios between each dose levels and sitagliptin will be presented together with 95 % confidence intervals and two-sided p-values for test of no difference. This endpoint will be evaluated after week 26, after week 52 and after week 78.

17.4.2.2 Safety endpoints

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

Adverse events

- Number of TEAEs during exposure to trial product, assessed up to approximately 83 weeks

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

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

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

Other safety endpoints

Change from baseline to week 78 in:

- Amylase
- Lipase
- Pulse
- Systolic blood pressure
- Diastolic blood pressure

The above safety endpoints will be evaluated using the primary analysis for the primary estimand based on SAS using the in-trial observation period and using the primary analysis for the secondary estimand based on SAS using the on-treatment observation period. Endpoints will be analysed

separately as described above for continuous efficacy endpoints. Results will be presented at week 26, 52 and 78. Amylase and lipase endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

Change from baseline to week 78 in:
- Haematology
- Biochemistry (except for amylase and lipase)
- Calcitonin
- Electrocardiogram (ECG) evaluation
- Physical examination

Occurrence of anti-semaglutide antibodies (positive/negative):
- Anti-semaglutide binding antibodies
- Anti-semaglutide neutralising antibodies
- Anti-semaglutide binding antibodies cross reacting with native GLP-1
- Anti-semaglutide neutralising antibodies cross reacting with native GLP-1

Anti-semaglutide binding antibody levels

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

Pharmacokinetics
Please refer to Section 17.5.

Hypoglycaemia
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 83 weeks
- Treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 83 weeks (yes/no)

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

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

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

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

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

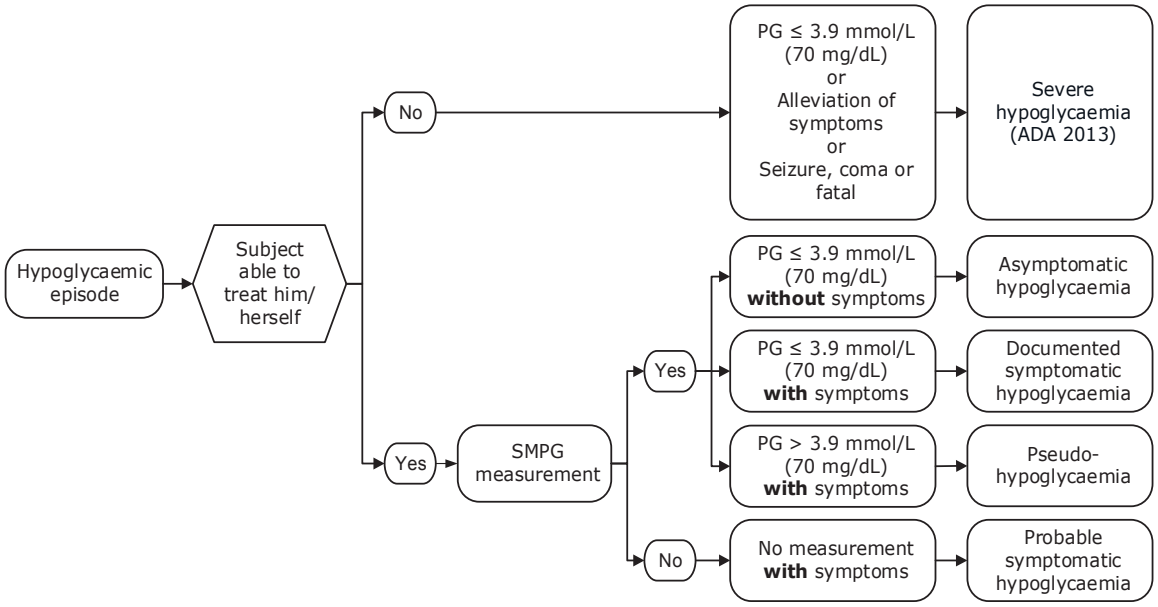
Novo Nordisk classification of hypoglycaemia
In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L (56 mg/dL)[59]. Therefore, Novo Nordisk has included hypoglycaemia with PG levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

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

- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[33] or BG confirmed by a PG value < 3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.

ADA classification[33] of hypoglycaemia

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



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

Figure 17–2 ADA classification of hypoglycaemia

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

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

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

17.5 Pharmacokinetic modelling

Exploratory population PK modelling will be used to evaluate semaglutide exposure and the effects of pre-specified covariates on the exposure. As a minimum, the covariates sex, body weight at

baseline and age at baseline will be explored. The modelling will include data from approximately 50 % of randomised subjects that were exposed to semaglutide in this trial and will be performed as a meta-analysis across phase 3a trials. Actual time points for dose administration and PK sampling will be used. Results will be presented using criteria which will be pre-specified in a modelling analysis plan that is to be finalised before DBL. The modelling will be performed by Quantitative Clinical Pharmacology at Novo Nordisk A/S and will be reported separately from the CTR.

Covariate analysis

Covariates will be tested on CL/F. Covariates for inclusion:

- Body weight
- Age group (< 65, 65-75 and ≥ 75 years)
- Sex (Male/Female)
- Race (White/ Black or African American/ Asian/ Hawaiian or Pacific Islander/ Other)
- Ethnicity (Hispanic or Latino/ not Hispanic or Latino)
- Upper GI comorbidity (Yes/No)

17.6 Health economics and/or patient reported outcomes

PROs

Change from baseline to week 26, 52 and 78 in:

- SF-36v2™ (acute version) health survey: Total score and scores from the 8 domains
- IWQoL-Lite Clinical Trial Version: Total score of the 23 items
- CoEQ: Scores from the 4 domains and scores from 19 individual items

The PRO questionnaires, SF-36v2™, IWQOL and Control of Eating questionnaire will be used to evaluate the objective regarding Quality of Life. The PRO endpoints will be analysed separately as the other continuous efficacy endpoints using a similar model approaches as for the primary endpoint with the associated baseline response as a covariate.

18 Ethics

18.1 Benefit-risk assessment of the trial

18.1.1 Risks and precautions

18.1.1.1 Oral Semaglutide

The non-clinical safety programme of oral semaglutide has not revealed any safety issues precluding use in humans (see Section 3.1.4).

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

Thyroid C-cell tumours

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 guidance for investigators of further evaluation and action on elevated calcitonin concentrations is included in Appendix A. This will ensure appropriate and consistent handling of elevated calcitonin levels.

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, throughout the trial, pregnancy tests will be done at site visits.

Gastrointestinal adverse events

Consistent with findings with other GLP-1 RAs, the most frequently reported AEs in clinical trials with oral semaglutide have been GI disorders (nausea, vomiting, diarrhoea, dyspepsia and constipation). Clinical trials have indicated that a low starting dose with gradual dose escalation diminishes GI AEs compared with more aggressive dosing regimens. Consequently, a low starting dose and gradual dose escalation with 4 weeks between dose-escalation steps have been implemented in the trial in order to mitigate GI side effects.

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 occurs.

Hypoglycaemia

Based on current knowledge about the GLP-1 RA drug class, there is a risk of hypoglycaemic episodes. Hypoglycaemic episodes have mainly been observed when a GLP-1 RA is combined with SU or insulin. The risk for development of hypoglycaemia with oral semaglutide in combination with SU and insulin is unknown due to limited data. In this trial subjects can be on anti-diabetic background medication with SU, but not insulin (however, if rescue medication is needed insulin can be prescribed as add-on to randomised treatment). If a subject on SU develops unacceptable hypoglycaemia the dose of SU can be reduced.

Acute renal impairment

In subjects treated with GLP-1 RAs including oral semaglutide GI AEs such as nausea, vomiting and diarrhoea may lead to significant dehydration and secondary acute renal impairment. Subjects with adverse GI events should be recommended to drink plenty of fluids in order to avoid dehydration. Also serum creatinine and urea will be measured throughout the trial and eGFR will be calculated.

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

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 measured throughout the trial.

General precautions

All subjects will be included after a thorough evaluation in regards to in- and exclusion criteria defined in order to ensure that subjects are eligible for trial treatment. There are also strict glycaemic rescue criteria in place to ensure acceptable glycaemic control during the trial. If rescue medication is required it should be in accordance with ADA/European Association for the Study of

Diabetes[25,26] (excluding GLP-RAs, DPP-4 inhibitors and amylin analogues). It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2014 Standards of Medical Care in Diabetes[60].

18.1.1.2 Sitagliptin

The most commonly reported side effects are upper respiratory tract infection, nasopharyngitis and headache. Also acute pancreatitis, acute renal failure, hypersensitivity reactions and hypoglycaemia have been reported[50].

18.1.2 Benefits

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

Similarly treatment with sitagliptin is expected to provide clinically significant improvements in glycaemic control[50].

In addition, it is expected that all subjects will benefit from participation through close contact with the study site, with close follow-up of their T2DM and a careful medical examination; all of which will most likely result in an intensified management of their T2DM.

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

18.1.3 Risk and benefit conclusion

The safety profile of oral semaglutide generated from the non-clinical and clinical development programme has not revealed any safety issues that would prohibit administration of doses in accordance with the planned clinical trial. The phase 2 results indicate that oral semaglutide will provide clinically significant improvements in glycaemic control and body weight. Sitagliptin is already a marketed drug approved for the use in subjects with T2DM. In conclusion, the potential risk to the subjects in this trial is considered low and acceptable in view of the anticipated benefits oral semaglutide/sitagliptin will provide to subjects with T2DM.

18.2 Informed consent

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

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

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

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

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

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

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

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

18.3 Data handling

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

- Data already collected and data collected at the end-of-trial visit 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.

18.4 Information to subject during trial

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

18.5 Premature termination of the trial and/or trial site

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

If a 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.

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

Only applicable for US trial sites:

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

For Japan only: A seal is accepted as signature.

FDA form 1572:

For US sites:

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

For sites outside the US:

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

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

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

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 unauthorized persons can get access to the data.

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

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

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

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

23 Reports and publications

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

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

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

One or two investigators will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator(s) will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[61].

23.1 Communication of results

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

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[4].

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

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

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

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

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

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[61] (sometimes referred to as the Vancouver Criteria). Novo Nordisk will appoint investigator(s) to prepare publications in collaboration with Novo Nordisk.

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

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

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

23.2 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database.

Individual investigators will have their own research subjects' data and will be provided with the randomisation code after results are available.

24 Retention of clinical trial documentation and human 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

Antibody samples may be stored at the special laboratory until market authorisation in case Health Authorities requests further characterisation of the antibody response (maximum up to 15 years from end of trial).

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

None of the data will be identified by name. Antibody samples and semaglutide PK samples will be identified only by a subject number, a visit number and a trial identification number. The trial staff is responsible for maintaining a code list which links to the subject number. The code list must be kept for at least 15 years. The code list may be reviewed by Novo Nordisk staff including auditors

or representatives from regulatory authorities, but Novo Nordisk staff will not make any copies of this list if names are included.

In the event that the blood samples collected for antibody analysis will be used in the future, the investigator will become directly informed by Novo Nordisk about the results if the findings are deemed clinically relevant. In such case, a written summary of the findings, including listings of subject specific values, will be provided once a firm conclusion from the results has been drawn by Novo Nordisk. Subjects may at any time contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

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

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

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

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

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

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

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

Regulatory Authorities:

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

26 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with:

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

For 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 France only: The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX Journal Officiel of 11 August 2004. "The sponsor is responsible for identification of the harmful consequences of the biomedical research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research.

For Mexico only:

a) *Novo Nordisk carries product liability for its products 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.*
b) *If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the study medication and/or a study procedure that otherwise would not have been part of his/her regular medical care, the subject will receive from the Institution or Medical Care Establishment and free of charge, the appropriate medical treatment as required. In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by the trial sponsor in accordance with the terms provided by all applicable regulations; even if the subject discontinues his/her participation in the study by his own will or by a decision from the investigator.*
c) *By signing the informed consent, the subject will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional*

expense as a result of his/her participation in the trial; any additional expense resulting from the subject's participation in the trial will be covered by the trial sponsor.

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Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Appendix A

Monitoring of Calcitonin

1 Background

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

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

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

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

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

2 Calcitonin monitoring

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

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

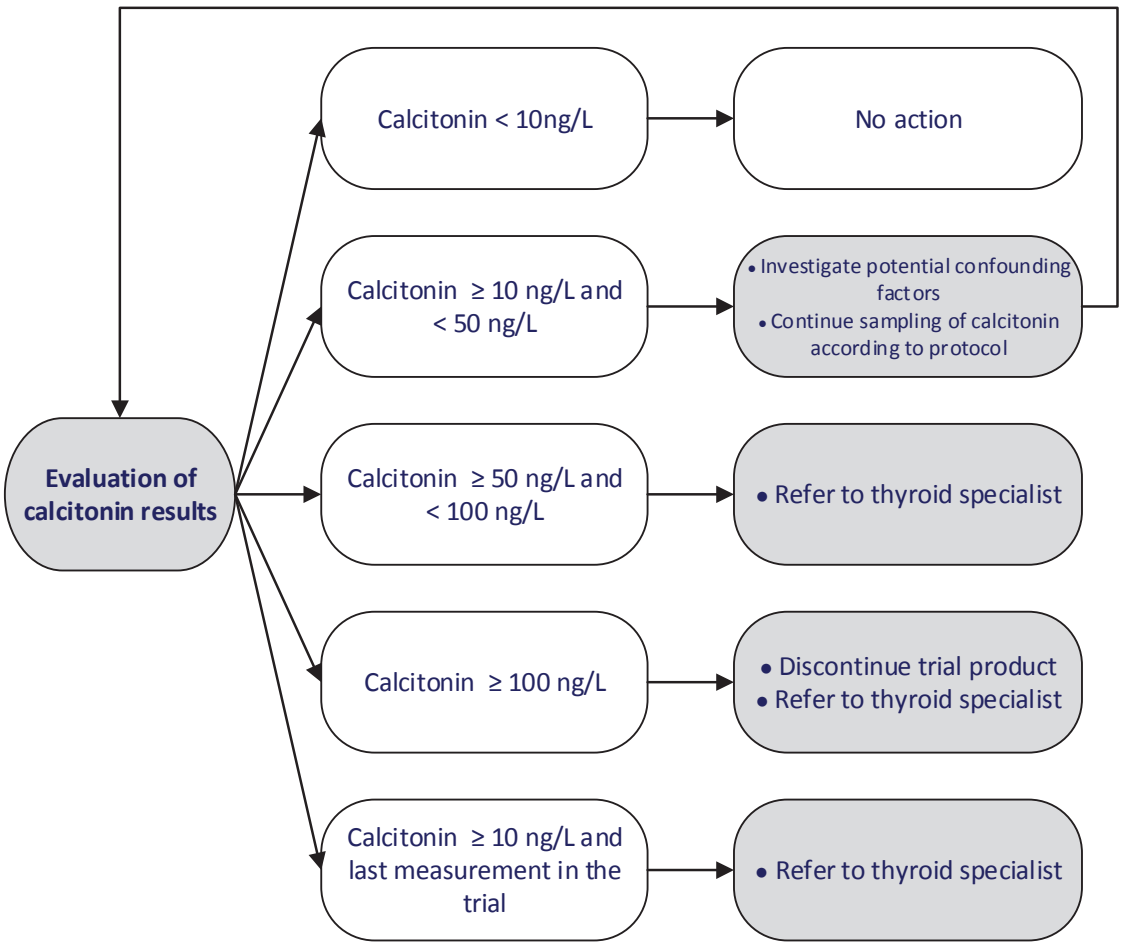

Figure 1 Flow of calcitonin monitoring

2.1 Calcitonin ≥ 100 ng/L

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

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

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

Diagnostic evaluation should include:

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

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

2.2 Calcitonin ≥ 50 and < 100 ng/L

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

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

Diagnostic evaluation should include:

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

2.3 Calcitonin ≥ 10 and < 50 ng/L

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

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

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

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

3 References

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Appendix B

Adverse events requiring additional data collection

1 Adverse Events requiring additional data collection

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

- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or TIA)
- Heart failure requiring hospitalisation
- Pancreatitis
- Neoplasm (excluding thyroid neoplasm)
- Thyroid disease (including thyroid neoplasm)
- Renal event
- Hypersensitivity reactions
- Acute gallstone disease
- Medication error (concerning trial products):
    - Administration of wrong drug.
      Note: Use of wrong DUN is not considered a medication error.
    - Wrong route of administration.
    - Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
    - Accidental administration of a higher dose than intended. A higher dose is a dose of at least one tablet more than the intended dose; however the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.
- Lactic acidosis
- Creatine kinase (CK) > 10x UNL
- Hepatotoxicity events:
    - ALT or AST > 10x UNL and total bilirubin ≤ 2x UNL
    - Hepatotoxicity leading to trial product discontinuation

In case any of these events fulfil the criteria for an SAE, please report accordingly, see Section 12.2.

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

1.1 Acute coronary syndrome

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

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

1.2 Cerebrovascular event

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

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

1.3 Heart failure 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 observed during the trial the following additional information must be reported if available:

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

1.4 Pancreatitis

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

- Signs and symptoms of pancreatitis
- Specific laboratory test supporting a diagnosis of pancreatitis:

- Imaging performed and consistency with pancreatic disease
- Treatment for and complications of the event
- Relevant risk factors for pancreatic disease
- Family history of pancreatic disease

Please see Section 8.7.1 for further details on assessments in case of suspicion of acute pancreatitis.

1.5 Neoplasm

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

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

1.6 Thyroid disease

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

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

1.7 Renal event

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

- Signs and symptoms of renal failure
- Specific laboratory 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 reactions

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

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

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

Please see Section 8.7.2 for further details on assessments in case of suspicion of hypersensitivity reactions.

1.9 Acute gallstone disease

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

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

1.10 Medication error

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

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

For definition of medication error, see Section 12.1.

1.11 Lactic acidosis

- If an event of lactic acidosis is observed during the trial the following additional information must be reported if available:
  - Signs and symptoms of lactic acidosis
  - Specific laboratory test results describing the event
  - Possible cause(s) of the event

1.12 Creatine kinase (CK) > 10x UNL

- If an event of CK > 10x UNL is observed during the trial the following additional information must be reported if available:
  - Signs and symptoms associated to the event
  - Recent physical activity
  - Possible cause(s) of the event

Please see Section 8.7.3 for further details on assessments in case of increased levels of CK.

1.13 Hepatotoxicity events

- ALT or AST > 10x UNL and total bilirubin ≤ 2x UNL
- Hepatotoxicity 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 8.7.4 for further details on assessments in case of increased levels aminotransferases.

Protocol Amendment

no 1
to Protocol, final version 2
dated 24 August 2015

Trial ID:NN9924-4222

PIONEER 3 - vs. DPP-4 inhibitor

Efficacy and long-term safety of oral semaglutide versus sitagliptin 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

In addition to the below, minor inconsistencies and errors have been corrected.

1.1 Section 2 Flowchart

In the flowchart the timing of visit 16A (V16A) and the visit window of +3 days has been added for clarity.

An 'x' at visit 2 (Randomisation) for drug accountability has been added as the site should enter the date of dispensing the trial product in the interactive web response system (IWRS).

1.2 Section 4.2.2.2 Supportive secondary endpoints

Time to rescue medication will only be analysed at the end of the trial and the text describing different time points for assessment has been deleted.

1.3 Section 8.1.5 Premature discontinuation of trial product and Follow-up (visits 16A and 17A)

The timing of V16A and visit window of +3 days has been added for clarity.

1.4 Section 8.4.4 Electrocardiogram – 12 -lead

A confirmatory ECG is required for all post-baseline ECGs suggestive of a new myocardial infarction (MI), as assessed by the central ECG reader. The rationale for this confirmatory ECG is to confirm that the ECG findings suggestive of a new MI are valid.

1.5 Section 8.4.7 Antibodies

Anti-semaglutide neutralising antibodies has been changed to anti-semaglutide binding antibodies in Section 8.4.7 as it does not make sense to characterise neutralising antibodies for neutralising effect, however, it does make sense to characterise binding antibodies for neutralising effect. Binding antibodies should be seen as all antibodies binding to the drug (semaglutide), a fraction of these antibodies may be neutralising.

1.6 Sections 8.7.4 Assessments in case of increased levels of aminotransferases, 12.1 definitions, Appendix B Section 1 Adverse Events requiring additional data collection and Appendix B Section 1.13 Hepatotoxicity events

The cut off level for repeat testing of increased levels of aminotransferases has been updated from ALT/AST >10x UNL to >5x UNL in section 8.7.4. The rationale is to prompt follow-up of potential clinical significant aminotransferase levels.

Definition of elevated liver enzymes to be reported as adverse events (AEs) requiring additional data collection has been updated in section 12.1 and appendix B to align with 8.7.4 and ensure that all potential hepatotoxicity events are captured and can be assessed appropriately.

Suspicion of transmission of infectious agents via the trial product and events fulfilling Hy's law are included underneath the defined seriousness criteria in section 12.1 to clarify that these are specific AEs that always fulfil the seriousness criteria.

The definition of Hy's law in section 12.1 has been updated to align with the FDA guidance document "*Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation"*.

1.7 Section 9.4 Drug accountability and destruction

To ensure proper trial product accountability sites are requested to account for non-allocated trial product as well.

1.8 Section 12.2 Reporting of adverse events

Figure 12-1 has been updated as the previous AE flow did not contain the full AE process flow as described in the protocol text.

1.9 Sections 17 Statistical considerations, 17.3.1 Primary analysis for the primary estimand, 17.4.2.1 Efficacy endpoints and 17.4.2.2 Safety endpoints

The text regarding stratification factors in the statistical section 17 has been updated to make it more clear how these are included in the statistical analyses.

Two wrong units have been corrected and irrelevant data removed from Table 17.1.

For the primary analysis to the primary estimand, missing data will not be imputed based on the stratification factor, but only treatment and treatment adherence/rescue status i.e. 16 groups are change to 8 groups. In the analysis after 52 weeks 32 groups has been changed to 16 due to the same decision. The stratification factor has instead been added as a categorical fixed effect in the ANCOVA analysis.

The text below the time to event endpoint has been removed from the statistical section as well, since the endpoint will only be analysed at the end of the trial.

In Section 17.4.2.2 treatment emergent hypoglycaemic events are defined twice by mistake, thus the second paragraph on the definition is deleted.

2 Changes

In this protocol amendment:

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

2.1 Section 2 Flowchart

For V16A:
Visit window (days): *+3 days* for Visit 16A
~~Shortly after~~ *Day of* discontinuation of trial product

For V2:
'x' in Drug accountability.

2.2 Section 4.2.2.2 Supportive secondary endpoints

[…]
Time to event endpoint

- Time to rescue medication

~~This endpoint will be evaluated after week 26, after week 52 and after week 78.~~

2.3 Section 8.1.5 Premature discontinuation of trial product and Follow-up (visits 16A and 17A)

Subject who discontinue trial product prematurely should attend visit 16A, scheduled to take place ~~shortly~~ after discontinuation of trial product *(+3 days visit window).*

2.4 Section 8.4.4 Electrocardiogram – 12 – Lead

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

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

If the central ECG evaluation of a post-baseline ECG is suggestive of new ~~myocardial infarction (~~MI~~)~~, the investigator will be notified and *a confirmatory ECG should be performed.*~~, u~~*U*nless already done, the investigator should report this as AE or SAE at investigator's discretion (see Section 12.1).

2.5 Section 8.4.7 Antibodies

Samples which are positive for anti-semaglutide ~~neutralising~~ *binding* antibodies […]

2.6 Section 8.5 Laboratory assessments

For some of the analyses described in Section 8.7.1 and ~~8.7.1~~ *8.7.2* a local laboratory must be used.

2.7 Section 8.7.4 Assessments in case of increased levels of aminotransferases

In case of

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

~~the event must be reported as an SAE (see Section 12.1).~~

2. ALT or AST >~~10~~*5*x UNL and total bilirubin ≤2x UNL,

the event should be reported as an AE requiring additional data collection (see Section 12.1 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.

2.8 Section 9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator.

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

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

Drug accountability is performed by using the IWRS. ~~Only dispensed DUNs returned by the subject (used/partly used or unused) are accounted for.~~ Drug accountability should be done on tablet level.

Destruction will be done according to local procedures after accountability is finalised and verified by the monitor. Destruction of products must be documented and recorded in IWRS including destruction confirmation.

2.9 Section 12.1 Definitions

Serious adverse event

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

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

[…]

~~**Trial specific serious adverse event**~~

~~The following laboratory abnormalities must be reported as an SAE:~~

- ~~ALT or AST >3x UNL **and** total bilirubin >2x UNL~~

~~Additional assessments should be made for events meeting the above criterion (see Section 8.7.4).~~

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

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

[…]

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). The AEs requiring additional data collection are:

[…]

- Hepatotoxicity events:
  - ALT or AST > ~~10~~5x UNL and total bilirubin ≤ 2x UNL
  - *ALT or AST > 3x UNL and total bilirubin > 2 UNL*
  - *Hepatic event*~~Hepatotoxicity~~ leading to trial product discontinuation

2.10 Section 12.2 Reporting of adverse events

[…]

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 event*s* ~~specific forms~~ and the additional information to report).

[…]

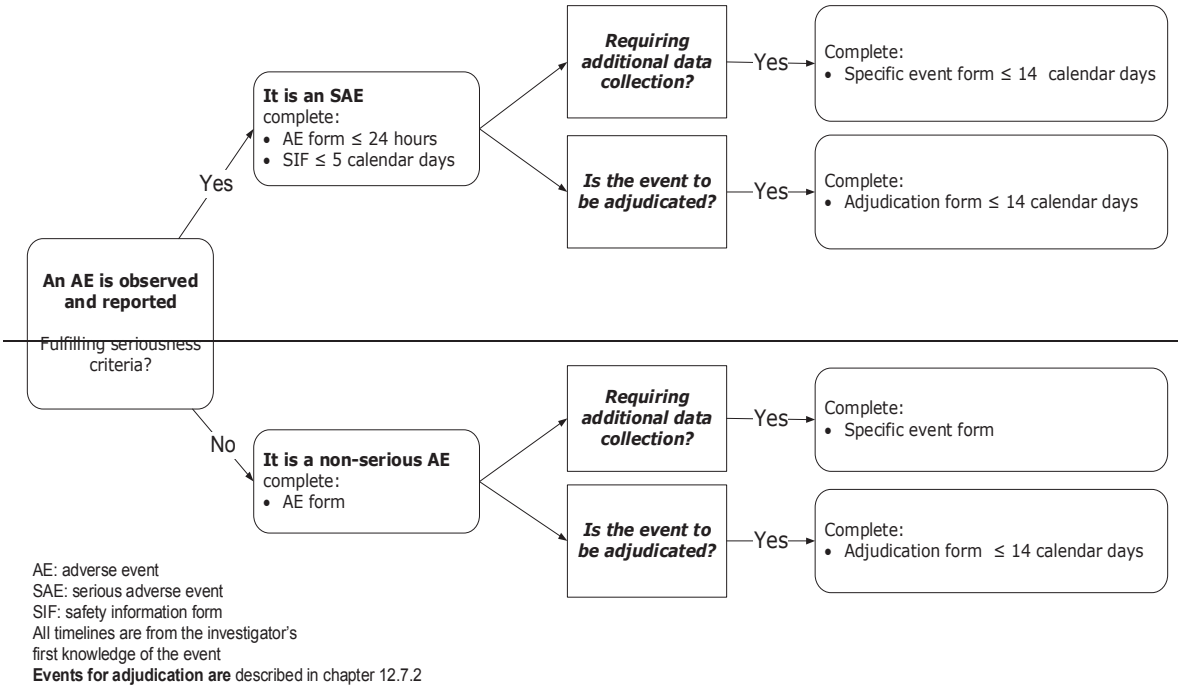

Figure 12-1 Initial reporting of AEs

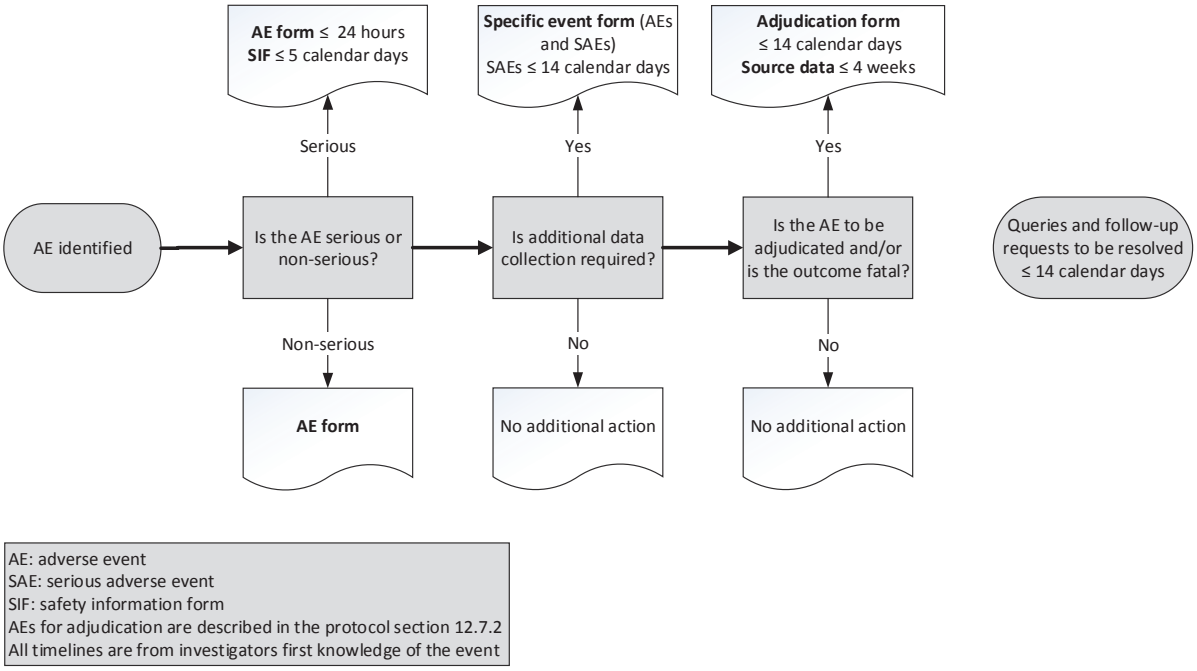

Figure 12-1 Initial reporting of AEs

2.11 Section 17 Statistical considerations

General considerations

[…]

The randomisation is stratified based on pre-trial therapy at screening (metformin or metformin+SU) and descent (Japanese subjects/non-Japanese subjects). In the statistical analyses descent is a part of region and pre-trial therapy at screening is referred to as stratification factor.
~~In statistical analyses where stratification is included,~~*t*The two combinations (metformin; metformin+SU) *in the stratification factor* will be included based on the actual information collected through the eCRF. In case of missing eCRF information the information collected from IWRS system will be used.

Table 17–1 Assumptions for sample size calculation

Oral semaglutide vs. sitagliptin	HbA_{1c}			Body weight		
Treatment dose	14 mg	7 mg	3 mg	14 mg	7 mg	3 mg
Treatment effect (TE) .	-0.5%	-0.3%	-0.1%	-3.0 kg	-2.0 kg	-1.0 kg
Adjusted TE, non-inferiority	-0.395%	-0.255%	-0.055%	~~-2.52 kg~~	~~-1.67 kg~~	~~-0.82 kg~~
Adjusted TE, superiority	-0.425%	-0.255%	-0.085%	-2.55 kg	-1.70~~%~~*kg*	-0.85~~%~~*kg*
Standard deviation	1.1%	1.1%	1.1%	4.0 kg	4.0 kg	4.0 kg

2.12 Section 17.3.1 Primary analysis for the primary estimand

The primary estimand will be estimated based on the FAS using week 26 measurements from the in-trial observation period. The primary statistical analysis will be a pattern mixture model using multiple imputation to handle missing data assuming that the missing data mechanism is missing at random (MAR). Imputation of missing data at week 26 will be done within ~~16~~ *8* groups of subjects defined by randomised treatment arm~~, stratification factor~~ and whether subjects at week 26; (i) have discontinued treatment or initiated rescue medication or (ii) still on treatment and have not initiated rescue medication. It is hereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who at week 26 are similar in terms of randomised treatment arm and treatment adherence/rescue status.

Missing values for each group will be imputed as follows:

- An analysis of covariance (ANCOVA) with region *and stratification factor* as ~~a~~ categorical fixed effect*s* and baseline HbA1c measurement as a covariate will be fitted to observed values of the change from baseline in HbA1c at week 26.
- The estimated parameters for location and dispersion will be used to impute 100 values for each subject with missing week 26 data based on region, *stratification factor* and baseline HbA1c. Thus, 100 complete data sets will be generated including observed and imputed values.

Analysis used for confirming superiority versus sitagliptin at week 26:
For each of the 100 (now complete) imputed data sets the change from baseline to week 26 will be analysed using an ANCOVA with treatment, region *and stratification factor* as categorical fixed effects and baseline HbA_{1c} as covariate. The results obtained from analysing the datasets will be combined using Rubin's rule to draw inference.

2.13 Section 17.4.2.1 Efficacy endpoints

[…]
For evaluation of the primary estimand the analysis will be performed separately for week 26, 52 and 78. For the analysis at week 52 and at week 78, the imputation of missing data will be further differentiated by whether subjects have discontinued trial product or initiated rescue medication prior to week 26 or at or after week 26. This will result in imputation of missing data within *16* ~~32~~ groups of subjects instead of the ~~16~~ *8* groups as described for the week 26 evaluation in Section 17.3.1. The frequency of missing data is expected to be slightly larger at week 52 and week 78 compared to week 26. The rate of missing data is expected to decline over time.

[…]

Time to event endpoint

- Time to rescue medication

Subjects completing the study without need for rescue medication will be censored at the time point of actual date of last trial product. Start time is date of first trial product. Time to rescue medication will be described and compared for each of the oral semaglutide dose level versus sitagliptin 100 mg using likelihood ratio tests obtained from a proportional Cox hazards model. From this analysis the estimated Hazard ratios between each dose levels and sitagliptin will be presented together with 95 % confidence intervals and two-sided p-values for test of no difference. ~~This endpoint will be evaluated after week 26, after week 52 and after week 78.~~ *Furthermore, the endpoint will be presented by a Kaplan-Meier plot.*

2.14 Section 17.4.2.2 Safety endpoints

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

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

~~A treatment emergent hypoglycaemic episode is defined as a hypoglycaemic episode with onset in the on-treatment observation period (see definition of observation periods in Section 17.2).~~

2.15 Appendix B: Section 1 Adverse Events requiring additional data collection

- Hepatotoxicity events:
  - ALT or AST > *5*~~10~~x UNL and total bilirubin ≤ 2x UNL
  - *ALT or AST > 3x UNL and total bilirubin > 2x UNL*
  - *Hepatic event*~~Hepatotoxicity~~ leading to trial product discontinuation

2.16 Appendix B: Section 1.13 Hepatotoxicity events

  - ALT or AST > *5*~~10~~x UNL and total bilirubin ≤ 2x UNL
  - *ALT or AST > 3x UNL and total bilirubin > 2x UNL*
  - *Hepatic event*~~Hepatotoxicity~~ leading to trial product discontinuation

Protocol Amendment

no 2
to Protocol, final version 3
dated 12 November 2015

Trial ID: NN9924-4222

PIONEER 3 - vs. DPP-4 inhibitor

Efficacy and long-term safety of oral semaglutide versus sitagliptin 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 on diabetic retinopathy
2. Investigator's responsibility in ensuring evaluation and management of certain risk factors and complications
3. Clarification of the criteria for completion, withdrawal and lost to follow-up
4. Other minor corrections and clarifications

1.1 Additional eye examinations and additional data collection on diabetic retinopathy

Protocol sections updated: 2, 4.2.2.2, 8.4.3, 12.1, 12.2, 17.2, 17.4.2.2, 18.1.1.1, 27; Appendix B section 1 and 1.14 (new).

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

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

Protocol sections updated: 8.4.1, 18.1.1.1, 27.

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

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

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

Protocol sections updated: 6.6, 8.1, 8.1.4, 8.1.5, 8.1.6.1 (new).

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

1.4 Other minor adjustments, clarifications and correction of typographical errors

Laboratory analysis

Protocol sections updated: 8.4.7, 8.5, 8.7.1.

The protocol is updated to reflect that on suspicion of acute pancreatitis the investigator has the option of performing measurement of lipase and amylase not only via local laboratory but also via central lab in accordance with the specific clinical situation.

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

Statistical considerations

Protocol sections updated: 17.3.1, 17.4.2.1.

For the pattern mixture model using multiple imputation, the number of imputations will be increased from 100 to 1000 data sets, to ensure a greater precision of the estimates. In addition, an error in the number of groups used for imputation is corrected. Furthermore, the description of the Cox hazard model used for the time to event endpoint has been clarified.

Adverse events for Adjudication

Protocol sections updated: 12.7.2.

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

Initial reporting of AEs

Protocol sections updated: 12.2.

Figure 12-1 has been aligned with PIONEER trials to reflect the legislation of "within" timelines which is now interpreted as "less than".

Background medication

Protocol sections updated: 5.3.2.

Section has been updated to specify that dose changes of background medication is allowed in case of a safety concern.

Rescue criteria

Protocol sections updated: 6.4.

The section has been updated to specify that rescue medication should be offered until end of treatment and not end of trial as previously specified. After end of treatment, the protocol section 5.4 applies.

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

For V12, V16 and V16A: '*x*' in 'Eye examination'

Footer	Description
X[5]	Dilated fundoscopy/fundus photography performed within 90 days prior to randomisation is acceptable if results are available for evaluation at V2, unless worsening of visual function since last examination. *Dilated fundoscopy/fundus photography must be performed again:* • *at V12 or within 5 weeks prior to or after V12 (applicable for all subjects)* • *at V16 or within 5 weeks thereafter (for subjects completing treatment)* • *at V16A or within 5 weeks thereafter, and again within 5 weeks prior to V16 (for subjects who have prematurely discontinued trial product)*

2.2 Section 4.2.2.2 Supportive secondary endpoints

Supportive secondary safety endpoints

- Number of TEAEs during exposure to trial product, assessed up to approximately 83 weeks*
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 83 weeks*
- Treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 83 weeks (yes/no)

Change from baseline to week *26, 52 and* 78 in:

- Haematology
- Biochemistry
- Calcitonin
- Pulse
- Systolic blood pressure
- Diastolic blood pressure
- Electrocardiogram (ECG) category
- Physical examination *(week 52 and 78 only)*
- *Eye examination category (week 52 and 78 only)*

2.3 Section 5.3.2 Background medication

After inclusion (V1), subjects must continue anti-diabetic pre-trial background medication (i.e. metformin alone or in combination with SU) throughout the entire trial. The background medication must be maintained at the stable, pre-trial dose and at the same frequency during the whole treatment period unless rescue medication is needed (see Section 6.4),~~or~~ if the subject has unacceptable hypoglycaemia on a background of SU in which case the dose of SU can be reduced *or if another safety concern related to the background medication arises.*

2.4 Section 6.4 Rescue criteria

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification. To allow time for dose escalation and to observe the expected effect of treatment on glycaemic parameters, rescue criteria will be applied from week 8 and onwards. If any of the FPG values (including fasting SMPG) exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified, a confirmatory FPG (at central laboratory) should be obtained by calling the subject for a re-test:

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

If the confirmatory FPG also exceeds the values described above, the subject should be offered rescue medication (i.e. intensification of existing anti-diabetic background medication and/or initiation of new anti-diabetic medication).

In addition, subject should be offered rescue medication if:

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

2.5 Section 6.6 Withdrawal criteria

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected.

A subject who does not complete the trial is also considered withdrawn from the trial. Hence, a subject is considered withdrawn from trial if the following applies:

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

2.6 Section 8.1 Visit procedures

[…]

~~If a subject is unable or unwilling to attend all subsequent visit(s) the investigator should at least aim to have the subject attend the V8, V12 and the End-of-treatment visit (V16) as these visits should be performed for all subjects (except subjects who withdraw informed consent, see Section 8.1.6).~~

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

2.7 Section 8.1.4 End-of-treatment (visit 16) and Follow-up (visit 17)

At V16 the subject should be reminded about the importance of attending the follow-up visit (V17). If the subject, nonetheless, does not attend V17, the site should make efforts to obtain contact with the subject within the visit window.

A trial completer is defined as a subject who attends, or are in contact with the site, at the subject's last scheduled visit. For subjects who complete treatment, the last scheduled visit is V17. (For subjects who discontinue trial product, see Section 8.1.5).

~~In case the subject cannot be reached (by clinic visit or phone contact) at the scheduled visit 17 and the subject has consented to it, the site should consult the contacts provided by the subject (e.g. close relatives), relevant physicians, medical records and locator agencies (if allowed according to local law) to collect health status. If no health status can be collected, the subject should be considered lost to follow.~~

2.8 Section 8.1.5 Premature discontinuation of trial product and follow-up (visits 16A and 17A)

Subjects who discontinue trial product prematurely should attend visit 16A, scheduled to take place after discontinuation of trial product (+3 days visit window). Visit 17A should be scheduled 5 weeks (+3 days visit window) after the last date on trial product. A treatment discontinuation session must be performed in the IWRS at visit 16A (see Section 10).

Subjects should continue with the originally scheduled site contacts after visit 17A and up to *and including* visit 16. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after V17A. However, ~~as a minimum, these subjects should be asked to attend the scheduled V8 at week 26, V12 at week 52 and End-of-treatment (V16) at week 78~~. *if a subject is unable or unwilling to attend all subsequent visit(s), the investigator should at least aim to have the subject attend V8 (week 26), V12 (week 52) and End-of-treatment (V16) (week 78) as these*

visits should be performed for all subjects, if at all possible (except subjects who withdraw consent, see Section 8.1.6).

~~In case the subject cannot be reached (by clinic visit or phone contact) at the scheduled visit 17 and the subject has consented to it, the site should consult the contacts provided by the subject (e.g. close relatives), relevant physicians, medical records and locator agencies (if allowed according to local law) to collect health status. If no health status can be collected, the subject should be considered lost to follow up.~~

A subject who prematurely discontinues trial product is still considered a trial completer if the subject attends or is in contact with the site, at the subject's last scheduled visit.

For subjects who prematurely discontinue trial product, the last scheduled visit is V16 (or V17A if it is scheduled after V16). (For subjects completing treatment, see Section 8.1.4). The site should in due time prepare for establishing contact with the subject within the visit window of the scheduled V8, V12 and V16 respectively, if the subject has agreed to attend these visits.

2.9 Section 8.1.6.1 Lost to follow-up

In case contact to the subject is lost during the trial, the site should immediately undertake efforts to re-establish contact. If the subject cannot be reached (by clinic visit or phone contact) and the subject has consented to it, the site should consult the contacts provided by the subject (e.g. close relatives), relevant physicians, medical records and locator agencies (if allowed according to local law) in an attempt to regain contact with the subject or to obtain relevant safety information from other sources. Efforts to regain contact should continue until the end of the subject's last scheduled visit: V17 for subjects who have completed treatment, whereas for subjects who have discontinued trial product prematurely the last scheduled visit is V16 (or V17A if it is scheduled after V16). Only if contact with the subject is not regained by the end of the visit window of the subject's last scheduled visit, can the subject be considered lost to follow up (see Section 6.6).

2.10 Section 8.4.1 Physical examination

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

- General appearance
- Head, ears, eyes, nose, throat, neck
- Thyroid gland*
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Musculoskeletal system

- Central and peripheral nervous system
- Skin
- Lymph node palpation

**Please note that the diagnostic evaluation of thyroid nodules should be in accordance with the American Thyroid Association Management Guidelines or any updates hereof[62], and adapted to local treatment guidelines if applicable.*

2.11 Section 8.4.3 Eye examination

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

2.12 Section 8.4.7 Antibodies

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

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

2.13 Section 8.5 Laboratory assessments

The laboratory analyses will mainly be performed by a central laboratory. Anti-semaglutide antibodies, *in vitro* neutralising effect, IgE anti-semaglutide antibodies and PK samples will be analysed by a special laboratory ~~and~~*or* Novo Nordisk A/S (see Sections 8.4.7, 8.6.1 and 8.7.2. For some of the analyses described in Section 8.7.1 and 8.7.2 a local *or central* laboratory must be used.

2.14 Section 8.7.1 Assessments in case of suspicion of acute pancreatitis

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

2.15 Section 12.1 Definitions

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). The AEs requiring additional data collection are:

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

2.16 Section 12.2 Reporting of adverse events

Table 12-1 Overview of AEs requiring additional data collection and AEs subject to event adjudication[Note: In this document only the additional event is shown, all other events are unchanged]

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

[Note: In the below figure all "≤" are substituted with "<". The text in boxes will align once the update is done]:

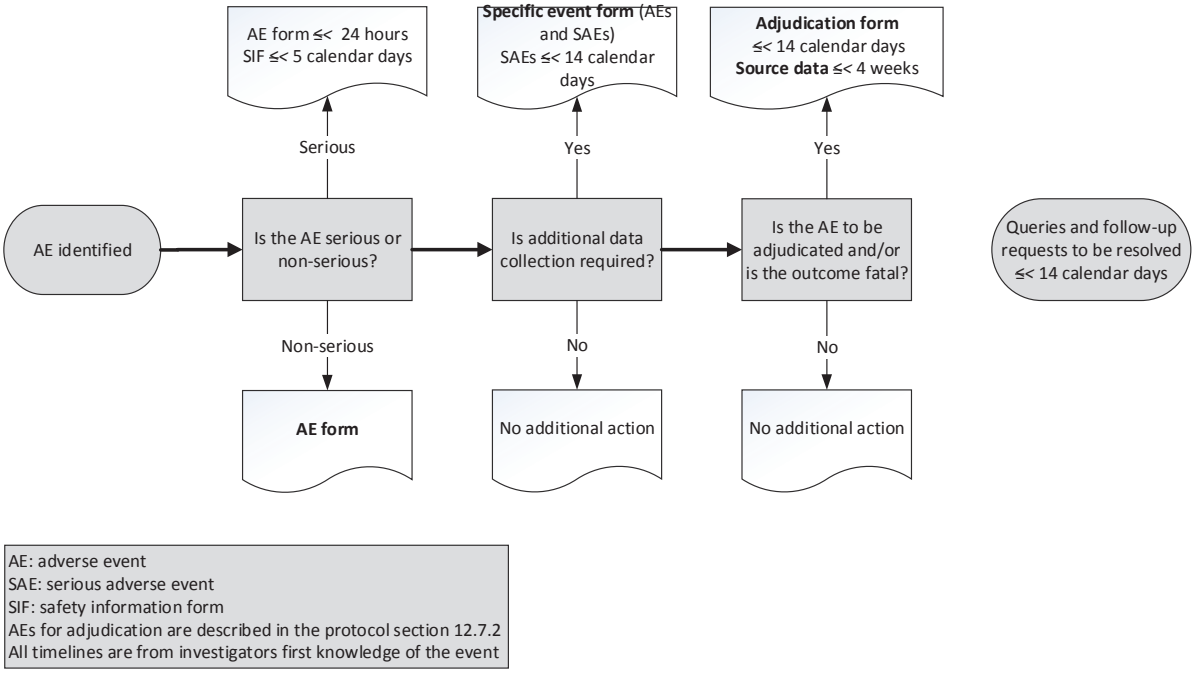

Figure 12-1 Initial reporting of AEs

2.17 Section 12.7.2 Event adjudication committee

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

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

2.18 Section 17.2 Definition of analysis sets

On-treatment: This observation period is a subset of the in-trial observation period and represents the time period in which a subject is considered exposed to trial product. For adjudicated events, ECGs, *eye examination category,* anti-semaglutide antibodies and AEs including hypoglycaemic episodes information collected on or after the first date of trial product up to and including the first date of (i) the follow-up visit V17, (ii) the follow-up prematurely discontinuation visit V17A, (iii) the last date on trial product +38 days or (iv) the end-date for the in-trial observation period will be used.

2.19 Section 17.3.1 Primary analysis for the primary estimand

Missing values for each group will be imputed as follows:

- An analysis of covariance (ANCOVA) with region, stratification factor as categorical fixed effects and baseline HbA_{1c} measurement as a covariate will be fitted to observed values of the change from baseline in HbA_{1c} at week 26.
- The estimated parameters for location and dispersion will be used to impute ~~100~~ *1000* values for each subject with missing week 26 data based on region, stratification factor and baseline HbA_{1c}. Thus, ~~100~~ *1000* complete data sets will be generated including observed and imputed values.

Analysis used for confirming superiority versus placebo at week 26:
For each of the ~~100~~ *1000* (now complete) imputed data sets the change from baseline to week 26 in HbA_{1c} will be analysed using an ANCOVA with treatment, stratification factor and region as categorical fixed effects and baseline HbA_{1c} as covariate. The results obtained from analysing the datasets will be combined using Rubin's rule[55] to draw inference.

2.20 Section 17.4.2.1 Efficacy endpoints

Continuous efficacy endpoints

[…]
For evaluation of the primary estimand the analysis will be performed separately for week 26, 52 and week 78. For the analysis at week 52 and at week 78, the imputation of missing data will be further differentiated by whether subjects have discontinued trial product or initiated rescue medication prior to week 26 or at/~~or~~ after week 26. This will result in imputation of missing data within ~~16~~*12* groups of subjects instead of the 8 groups as described for the week 26 evaluation in Section 17.3.1. *If less than five subjects have available data in one of the 12 groups, the imputation will be made within the 8 groups specified for the primary evaluation.* The frequency of missing data is expected to be slightly larger at week 52 and week 78 compared to week 26. The rate of missing data is expected to decline over time.

[…]

Handling of missing data for the response status of the above categorical endpoints will be determined from the imputed continuous responses. A total of ~~100~~*1000* imputed data sets will be created based on the same models as used to analyse HbA_{1c} and body weight. For the secondary estimand the MMRM based analysis will be implemented in a MI setting. The imputed complete data sets will be analysed using a logistic regression model with treatment, stratification factor and region as categorical fixed effects and baseline response as covariate (i.e. baseline HbA_{1c} for binary HbA_{1c} endpoints, baseline weight for binary weight endpoints and both baseline HbA_{1c} and body weight for the binary endpoint that combines both parameters). Inference comparing treatments will be drawn using Rubin's rule[55].

Time to event endpoint

- Time to rescue medication

Subjects completing the study without need for rescue medication will be censored at the time point of actual date of last trial product. Start time is date of first trial product. Time to rescue medication will be described and compared for each of the oral semaglutide dose level versus sitagliptin 100 mg using likelihood ratio tests obtained from a proportional Cox hazards model *with treatment, stratification factor and region as categorical fixed effects and baseline HbA_{1c} as a covariate*. From this analysis the estimated Hazard ratios between each dose levels and sitagliptin will be presented together with 95 % confidence intervals and two-sided p-values for test of no difference. Furthermore, the endpoint will be presented by a Kaplan-Meier plot.

2.21 Section 17.4.2.2 Safety endpoints

Other safety endpoints

[…]

Other safety endpoints

Change from baseline to week *26, 52 and* 78 in:

- Amylase
- Lipase
- Pulse
- Systolic blood pressure
- Diastolic blood pressure

[…]

Change from baseline to week *26, 52 and* 78 in:

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

- Physical examination *(week 52 and 78 only)*
- *Eye examination category (week 52 and 78 only)*

2.22 Section 18.1.1.1 Oral Semaglutide

Diabetic retinopathy complications

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive antidiabetic treatment[63-65]. 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[66,67] even in intensively treated patients who experienced early worsening[64]. 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[68]. As a precaution in this trial, all subjects are required to have a fundus photography or dilated fundoscopy performed before enrolment into the trial; moreover, subjects with proliferative retinopathy or maculopathy requiring acute treatment will be excluded. As part of good diabetes management the investigator is encouraged to ensure adequate monitoring and treatment of diabetic retinopathy in subjects enrolled into the trial[69].

General precautions

All subjects will be included after a thorough evaluation with regards to in- and exclusion criteria defined in order to ensure that subjects are eligible for trial treatment. There are also strict glycaemic rescue criteria in place to ensure acceptable glycaemic control during the trial. If rescue medication is required, it should be in accordance with ADA/European Association for the Study of Diabetes[25,26] (excluding GLP-1 RAs, DPP-4 inhibitors, amylin analogues and SGLT-2 inhibitors).

It is the responsibility of the investigator to ensure the best possible care *of the subject. This includes adequate glycaemic control, appropriate risk factor modification such as optimal treatment of hypertension, dyslipidaemia and other cardiovascular risk factors, as well as regular monitoring and treatment of diabetic kidney disease and diabetic retinopathy[69].*

2.23 Section 27 References

62. 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.

63. Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin

dependent diabetes mellitus: the Oslo study. Br Med J (Clin Res Ed). 1985;290(6471):811-5.

64. *The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol. 1998;116(7):874-86.*
65. *Varadhan L, Humphreys T, Walker AB, Varughese GI. The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. Diabetes Res Clin Pract. 2014;103(3):e37-9.*
66. *Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837-53, Erratum 1999; 354: 602.*
67. *The Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Eye Study Group and the Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study Group. Persistent Effects of Intensive Glycemic Control on Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study. Diabetes Care. 2016;39(7):1089-100.*
68. *Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016.*
69. *American Diabetes Association. Standards of medical care in diabetes - 2016. Diabetes Care. 2016;39 (Suppl. 1).*

2.24 Reference numbers

Numbers will change throughout the updated protocol when the above new references are introduced.

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

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

- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or TIA)
- Heart failure requiring hospitalisation
- Pancreatitis
- Neoplasm (excluding thyroid neoplasm)
- Thyroid disease (including thyroid neoplasm)
- Renal event
- Hypersensitivity reactions
- Acute gallstone disease
- Medication error (concerning trial products):

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

- Lactic acidosis
- Creatine kinase (CK) > 10x UNL
- Hepatotoxicity events:
  - 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*

2.26 Appendix B, *Section 1.14 Diabetic retinopathy and related complications*

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

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

3 References

1. Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. Br Med J (Clin Res Ed). 1985;290(6471):811-5.
2. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol. 1998;116(7):874-86.
3. Varadhan L, Humphreys T, Walker AB, Varughese GI. The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. Diabetes Res Clin Pract. 2014;103(3):e37-9.
4. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016.

Local Amendment

no 1-FR

Trial ID: NN9924-4222

PIONEER 3 - vs. DPP-4 inhibitor

Efficacy and long-term safety of oral semaglutide versus sitagliptin in subjects with type 2 diabetes

Applicable to FRANCE

Amendment originator:

[redacted]

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2 Changes 4

1 Introduction including rationale for the local amendment

The rationale for issuing this substantial amendment is to add 2 new sites and to delete one site that withdrawn its participation.

New sites :

[redacted]

[redacted]

Deletion of site form Nantes: [redacted]

Attachment II and List of investigators are updated accordingly.

In this protocol amendment:

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

2 Changes

The following changes to List of investigators to NN9924-4222:

Attachment II – Addition of new sites

Investigator: *Name:* [redacted]

Title: [redacted]

Address: [redacted]

Tel:

Fax:

E-mail: [redacted]

Investigator: *Name:* [redacted]

Title: [redacted]

Address: [redacted]

Tel: [redacted]

Fax:

E-mail: [redacted]

Deletion of site:

~~Investigator:~~	~~Name:~~	[redacted]
	~~Title:~~	[redacted]
		[redacted]
	~~Address:~~	[redacted]
		[redacted]
		[redacted]
		[redacted]
	~~Tel:~~	[redacted]
	~~Fax:~~	[redacted]
	~~E-mail~~	[redacted]

1. **List of Investigators** – Addition of a new sub-investigator at site [redacted] 2 new sites ([redacted] and [redacted] and deletion of site [redacted]

[redacted]

Local Amendment

no 2-FR

Trial ID: NN9924-4222

PIONEER 3 - vs. DPP-4 inhibitor

Efficacy and long-term safety of oral semaglutide versus sitagliptin in subjects with type 2 diabetes

Applicable to FRANCE

Amendment originator:

[redacted]

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1 Introduction including rationale for the local amendment 3

2 Changes 4

1 Introduction including rationale for the local amendment

The rationale for issuing this substantial amendment is to add 1 new site, to modify the Investigator of one site and to add sub-investigators at one site.

- New site :

[redacted]

- Modification of the Investigator for the site from [redacted] (site [redacted] due to change in local organisation and the existing Investigator become an investigator from satellite's site:

[redacted]

and addition of a satellite site : [redacted]

- Addition of a new sub-investigator : [redacted]

Attachment II and List of investigators are updated accordingly.

In this protocol amendment:

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

2 Changes

The following changes to Attachment II to NN9924-4222:

1. **Attachment II** – Addition of a new site and change of Investigator to another site with new satellite site associated

Investigator:	*Name:*	[redacted]
	Title/ qualification:	[redacted]
	Address:	[redacted]
	Tel:	
	Fax:	
	E-mail:	[redacted]
Modification of the PI for one site:		
~~Investigator:~~	~~Name:~~	[redacted]
	~~*Title/ qualification:*~~	[redacted]
	~~Address:~~	[redacted]
	~~Tel:~~	
	~~Fax:~~	
	~~E-mail:~~	[redacted]

Investigator:

Name: [redacted]

Title/ qualification:

Address: [redacted]

Tel:

Fax:

E-mail: [redacted]

Satellite site:
Name: [redacted]

Title/ qualification: [redacted]

Address: [redacted]

Tel:

Fax:

E-mail: [redacted]

2. **List of Investigators** – Addition of 1 new sub-investigator at site [redacted], modification of the Investigator at site [redacted] addition of 2 new sub-investigators at site [redacted] and addition of a new site [redacted]

[redacted]

Local Amendment

no 3-FR

Trial ID: NN9924-4222

PIONEER 3 - vs. DPP-4 inhibitor

Efficacy and long-term safety of oral semaglutide versus sitagliptin in subjects with type 2 diabetes

Applicable to FRANCE

Amendment originator:

[redacted]

Table of contents "Double click to update Table of Content"

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1 Introduction including rationale for the local amendment 3

2 Changes 4

1 Introduction including rationale for the local amendment

The rationale for issuing this substantial amendment is to add sub-investigators at 4 sites.

- Addition of a new sub-investigators :
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

List of investigators is updated accordingly.

In this protocol amendment:

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

2 Changes

1. **List of Investigators** – Addition of 1 new sub-investigator at sites [redacted] and [redacted].