Cover Page for Protocol

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16.1.1 Protocol and protocol amendments

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

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Protocol

Trial ID: NN9924-3790

Multiple dose trial examining dose range, escalation and efficacy of oral semaglutide in subjects with type 2 diabetes

Trial phase: 2

Protocol originator:

[redacted]

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the curve
BMI	body mass index
CMC	calcitonin monitoring committee
CRF	case report form
CT	computerised axial tomography
CTR	clinical trial report
CVD	cardiovascular disease
DFU	directions for use
DPP-4	dipeptidyl peptidase-4
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EE	ethinylestradiol
EMA	European Medicines Agency
eSIF	electronic safety information form
FAS	full analysis set
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSFV	first subject first visit
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin

hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HOMA-B	homeostasis model assessment of beta-cell function
HOMA-IR	homeostasis model assessment of insulin resistance
IB	Investigator's Brochure
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IV/WRS	interactive voice/web response system
LDL	low density lipoprotein
LN	levonorgestrel
LOCF	last observation carried forward
LSFV	last subject first visit
MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	multiple endocrine neoplasia type 2
MESI	medical event of special interest
MMRM	mixed model for repeated measurements
MRI	magnetic resonance imaging
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
OAD	oral antidiabetic drug
OD	once-daily
OW	once-weekly
PD	pharmacodynamics
PK	pharmacokinetics
PRO	patient reported outcome
SAE	serious adverse event

SAP	statistical analysis plan
s.c.	subcutaneous
SD	standard deviation
SF-36	medical outcomes study 36-item short-form health survey
SIF	safety information form
SNAC	sodium N-[8-(2-hydroxybenzoyl) amino] caprylate / salcaprozate sodium
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TEAE	treatment emergent adverse events
t_{max}	time to maximal concentration
TMM	Trial Materials Manual
USP	United States Pharmacopeia
UTN	Universal Trial Number
VLDL	very low density lipoprotein

1 Summary

Objectives and endpoints:

Primary objective

- To compare the efficacy on glycaemic control of oral semaglutide in a SNAC formulation against placebo in subjects with T2D

Key secondary objectives

- To compare the efficacy on glycaemic control of oral semaglutide in a SNAC formulation against s.c. semaglutide in subjects with T2D
- To compare the safety and tolerability of three dose escalation schemes using a single end dose level during 26 weeks administration of oral semaglutide and SNAC in a tablet formulation in subjects with T2D

Primary endpoint

- Change in HbA_{1c} from baseline to after 26 weeks of treatment

Key secondary endpoints

- Subjects who, after 26 weeks of treatment, achieve (yes/no) HbA_{1c} <7% (53 mmol/mol)
- Change in body weight from baseline to after 26 weeks of treatment
- Change in waist circumference from baseline to after 26 weeks of treatment
- Change in body mass index (BMI) from baseline to after 26 weeks of treatment
- Number of treatment emergent adverse events (TEAEs) recorded from baseline until week 31
- Number of confirmed hypoglycaemic episodes recorded from baseline until week 31

Trial design:

This is a randomised, partially-blinded, multiple-dose, multicentre trial with a total of nine treatment arms; seven oral semaglutide treatment arms, an oral placebo arm and an s.c. semaglutide arm in a parallel design. The trial will include subjects with T2D who have failed on diet and exercise and/or metformin.

Subjects with T2D will be randomised in an equal manner with 67 subjects planned to be randomised per treatment arm. Treatment arms 1-8 will include once-daily dosing of a tablet and will be blinded. Treatment arm 9 features once-weekly s.c. injection. All arms include 26 weeks of treatment and a 5 week follow-up period.

The trial medication will be add-on to previous metformin therapy or as monotherapy in the case where the subject is treated with diet and exercise alone.

Trial population:

A total of 603 subjects with T2D will be randomised.

Key inclusion criteria:

- Male or female, age ≥ 18 years at the time of signing inform consent
- BMI ≥25 and ≤40 kg/m^2
- Subjects diagnosed with T2D treated with diet and exercise and/or who have been on a stable dose of metformin for at least 30 days prior to screening
- HbA_{1c} 7.0-9.5% (53-80 mmol/mol) (both inclusive)

Key exclusion criteria

- Subjects on selected oral medication with a narrow therapeutic window, such as warfarin, digoxin, tricyclic antidepressants, lithium, aminophylline, theophylline and anticonvulsants
- History of chronic pancreatitis or idiopathic acute pancreatitis
- Chronic malabsorption, regardless of aetiology
- History of Crohn's disease, ulcerative colitis, or other inflammatory bowel disease
- Treatment with glucose lowering agent(s) other than metformin as stated in the inclusion criteria in a period of 90 days before the screening visit

Assessments:

Efficacy assessment

Measurements of laboratory parameters (HbA_{1c}, glucose metabolism parameters and lipids), BMI and waist circumference. Patient reported outcomes will be based on the SF-36 questionnaire and assessed at baseline and end of treatment.

Safety assessment

Adverse events, laboratory safety variables (haematology, biochemistry, calcitonin and urinalysis), vital signs, electrocardiograms, physical examinations and hypoglycaemic episodes recorded from the first trial-related activity and until completion of the post treatment follow-up visit of the trial.

PK assessment

Trough and peak plasma concentrations of semaglutide will be assessed throughout the trial.

Trial product(s):

The investigational medicinal products used in the trial will be for once-daily oral administration as tablets and once-weekly s.c. administration using a pen injector system. The investigational medicinal products are:

- Semaglutide 2.5 mg tablets
- Semaglutide 5.0 mg tablets
- Semaglutide 10 mg tablets
- Semaglutide 20 mg tablets
- Semaglutide 40 mg tablets
- Placebo tablets
- Semaglutide 1.34 mg/mL, solution for injection, 1.5 mL pre-filled PDS290 pen-injector

2 Flow chart

Trial Periods		Screening[1]	Randomisation	Treatment								End-of-treatment[2]	Follow-up[2]	End-of-trial – premature discontinuation[3]
Visit number		1	2	3	4	5	6	7	8	9	10	11	12	11X
Timing of visit	Weeks	-2	0	2	4	6	8	12	16	20	24	26	31	26
Visit window	Days			±3	±3	±3	±3	±5	±5	±5	±3	±3	+5	±3
SUBJECT RELATED INFO/ASSESSMENTS														
Informed consent		x												
In- and exclusion criteria		x	x											
Concomitant medication		x	x	x	x	x	x	x	x	x	x	x		x
Concomitant illness		x												
Demography		x												
Diagnosis of diabetes		x												
Diabetes treatment history		x												
Medical history		x												
Smoking habits		x												
History of gallbladder disease		x												
History of cardiovascular disease		x												
Renal impairment history		x												
Randomisation			x											
Withdrawal criteria			x	x	x	x	x	x	x	x	x	x		
Post-dose fasting routines												x		
EFFICACY														
Height		x												
Body weight		x	x	x	x	x	x	x	x	x	x	x		x
Waist circumference			x	x	x	x	x	x	x	x	x	x		x
HbA_{1c}		x	x		x		x		x			x		x
Glucose metabolism			x		x		x		x			x		
Lipids			x						x			x		

Trial Periods		Screening[1]	Randomisation	Treatment								End-of-treatment[2]	Follow-up[2]	End-of-trial – premature discontinuation[3]
Visit number		1	2	3	4	5	6	7	8	9	10	11	12	11X
Timing of visit	Weeks	-2	0	2	4	6	8	12	16	20	24	26	31	26
Visit window	Days			±3	±3	±3	±3	±5	±5	±5	±3	±3	+5	±3
SUBJECT RELATED INFO/ASSESSMENTS														
PRO questionnaire			x									x		
SAFETY														
Adverse events			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
ECG, overall interpretation[4]			x									x		
Fundoscopy/fundus photography			x											
Physical examination		x										x		
Vital signs		x	x	x	x	x	x	x	x	x	x	x		
Antibodies[5]			x						x			x	x	
Biochemistry			x						x			x		
Creatinine		x							x			x		
Calcitonin		x							x			x		
Haematology			x						x			x		
PK sampling				x	x	x	x	x	x	x	x	x		
PK sampling (trough + peak)[6]					x				x			x		
Blood pregnancy test[7]		x	x		x		x	x	x	x	x	x	x	x
Urinalysis			x						x			x		
TRIAL MATERIAL														
IV/IWRS call		x	x	x	x	x	x	x	x	x	x	x		
Dispensing visit			x	x	x	x	x	x	x	x	x			
Hand out directions for use of s.c. trial product			x	x	x	x	x	x	x	x	x			
Drug accountability				x	x	x	x	x	x	x	x	x		
REMINDERS														

Trial Periods		Screening[1]	Randomisation	Treatment								End-of-treatment[2]	Follow-up[2]	End-of-trial – premature discontinuation[3]
Visit number		1	2	3	4	5	6	7	8	9	10	11	12	11X
Timing of visit	Weeks	-2	0	2	4	6	8	12	16	20	24	26	31	26
Visit window	Days			±3	±3	±3	±3	±5	±5	±5	±3	±3	+5	±3
SUBJECT RELATED INFO/ASSESSMENTS														
Dispense glucose meter		x												
Dispense subject identity card		x												
Dispense diary		x	x	x	x	x	x	x	x	x	x	x		
Collect and review diary			x	x	x	x	x	x	x	x	x	x	x	
Attend visit fasting[8]			x		x		x		x			x	x	
Affirmation statement or Case book signed[9]													x	x
End of trial[9]													x	x

Abbreviations in table: ECG = electrocardiogram, HbA_{1c} = glycosylated haemoglobin, IV/WRS = interactive voice/web response system, PK = pharmacokinetics, PRO = patient reported outcome

2.1 Flow chart foot notes

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 (Visit 2).
x[2]	The End-of-treatment and Follow-up visits are applicable for all randomised subjects including subjects who have discontinued trial product prematurely.
x[3]	Subjects discontinuing trial product prematurely will be asked to attend the End-of-treatment (V11) as soon as possible after treatment discontinuation and the Follow-up – premature discontinuation (V12) five weeks later (+5 days visit window). Furthermore, they are asked to attend the End-of-trial – premature discontinuation visit (V11X) (see Section 8.1.9).
x[4]	An ECG performed for any reason unrelated to the trial within 30 days prior to the randomisation visit is acceptable as Visit 2 data, provided no clinical symptoms suggestive of cardiac disease has occurred in the meantime.
x[5]	At the randomisation visit, the antibody assessment must be done pre-dose.
x[6]	Trough and peak PK sampling is only applicable for subjects in the oral treatment arms. Subjects must attend the visit without having taken the tablet on the same day (see Section 8.4.10)
x[7]	For women of child bearing potential: Serum pregnancy tests must be performed.
x[8]	Fasting is defined as having consumed only water since midnight. For the Follow-up visit (V12) attending fasting is defined as having consumed only water for at least the preceding 2 hours.
x[9]	Affirmation statement/case book signing and end of trial are at the Follow-up visit (V12). Only patients who have discontinued treatment prematurely are asked to attend the End-of-trial – premature discontinuation visit (V11X) which will then be end of trial.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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

3.1 Type 2 diabetes mellitus and glucagon-like peptide-1

Type 2 diabetes (T2D) is a major global health problem. The disease aetiology is multi-factorial and includes genetic predisposition in combination with sedentary life style factors such as physical inactivity and obesity.

T2D is a multi-organ disease characterised by defective insulin sensitivity in liver and skeletal muscle and a relative impairment of insulin secretion capacity. Furthermore, a blunted secretion and/or action of incretin hormones (glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP)) from the gastrointestinal (GI) tract (L-cells) in response to meals are also characteristics of T2D. GLP-1 is an important post-prandial hormone secreted from the L-cells in the intestine with a stimulating effect on insulin secretion and an inhibitory role on glucagon secretion from the endocrine pancreas in a glucose-dependent manner. In addition, GLP-1 restores beta-cell sensitivity to glucose. Animal studies suggest that GLP-1 also increases beta-cell mass. Extra-pancreatic effects include delaying of gastric emptying and effects on insulin sensitivity, although the latter is less clear. Pharmacological levels of GLP-1 reduce food intake and induce weight loss. As the majority (>80%) of T2D patients are overweight, the weight reduction properties of GLP-1 analogues are perceived to be advantageous compared to many other therapies for T2D. Due to the beneficial effects of GLP-1 on both glycaemic and weight control, treatment of T2D patients with GLP-1 analogues is considered favourable.

3.2 Semaglutide and SNAC

Semaglutide is a long-acting GLP-1 analogue that has achieved clinical proof of concept when administered subcutaneously (s.c.). Currently, semaglutide is in clinical development (NN9535) as a once-weekly s.c. injection for the treatment of T2D. The NN9535 project is in phase 3 development, encompassing six major safety and efficacy trials (see Section 3.2.3.2 for clinical data on s.c. semaglutide).

Oral administration inherently represents a different absorption route to reach systemic circulation compared to s.c. administration.

Native GLP-1 and GLP-1 analogues have in general very low oral bioavailability when administered in a formulation without absorption enhancement. Formulation with an absorption enhancing excipient is therefore needed to increase the oral bioavailability. However, exposure

exhibits a substantially greater dose-to-dose variation following oral administration compared to s.c. administration. An oral drug product with this chemical structure and properties will, because of the compound's PK properties (i.e., very low clearance and long terminal half-life), and by using once-daily administration, limit the variation in steady state plasma exposure. The initial side effects like nausea may therefore be low or absent following gradual dose escalation. Food interaction is expected to limit absorption, but a long-acting GLP-1 analogue product will allow dosing in the fasting state, without compromising the effective plasma profile. In addition, GLP-1 therapy generally does not induce hypoglycaemia on its own, which potentially could have been problematic given the large intra-patient plasma exposure variation.

Sodium N-[8-(2-hydroxybenzoyl) amino] caprylate / salcaprozate sodium (SNAC) has been studied in combination with acyclovir, peptide tyrosine tyrosine (PYY), cromolyn, ibandronate and heparin. Impact on metformin when co-administering SNAC and metformin was investigated as part of another trial involving healthy volunteers. The trial did not show any increase in metformin exposure when adding SNAC[3]. When co-formulated with SNAC, exposure of ibandronate (a nitrogen-containing bisphosphonate), is increased by 11- and 17-fold (AUC and C_{max}, respectively). On the other hand, when co-administered with SNAC (in separate formulations) exposure was not affected compared to dosing ibandronate without SNAC, suggesting that the drug-drug interaction potential between SNAC and co-administered drugs with comparable physiochemical properties (compounds with permeability limited absorption) is low[4].

The most extensive safety and PK data are available from the heparin formulated with SNAC programme including 32 phase 1 studies (daily SNAC doses ranged from 0.172 g – 10.5 g) of which three investigated SNAC alone. The studies covered formulation development, food effect, hepatic and renal impairment, age effect and drug-drug interactions. Three phase 2 and 3 studies have assessed effects of orally delivered heparin solution (>1.5 g SNAC three times daily). At present, no drugs containing SNAC have received regulatory approval.

3.2.1 Nonclinical data

The non-clinical programme for semaglutide was designed according to the International Conference on Harmonisation (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 is generally well tolerated, with expected GLP-1 effects on food intake and body weight being the dose limiting effects, when dosed s.c. for up to two years in studies with rats and mice. No signs of overt toxicity, including safety concerns related to effects on the GI tract, were observed after oral administration of semaglutide for up to 26 weeks in rats and 17 weeks in cynomolgus monkeys. Two potential safety issues have been identified.

3.2.1.1 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. Early C-cell changes were also identified in repeated dose toxicity studies with semaglutide in mice. However this was not the case in other species including a 52-week repeat dose study in non-human primates at exposure levels up to 36-fold above the expected clinical exposure. The observed pattern of effects in mice and rats (thyroid C-cell proliferation preceded by increase in serum calcitonin) 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 receptor agonists, including liraglutide. The relevance for human subjects is unknown.

3.2.1.2 Teratogenicity in rats

Semaglutide has been concluded teratogenic in rats, with exposure at no observable adverse effect level (NOAEL) below expected human exposure. This effect is regarded to be caused by impairment of nutrient supply to the embryo across the inverted yolk sac with placental function which is specific to rats. Non-human primates and humans do not depend on a yolk sac with placental function to supply nutrients to the embryo early in pregnancy. The effect on rat embryo-foetal development is therefore not likely to be relevant to humans. Preliminary and main embryo-foetal development (EFD) and pre- and postnatal development (PPND) studies with doses corresponding to 7-fold expected clinical exposure in cynomolgus monkeys have been finalised. In the main EFD study sporadic abnormalities were reported across all dose groups and in the PPND study a dose dependent increase in early pregnancy losses were observed. The findings observed across the three studies in cynomolgus monkeys are not indicative of teratogenic potential of semaglutide in this species. The increase in early pregnancy losses is indicative of embryo-toxicity, which may be related to the maternal effect of semaglutide (marked body weight loss). A developmental toxicity NOAEL was determined at an exposure 0.8-fold the expected clinical exposure (1 mg/week). A risk for the developing human embryo or foetus cannot be definitely ruled out, but the absence of findings indicative of teratogenicity in the EFD and PPND studies in cynomolgus monkey decrease the level of concern.

A comprehensive review of results from the non-clinical studies can be found in the IB for Semaglutide (subcutaneous administration), Edition 8[5] and the IB for Oral administration of semaglutide (NN9924), Edition 5[6], or any updates of these documents

3.2.1.3 SNAC toxicology

The nonclinical safety programme for SNAC includes safety pharmacology, metabolism and PK and toxicology and is in line with the ICH M3 guideline[7]. SNAC was developed as an absorption enhancing excipient for the oral route of administration.

SNAC is rapidly absorbed (time to maximal concentration (t_{max}) within 1 hour) and eliminated ($t_{½}$ = 1 and 3 hours across species). SNAC is metabolised mainly via stepwise beta-oxidation and de-acetylation of the side chain and the parent compound and its metabolites also undergo conjugation with glucuronic acid. The main elimination route for SNAC metabolites is via urinary excretion.

SNAC was generally well tolerated in animals at and below oral doses of 500 mg/kg/day (NOAEL) for up to nine (Rhesus monkey) and twelve (rat) months. Although no overt specific organ toxicity has been observed, [redacted]. A series of nonclinical studies to explore possible cause of death have been initiated. These studies include investigations to expand the standard package of nonclinical studies on CV and respiratory function, and systematic investigations of histological changes in the GI tract and liver after dosing of high concentration/high volumes of SNAC. To support the assessment of exposure margins between rats and humans, extensive PK and metabolism studies in rats are carried out. The quantification of SNAC metabolites will also be assessed in the on-going multiple dose (MD) clinical trial (NN9924-3991).

In an on-going two-year carcinogenicity study with rats, one unexplained death occurred at a dose of 200 mg/kg/day. Several cases of unexplained death were observed at 900 mg/kg/day in repeat dose toxicity studies of 26 weeks and 52-weeks duration. A NOAEL for SNAC has been determined to be 90 mg/kg/day (corresponding to ~4 to 6 times a human dose of 300 mg based on exposure (area under curve)). Histological changes (perivascular lymphoid aggregates) have been observed in the lungs at all SNAC dose levels in the 6-month rat study. SNAC appeared to exacerbate these lesions which may be indicative of an immunosuppressant effect.

3.2.2 Nonclinical pharmacology and pharmacokinetics

The focus of the studies done in relation to oral administration of semaglutide in combination with SNAC has been on the following issues:

Mechanism *in vitro*

SNAC increases absorption of drug compounds through the GI epithelium, which has been shown in humans (e.g., for endogenous GLP-1). *In vitro* studies have indicated that transport of compounds occurs mainly via the trans-cellular route and the effect is dependent on both the concentration of SNAC and the duration of incubation.

Enhancement of absorption *in vivo*

SNAC enhances absorption of semaglutide from the stomach and small intestine in rats. There is considerable variability (coefficient of variation around 100%) with some animals showing no absorption. In the dog, there is higher bioavailability after oral dosing of tablets (1-2.5%) than after capsules (0.7%) or solution (0.07%). Semaglutide and SNAC have to be formulated in the same

tablet to get increased oral bioavailability of semaglutide, indicating that close interaction between the two molecules is necessary for enhancing the absorption. There is a strong reduction of bioavailability to practically zero when given concomitantly with food in dogs, and also an increasing amount of water dosed with the tablet seems to reduce oral bioavailability of semaglutide in this model, mimicking recent results in a human trial. Doses of SNAC of 150, 300 and 600 mg have been tested in dogs, and there was a tendency towards an optimum at 300 mg in terms of bioavailability. Furthermore, there is a tendency for non-linearity in bioavailability when increasing the amount of both SNAC and semaglutide in combination or semaglutide alone with constant SNAC content, whereas increasing amounts of SNAC alone (300 (one tablet) to 900 mg (three tablets)) with constant amount of semaglutide do not seem to significantly increase bioavailability.

Pharmacodynamics after oral administration

Semaglutide dosed in combination with SNAC is able to induce the same type of PD effects on blood glucose, food intake and body weight as seen after s.c. administration of semaglutide and other marketed GLP-1 analogues. Thus, semaglutide in combination with SNAC lowered blood glucose and body weight in diabetic db/db mice, and reduced food intake and body weight in normal rats.

3.2.3 Clinical data

3.2.3.1 Data from literature

Currently, no orally administered GLP-1 receptor agonist is available for the treatment of T2D.

There are, however, s.c. administered GLP-1 receptor agonists on the market and experience from their development has identified some potential safety issues for this class of compounds. Nonclinical thyroid C-cell tumours have been observed in rodents. Acute pancreatitis has been associated with chronic administration of GLP-1 receptor agonists in man. Elevated lipase has been observed in clinical studies but dose-response relationship and overall clinical significance is unclear. Hypoglycaemia, GI adverse events (i.e., nausea and vomiting), increased heart rate and renal dysfunction due to volume depletion following GI effects have also been observed.

3.2.3.2 Clinical data of s.c. semaglutide

As of 1 February 2013, 5 clinical pharmacology trials (NN9535- 1820, -3679, -3633, -3616 and -3819) and 1 phase 2 trial (NN9535-1821) have been completed using s.c. semaglutide. A total of 519 subjects have been exposed to s.c. semaglutide: 164 healthy subjects (both single and multiple dosing), 313 patients with T2D (up to 12 weeks of treatment) and 42 patients (4 subjects had T2D) with varying degrees of renal impairment (single dosing).

Pharmacokinetics

Results from 2 phase 1 trials (NN9535-3616 and 3819) show that s.c. semaglutide has pharmacokinetics (PK) properties compatible with once-weekly administration, with a median time to maximum concentration (tmax) of 36 hours post dosing and an elimination half-life (t½) in the range of 165-184 hours (~7 days, harmonic mean). Overall, the PK properties of s.c. semaglutide appear similar in Caucasian and Japanese subjects, and also in healthy subjects and subjects with T2D. In a trial with subjects with different degrees of renal impairment (NN9535-3616), data suggested that severe renal impairment result in a slightly higher exposure compared to subjects with normal renal function (AUC0- ∞ increased by approximately 22%), whereas subjects with mild or moderate renal impairment and subjects on haemodialysis had exposure similar to subjects with normal renal function. No safety signals were identified in either of the renal groups, and tolerability profiles appeared similar across renal groups; thus, a dose-reduction in subjects with severe renal impairment does not appear to be warranted.

Interaction with oral contraceptives was assessed at semaglutide 1.0 mg steady-state exposures in postmenopausal women with T2D (NN9535-3819). Steady-state exposures (AUC0-24h) of ethinylestradiol (EE) and levonorgestrel (LN) were slightly increased (by 10% and 21%, respectively), with bioequivalence established for EE but not for LN; the increase was seen when oral contraceptives were co-administered with semaglutide compared to oral contraceptives alone.

Bioequivalence was demonstrated for C_{max} of both EE and LN. These data indicate that semaglutide does not decrease the exposure of oral contraceptives, and suggest that no adjustments of oral contraceptive dose are warranted for women of childbearing potential using a low-dose oral contraceptive.

Efficacy

As of 1 February 2013, efficacy of s.c. semaglutide in the target population – subjects with T2D – has been investigated in one phase 2 dose range finding trial (NN9535-1821). The trial was a 12-week, randomised, double-blind, placebo- and active-controlled trial in which 411 adults with T2D received once-weekly s.c. injection of 1 of 5 semaglutide dose levels (0.1-1.6 mg) once-daily, open-label liraglutide (1.2 mg or 1.8 mg) or once-weekly placebo. 12 weeks of treatment, equivalent to 5-7 weeks in steady state on maintenance dose, provided statistically significant and clinically relevant improvement in glycaemic control for dose levels of 0.2 mg and above. Changes in HbA_{1c} from baseline was up to -1.19 % (placebo adjusted estimated treatment difference). Dose-dependent improvements in fasting plasma glucose (FPG) and postprandial plasma glucose were also observed. The improvement in glycaemic control was accompanied by weight loss for semaglutide doses of 0.8 mg and above (placebo adjusted estimated treatment difference up to -3.64 kg).

Safety

From the clinical trials conducted so far the following safety observations have been made.

Consistent with findings with other GLP-1 receptor agonists, common adverse events (AEs) included nausea and vomiting; most of them were mild to moderate in intensity. Hypoglycaemia has occurred in subjects receiving semaglutide and these events have mainly been minor.

An increase in heart rate has been observed in subjects exposed to semaglutide in line with the increase seen with other GLP-1 analogous. The implications of this increase are unknown.

As is the case with all protein-based pharmaceuticals, subjects treated with s.c. semaglutide may develop immunogenic and allergic reactions. Few allergic reactions have been reported in connection with semaglutide. These have mainly been mild and transient. However, more generalised reactions may occur.

Injection site reactions have been infrequently reported. These have mainly been mild and transient in nature.

Please see appropriate IB[5] for further details.

3.2.3.3 Clinical data of oral GLP-1

Clinical trials with increasing doses of oral semaglutide up to two tablets with 10 mg semaglutide and 300 mg SNAC have shown this to be safe and well tolerated. The oral semaglutide had acceptable bioavailability and a PK profile of two tablets with 10 mg semaglutide was similar to 0.5 mg s.c. semaglutide. Variability of the day-to-day PK profile was 3-4 times higher than compared to 0.5 mg s.c. once-weekly semaglutide but acceptable for further development.

The oral bioavailability of human GLP-1 has been demonstrated to increase several fold when formulated with SNAC with a t_{max} of approximately 15-30 min. In addition, even in healthy subjects a glucose-dependent insulinotropic action of GLP-1 upon oral delivery was shown.

Five phase 1 trials with oral semaglutide and SNAC have been completed:

- Single dose trial (NN9924-3691)
- Multiple dose trial 1 (NN9924-3692)
- Dosing condition trial (NN9924-3794)
- Pharmaco-scintigraphy trial (NN9924-3957)
- Multiple dose trial 2 (NN9924-3991)

For details on the individual trials, please see the current edition of the IB (Oral Administration of Semaglutide (NN9924)) Edition 5[6] and any updates hereof.

3.2.3.4 Clinical data of SNAC

The largest safety data set exists from the programme of orally administrated SNAC and heparin (all sponsored by [redacted]): 29 phase 1 trials (doses up to 10.5 g of SNAC), one phase 2 trial

(doses 1.5 g and 2.25 g of SNAC three times daily for 5 days) and two phase 3 trials (doses: 1.5 and 2.25 g of SNAC three times daily for 30 days) have been reported.

Oral SNAC exposure has most extensively been investigated in the phase 3 trial, named ERP-12. The objective of the trial was to investigate prevention of venous thrombotic complications following total hip replacement. Enrolled subjects were randomised in three treatments arms:

- Low dose SNAC (1.5 g) and heparin (60,000 USP units) thrice-daily for 30 days
- High dose SNAC (2.25 g) and heparin (90,000 USP units) thrice-daily for 30 days
- Enoxaparin sodium 30 mg s.c. twice-daily for 10 days

Total daily dose of oral SNAC was 4.5 g (low dose), 6.75 g (high dose) or 0 g (heparin s.c.). A total of 2,264 patients were enrolled with approximately 750 in each group.

The most frequently reported AEs were GI disorders with a dose relationship of SNAC and heparin, which also reflected the most common AEs reported for discontinuation. The SAEs were evenly distributed between the groups for all system organ classes other than GI disorders. Likewise, all deaths were evenly distributed between the groups and their nature and diversity did not indicate any causal relationship to trial drug. No other clinical significant safety issue was identified in the trial[8].

For further details please see the current edition of the IB (Oral Administration of Semaglutide (NN9924)) Edition 5[6] and any updates hereof.

3.3 Risks and benefits of the trial

There are s.c. administered GLP-1 receptor agonists on the market and experience from their development as well as experience from the s.c. semaglutide development programme have identified some potential safety issues for this class of compounds: 1) risk of teratogenicity, 2) risk of thyroid C-cell tumours, 3) risk associated to high doses of SNAC, 4) risk of carcinogenicity of SNAC, 5) risk of pancreatitis, 6) risk of antibody formation, 7) risk of allergic reactions, 8) risk of heart rate increase, 9) risk of severe risk of hypoglycaemia and 10) risk of altered renal function.

For further details please see the current edition of the IB (Oral Administration of Semaglutide (NN9924)) Edition 5[6] and any updates hereof.

In this trial, most subjects will receive a treatment anticipated to be more efficacious than the treatment they receive at the time of randomisation into the trial. It is expected that subjects will benefit from the trial treatment with respect to optimised glycaemic control, a reduced risk of long-term diabetic complications and a potential weight loss. The subjects in this trial will receive trial drug and auxiliary free of charge. Furthermore it is expected that all subjects participating in the trial will benefit from participation through close contact with the study site and close follow-up of

their T2D. Such careful medical examination will most likely result in an intensified management of their diabetes.

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile of semaglutide generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of once-daily doses of 2.5 to 40 mg semaglutide with 300 mg SNAC or once-weekly doses of 1.0 mg semaglutide in accordance with the planned clinical trial. The risk to the subjects in this trial is low and acceptable in view of the benefits an oral GLP-1 analogue would provide to subjects with T2D.

3.4 Rationale for the trial

The trial will compare efficacy of oral semaglutide formulated with a fixed dose of 300 mg SNAC. To facilitate the generation of clinical data in subjects with T2D, the NN9924-3790 trial has been designed to investigate a dose range expected to cover relevant therapeutic levels, including systemic exposure equivalent to 0.5 and 1.0 mg of once-weekly s.c. semaglutide. Additional dose levels are examined to elucidate a wider dose-response spectrum below and above the expected therapeutic range. In addition, the trial will explore the safety and tolerability of three different dose escalation approaches (i.e., slow, standard and fast). Finally, the trial will compare parameters of efficacy, safety and tolerability and population PK after 26 weeks of treatment between the treatment arms.

Data from the NN9924-3790 trial combined with the results of other trials investigating semaglutide will support the decision to continue into phase 3 development.

4 Objective(s) and endpoint(s)

The objectives of the trial, addressed after 26 weeks of treatment, are as follows:

4.1 Objectives

4.1.1 Primary objective

- To compare the efficacy on glycaemic control of oral semaglutide in a SNAC formulation against placebo in subjects with T2D

4.1.2 Secondary objectives

- To compare the efficacy on glycaemic control of oral semaglutide in a SNAC formulation against s.c. semaglutide in subjects with T2D
- To compare the safety and tolerability of three dose escalation schemes using a single end dose level during 26 weeks administration of oral semaglutide and SNAC in a tablet formulation in subjects with T2D
- To compare parameters of efficacy, safety and tolerability, and population PK as reflected by endpoints below after 26 weeks of treatment

4.2 Endpoints

4.2.1 Primary endpoint

- Change in HbA_{1c} from baseline to after 26 weeks of treatment

4.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

- Subjects who, after 26 weeks of treatment, achieve (yes/no) HbA_{1c} <7% (53 mmol/mol)*
- Change in fasting plasma glucose (FPG), C-peptide, fasting insulin and glucagon from baseline to after 26 weeks of treatment
- Change in insulin resistance (homeostatic model assessment index of insulin resistance (HOMA-IR)) and beta-cell function (homeostatic model assessment index of beta-cell function (HOMA-B)) from baseline to after 26 weeks of treatment
- Change in fasting lipid profile (total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL), triglycerides and free fatty acids) from baseline to after 26 weeks of treatment
- Change from baseline to week 26 in the patient reported outcome Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (generic questionnaire)
- Change in body weight from baseline to after 26 weeks of treatment*
- Change in waist circumference from baseline to after 26 weeks of treatment*

- Change in body mass index (BMI) from baseline to after 26 weeks of treatment*

Supportive secondary safety endpoints

- Number of treatment emergent adverse events (TEAEs) recorded from baseline until week 31*
- Number of confirmed hypoglycaemic episodes recorded from baseline until week 31*
- Change in vital signs (pulse, systolic- and diastolic blood pressure) from baseline to after 26 weeks of treatment
- Change in electrocardiogram (ECG) from baseline to after 26 weeks of treatment
- Change in physical examination from baseline to after 26 weeks of treatment
- Change in laboratory safety variables (haematology, biochemistry, hormone and urinalysis) from baseline to after 26 weeks of treatment
- Occurrence of antibodies against semaglutide during 26 weeks of treatment (positive/negative):
  - Anti-semaglutide antibodies
  - Anti-semaglutide antibodies with *in vitro* neutralising effect
  - Anti-semaglutide antibodies cross reacting with endogenous GLP-1
  - Cross reacting antibodies with *in vitro* neutralising effect to endogenous GLP-1
  - Antibody level during 26 weeks of treatment

Supportive secondary pharmacokinetic endpoint

- Semaglutide concentrations to be evaluated in a population PK analysis

* Key supportive secondary endpoint prospectively selected for posting on clinicaltrials.gov

5 Trial design

5.1 Type of trial

This is a randomised, partially-blinded, dose range, dose escalation, multicentre trial including nine treatment arms in total; seven oral semaglutide treatment arms, an oral placebo arm and an s.c. semaglutide arm with a parallel design (see Figure 5–1). All treatment arms include subjects with T2D who have failed on diet and exercise and/or metformin. The placebo tablets do not contain SNAC.

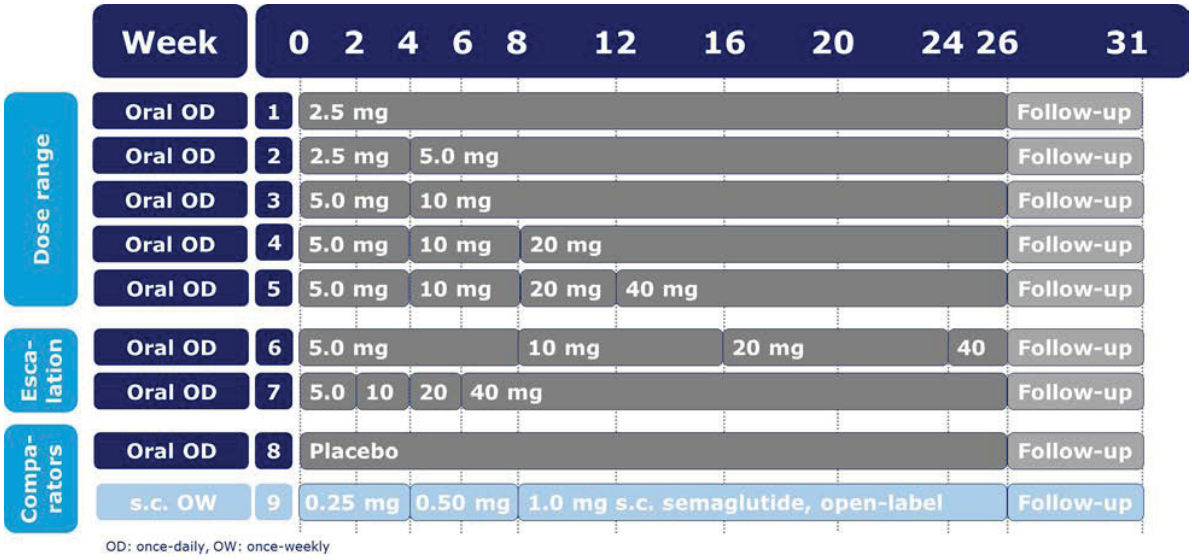

Figure 5–1 Trial design of NN9924-3790

Subjects with T2D will be randomised in an equal manner with 67 subjects planned to be randomised per treatment arm. Treatment arms 1-8 will include once-daily dosing of a tablet and will be blinded. Treatment arm 9 features open-label once-weekly s.c. injection. All arms include 26 weeks of treatment and a 5 week follow-up period. Oral dosing will be performed following specified fasting conditions (see Figure 5–2).

The nine treatment arms will include:

1. Semaglutide tablets once-daily: 2.5 mg for 26 weeks
2. Semaglutide tablets once-daily: 2.5 mg for 4 weeks, then 5.0 mg for 22 weeks
3. Semaglutide tablets once-daily: 5.0 mg for 4 weeks, then 10 mg for 22 weeks
4. Semaglutide tablets once-daily: 5.0 mg for 4 weeks, then 10 mg for 4 weeks, then 20 mg for 18 weeks

5. Semaglutide tablets once-daily: 5.0 mg for 4 weeks, then 10 mg for 4 weeks, then 20 mg for 4 weeks, then 40 mg for 14 weeks
6. Semaglutide tablets once-daily: 5.0 mg for 8 weeks, then 10 mg for 8 weeks, then 20 mg for 8 weeks, then 40 mg for 2 weeks
7. Semaglutide tablets once-daily: 5.0 mg for 2 weeks, then 10 mg for 2 weeks, then 20 mg for 2 weeks, then 40 mg for 20 weeks
8. Placebo tablets once-daily for 26 weeks
9. Semaglutide injections once-weekly: 0.25 mg for 4 weeks, then 0.50 mg for 4 weeks, then 1.0 mg for 18 weeks

For all groups the trial medication will be add-on to previous metformin therapy or as monotherapy in the case where the subject with T2D is treated with diet and exercise alone. At randomisation, subjects will be stratified according to one stratification value with two strata: Treatment with metformin at screening (yes/no).

5.2 Rationale for trial design

Parallel treatment groups and a randomised partially-blinded, controlled design have been chosen in accordance with the trial objectives. To avoid bias in the assessment of the different doses of oral semaglutide, the eight oral treatment arms are double-blind. The doses are escalated in standard four week intervals to limit gastrointestinal AEs. Escalation intervals of two weeks and six weeks are also being explored to investigate effect on onset of action and overall AEs.

The use of s.c. semaglutide as active comparator was chosen to confirm that oral semaglutide in at least one of the selected doses reach the same levels of systemic exposure as for s.c. semaglutide. The active comparator is open-label to limit unnecessary injections (e.g., by use of double-dummy) as the objectives of the trial are to investigate the effects of the oral formulation.

5.3 Treatment of subjects

The subjects will attend a screening visit to determine their eligibility. If found eligible, the subjects will return for the first treatment visit where they will be randomised and receive treatment. The total duration of the trial will be 31 weeks for all subjects from randomisation to last visit. The highest dose for any trial subject will be 40 mg oral semaglutide once-daily or 1.0 mg s.c. semaglutide once-weekly.

Metformin is considered background medication (non-investigational medicinal product) and will not be provided by Novo Nordisk. Metformin should be used at the discretion of the investigator. Treatment with metformin extended/slow release formulations is allowed.

For the safety of the subjects, medications with a narrow therapeutic window may not be used in the trial (see the exclusion criteria, Section 6.3).

Subjects will follow a fixed dose escalation regimen, which they have been randomised to, following the scheme in Figure 5–1.

5.3.1 Dose levels and escalation regimen for oral dosing

Subjects on the oral dosing (treatment arms 1-8) must administer the dose following specific rules:

- Fasting for at least six hours (e.g., in the morning following an overnight fast) before tablet ingestion
- Water and oral concomitant medication is allowed two hours prior to dosing
- Intake of maximum 120 mL of water is allowed when swallowing the tablet
- Subjects are required to abstain from food and fluid intake for at least 30 minutes after ingestion of oral semaglutide or placebo
- Oral concomitant medication can be taken two hours post-dosing. If taken with food, concomitant medication can be administered 30 minutes after ingestion of the semaglutide or placebo tablet

See illustration of oral dosing and fasting rules in Figure 5–2.

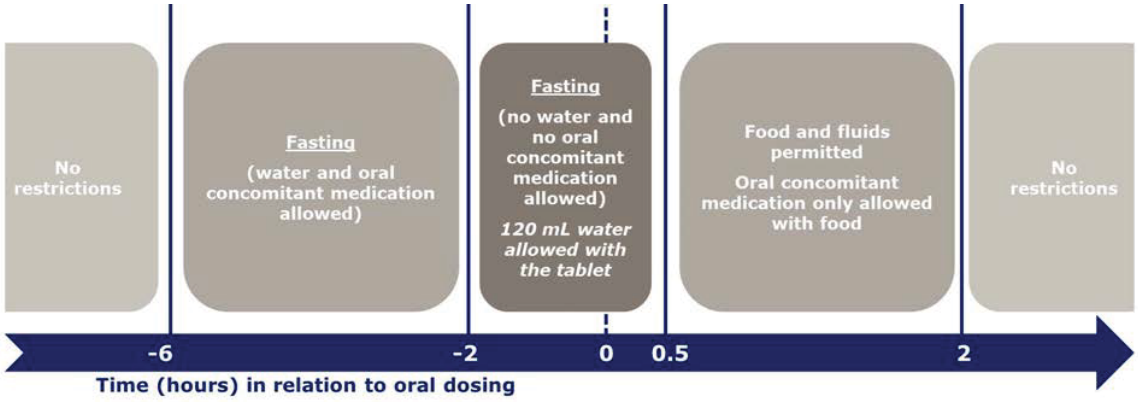

Figure 5–2 Dosing and fasting conditions for oral treatment (arms 1-8)

5.3.2 Dose levels and escalation regimen for s.c. dosing

Subjects randomised to the s.c. treatment arm will follow a fixed dose escalation for semaglutide. The maintenance dose of 1.0 mg will be reached after four doses (four weeks) of 0.25 mg, followed by four doses (four weeks) of 0.50 mg. The maintenance dose of 1.0 mg, once attained, may not be decreased for the duration of the study. Injections may be administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. The injections should be administered on the same day of the week during the trial.

5.4 Treatment after end of trial

The trial products will not be available to subjects after the end of trial.

When discontinuing trial products the subject should be switched to a suitable marketed product at the discretion of the investigator.

5.5 Rationale for treatment

The oral route of semaglutide administration investigated has been chosen to increase convenience and initiate earlier use of GLP-1 treatment of T2D patients, thus offering true GLP-1 benefits in a tablet format. The dose range of the oral treatment (2.5 mg, 5 mg, 10 mg, 20 mg and 40 mg) has been chosen based on phase 1 data and modelling derived from phase 1 trials with the aim to cover the same exposure as observed with s.c. semaglutide. The standard escalation scheme (i.e., dose escalation every four weeks to desired dose) has been chosen based on phase 1 data. The slow and fast dose escalation arms will investigate if AEs decrease or increase, respectively, compared to the standard dose escalation. The 26-week treatment period will provide additional data on safety and tolerability, investigate the variability at steady state exposure, test for efficacy and suggest which doses and escalation scheme to continue into pivotal development.

For further details please see the current edition of the IB (Oral Administration of Semaglutide (NN9924)) Edition 5[6] and any updates hereof.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 1,005
Number of subjects planned to be randomised: 603
Number of subjects expected to complete the trial: 482

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 inform consent
3. BMI ≥25 and ≤40 kg/m^2
4. Subjects diagnosed with T2D treated with diet and exercise and/or who have been on a stable dose of metformin for at least 30 days prior to screening
5. HbA_{1c} 7.0-9.5% (53-80 mmol/mol) (both inclusive)

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 informed consent
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice) for the duration of the trial and for three months following last dose
   Germany: Adequate contraceptive measures are implants, injectables, combined oral contraceptives, hormonal intrauterine device, sexual abstinence or vasectomised partner.
   Sweden: Adequate contraceptive measures are hormonal intrauterine devices, hormonal oral contraceptives, hormonal implants or injections, double barrier (a condom or diaphragm) with spermicide, sexual abstinence or vasectomised partner.
   United Kingdom: Established use of oral, injected or implanted hormonal methods of contraception, intrauterine device or intrauterine system, barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilisation or true abstinence when in line with the preferred and usual lifestyle of the subject.
4. Participation in another clinical trial within 30 days before the screening visit
5. Any chronic disorder or severe disease which, in the opinion of the investigator, might jeopardise subject's safety, compliance with the protocol and/or ability to complete the study

6. Subjects on selected oral medication with a narrow therapeutic window, such as warfarin, digoxin, tricyclic antidepressants, lithium, aminophylline, theophylline and anticonvulsants
7. History of chronic pancreatitis or idiopathic acute pancreatitis
8. Screening calcitonin value ≥ 50 ng/L
9. Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2)
10. Chronic malabsorption, regardless of aetiology
11. History of Crohn's disease, ulcerative colitis, or other inflammatory bowel disease
12. Previous gastrointestinal surgery such as invasive and corrective procedures involving the oesophagus, stomach, duodenum, gallbladder, pancreas or intestinal resections. Exempt are subjects that underwent uncomplicated surgical and diagnostic procedures such as appendectomy, hernia surgery, polypectomy, biopsies, as wells as colonic- and gastric endoscopy
13. Surgery scheduled for the trial duration period (excluding minor surgical procedures performed in local anaesthesia, according to the opinion of the investigator)
14. Treatment with glucose lowering agent(s) other than metformin as stated in the inclusion criteria in a period of 90 days before the screening visit
15. Mental inability, unwillingness or language barrier precluding adequate understanding of or compliance with study procedures
16. Impaired renal function defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 per Modification of Diet in Renal Disease (MDRD) formula
17. Heart failure, New York Heart Association (NYHA) class IV
18. Within the past 6 months before the screening visit, any of the following: Episode of unstable angina, acute coronary event, cerebral stroke/transient ischemic attack or other significant cardiovascular event as judged by the investigator
19. Uncontrolled hypertension (defined as systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥100 mmHg)
20. Known proliferative retinopathy or maculopathy requiring acute treatment according to the opinion of the investigator
21. Diagnosis of malignant neoplasm in the previous five years from the screening visit (except basal cell skin cancer or squamous cell skin cancer)

6.4 Rescue criteria

Subjects with unacceptable hyperglycaemia should be offered treatment intensification (rescue medication) according to local label at the discretion of the investigator as add-on to randomised treatment and should continue to follow the protocol-specified visit schedule. Rescue medication should exclude other incretin-based therapies such as other GLP-1 receptor agonists, DPP-4 inhibitors and amylin analogues.

Unacceptable hyperglycaemia in this trial is defined as:

- FPG >15 mmol/L (270 mg/dL) from baseline to week 6
- FPG >13.3 mmol/L (240 mg/dL) from week 6 to week 12
- FPG >11.1 mmol/L (200 mg/dL) or HbA_{1c} > 8.0% (64 mmol/mol) from week 12 to end of trial

6.5 Withdrawal criteria and discontinuation of trial product

6.5.1 Withdrawal from trial

The subject may withdraw at will at any time. The subject may be withdrawn from the trial at the discretion of the investigator due to a safety concern. Please see Section 8.1.10 for procedure to be performed in case of subject withdrawal.

A subject must be withdrawn from the trial if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Pregnancy
3. Intention of becoming pregnant

Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule, missing assessments, trial product discontinuation due to AE (see Section 6.5.2), unwillingness to cope with injection regimen, development of co-morbidities or clinical outcomes, hence this should not be considered as a valid reason for withdrawal from the trial.

Subjects considering withdrawing from the trial should be encouraged to have the procedures performed according to the End-of-treatment visit and the Follow-up visit, please see Section 8.1.8.

Subjects who are withdrawn will not be replaced.

6.5.2 Discontinuation of trial product

The trial treatment must be discontinued if the subject meets one of the following criteria:

1. The investigator suspects acute pancreatitis. All drugs suspected to relate to this condition should be discontinued until confirmatory tests have been conducted and appropriate treatment should be initiated. Subjects who are diagnosed with acute pancreatitis must be discontinued from trial treatment. Diagnosis is based on at least 2 of the following 3 criteria:
    a. characteristic abdominal pain
    b. amylase and/or lipase > 3x upper normal range, or
    c. characteristic findings on ultrasound / computerised axial tomography (CT) / magnetic resonance imaging (MRI)
2. Calcitonin level ≥50 ng/L. The subject should be referred to a specialist in thyroid disease. All drugs suspected to relate to this condition should be discontinued

3. Other safety concerns as evaluated by the investigator

A treatment discontinuation session must be performed in the interactive voice/web response system (IV/WRS). The primary reason for discontinuation of the IMP must be specified in the electronic case report form (eCRF).

Subjects discontinuing the IMP should be called in for the End-of-treatment visit as soon as possible after discontinuation of the IMP and for the Follow-up visit five weeks later. Furthermore, the subjects should attend the End-of-trial – premature discontinuation visit (see Section 8.1.9).

If the IMP is discontinued, the subject can be prescribed alternative therapy at the investigator's discretion.

6.6 Rationale for trial population

This trial will include adult subjects with T2D and insufficient glycaemic control following treatment with diet/exercise or metformin. The T2D subjects will have an HbA_{1c} of 7.0-9.5% and a BMI of 25-40 kg/m^2. The trial will be carried out in Europe, North America and single countries in Africa, Asia and the Middle East as the first global, multicentre trial and will include both genders. This population is expected to mimic the target population in both a future phase 3 programme and once marketed.

7 Milestones

Planned duration of recruitment period (i.e., first subject first visit (FSFV) on 2 Dec 2013 – last subject first visit on 21 Apr 2014): 20 weeks

End of trial is defined as last subject last visit: 8 Dec 2014

Recruitment

The clinical sites participating in the trial will recruit subjects according to a recruitment plan.

The screening and randomisation rate will be followed closely via the interactive voice/web response system (IV/WRS) 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 IV/WRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation will be randomised.

Trial registration

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[9], the Food and Drug Administration Amendment Act (FDAAA)[10], European Commission Regulation for EudraCT[11] 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

8.1.1 Introduction

Throughout the trial the investigator must ensure working in accordance with ICH GCP[1] and local regulations. The investigator must ensure that trial procedures are performed as described in the protocol. Any discrepancies will result in protocol and/or GCP deviations and the investigator must take appropriate actions to avoid recurrence of the detected discrepancies.

8.1.2 Visit 1 (Screening)

For procedures and assessments performed at screening, please see flow chart Section 2.

Investigators must obtain informed consent for each subject no later than at Visit 1 prior to any protocol-related procedures. For information on informed consent procedure please see Section 18.1.

All subjects will be provided with a copy of their own signed and dated informed consent form.

The IV/WRS must be contacted to register the subject as screened (see Section 10) at the screening visit. Subject will be assigned a unique number (lowest available number allocated to site) which is maintained throughout the trial.

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list and may be generated from IV/WRS.

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.

For screening failures the screening failure form must be completed with the reason for not continuing in the trial. Serious and non-serious adverse events from screening failures must be transcribed by the investigator into the electronic case report form (eCRF). Follow-up of serious adverse events (SAEs) must be carried out according to Section 12.3. A screening failure session must be made in the IV/WRS. The case book must be signed.

Re-screening of subjects having signed the informed consent is not allowed.

Once all data relating to Visit 1 have been obtained, these must be reviewed by the investigator to ensure that the subject is eligible to continue the trial.

8.1.3 Fasting visits

The subjects should attend several visits in a fasting state (see Section 2). Fasting is defined as having consumed only water since midnight. An exception from this is the Follow-up visit where fasting is defined as having consumed only water for the last two hours.

Subjects are allowed to take the IMP and oral concomitant medication during fasting if following the conditions outlined in Section 5.3. An exception is at three visits in the oral treatment arms where peak and trough PK will be measured and the oral IMP will be administered at the site (see Section 8.4.10).

If a subject attends a fasting visit in a non-fasting condition or a peak and trough PK meeting having taken the oral dose the same day, then blood sampling and body weight must be re-scheduled within the visit window. The date for each fasting assessment or PK assessment at the specific visit must be updated accordingly in the eCRF. All other assessments can be performed. Re-scheduling of fasting visits or peak and trough PK visits are not considered unscheduled visits.

8.1.4 Unscheduled visits

An unscheduled visit can be scheduled at any time at the discretion of the investigator. An unscheduled visit form must be completed in the eCRF indicating the reason for the visit. Coming to the site for any of the following reasons should not be considered as unscheduled visits:

- dispense additional trial products
- dispense additional auxiliary supplies
- re-test of blood- or urine sampling (not allowed if results are available)

In case of additional trial products being dispensed, a dispensing session should be made in the IV/WRS selecting additional medication.

8.1.5 Visit 2 (Randomisation)

For procedures and assessments performed at randomisation, see Section 2.

Visit 2 will take place within two weeks after Visit 1.

The randomisation session must be performed in the IV/WRS which will allocate the Dispensing Unit Number (DUN) of the IMP to be dispensed to the subject. Eligible subjects will be randomised into one of nine treatment arms.

The IMP will be dispensed to the subject by the trial site staff, hospital pharmacy staff or equivalent at each 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 oral IMP administration at every dispensing visit.

For subjects randomised to the s.c. injection, the investigator must document that a direction for use (DFU) is handed out at each dispensing visit. Ability and willingness to self-inject can be tested by administration of injections with a test pen for subjects who do not have prior experience with self-injection. Novo Nordisk will provide the test pens.

Please see Section 9 for further information about the IMPs.

8.1.6 Visit numbers

For visit numbers, timing of site 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 (see Section 2).

8.1.7 Visits 3-10 (Treatment)

For procedures and assessments performed at visits 3, 4, 5, 6, 7, 8, 9, and 10, see the flow chart in Section 2.

8.1.8 Visits 11-12 (End-of-treatment and Follow-up)

All subjects must attend the End-of-treatment visit (Visit 11) which should be scheduled when the subject has completed the treatment with the IMP and a Follow-up visit (Visit 12) should be performed at least 5 weeks after (+5 days visit window). A completion session must be performed in the IV/WRS. Please see the flow chart for details (Section 2).

The Follow-up visit serves to collect AEs, technical complaints, hyperglycaemic episodes and blood samples for anti-semaglutide antibodies.

8.1.9 Visit 11X (End-of-Trial – premature discontinuation)

For subjects who discontinue the IMP prematurely the End-of-treatment visit (Visit 11) should be scheduled shortly after the subject has discontinued the IMP. The Follow-Up visit (Visit 12) should be scheduled at least 5 weeks (+5 days visit window) after treatment discontinuation. Treatment discontinuation and drug accountability sessions must be done in the IV/WRS. Please see the flow chart for details (Section 2).

Subjects who discontinue their IMP prematurely must also be requested to attend the visit End-of-trial – premature discontinuation (Visit 11X) at the time of the scheduled end of treatment (i.e., 26 weeks after randomisation). Data on AEs and the primary endpoint from this final visit are important for the data quality of the trial.

8.1.10 Withdrawals

If a subject is withdrawn from the trial, the investigator must aim to undertake procedures similar to those for visit 11 (End-of-treatment) as soon as possible, and the Follow-up visit at least 5 weeks after. The end-of-trial form must be completed and the subject should return all trial products to the site to have final drug accountability performed. Drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be performed in the IV/WRS (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 discontinuation must be specified on the end-of-trial form in the eCRF (see Section 6.5.1):

8.1.11 Investigator's assessment

Review of diaries, laboratory reports, ECGs, eye examination (fundoscopy/fundus photography), physical examination and patient reported outcome (PRO) questionnaires must be documented with the investigator's or delegated site staff's dated signature either on the front page of the documents or in the subject's medical record. The documents should be signed prior to the following visit and must be retained at the investigator site as source documentation.

For ECGs and eye examinations the evaluations must be in the following categories:

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

For laboratory report values outside the reference range, the investigator must specify whether the value is non-clinically or clinically significant. All laboratory printouts must be signed and dated by the investigator on the day of evaluation.

In case of abnormal clinically significant findings (e.g., in laboratory reports, ECGs, eye examination or physical examination), the investigator must state a comment in the subject's medical record and record this on the concomitant illness form in the eCRF at the screening or randomisation visits. At subsequent visits any clinically significant changes or new clinically significant findings must be reported as an AE according to Section 12.2.

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.

8.2 Subject related information

8.2.1 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e., at the screening visit or found as a result of screening procedure). The concomitant illness should be recorded in the eCRF.
Medical history is a medical event that the subject has experienced in the past. Only medical history considered relevant 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.

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.

Smoking habit: Details of smoking habit must be recorded at the first visit. 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 smokes or has smoked, record approximately when the subject started smoking and, if applicable, when the subject stopped smoking.

Diabetes complications should be captured in the medical history or concomitant illness form and should include:

- diabetic retinopathy
- diabetic neuropathy
- diabetic nephropathy
- macroangiopathy including peripheral vascular disease
- other complications where relevant

8.2.2 Concomitant medication

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

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

The information collected for each concomitant medication includes:

- trade name or generic name
- indication
- start 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 recorded and reported according to Section 12.2. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.2.3 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)

8.2.4 Diagnosis of diabetes

The date of diagnosis of T2D will be recorded in the eCRF at screening.

8.2.5 Diabetes treatment history

The dose and the date of initiating treatment with metformin will be recorded in the eCRF at screening if the subject is currently treated with metformin.

8.2.6 History of gallbladder disease

Information related to history of gallbladder disease (i.e., pancreatitis, gallstone disease, cholecystis) will be recorded in the eCRF at screening visit.

8.2.7 History of cardiovascular disease

Information related to history of cardiovascular disease (CVD) (i.e., heart failure including NYHA class, hypertension or ischaemic stroke) or other risk factors for CVD will be recorded in the eCRF at screening visit.

8.2.8 Renal impairment history

Information related to history of renal impairment will be recorded in the eCRF at screening visit.

8.2.9 Post-dose fasting routines

The fasting routines following oral trial product administration should be recorded in the subject's diary handed out at Visit 10 and transcribed to the eCRF by the investigator at the End-of-treatment visit to determine the usual fasting time after tablet ingestion during the trial.

The post-dose fasting routines are recorded as time in minutes from IMP administration until the usual time of:

- food consumption (i.e., meal or snack)
- drinking (i.e., any beverage including water)

8.3 Assessments for efficacy

8.3.1 Blood samples

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

Glucose metabolism:

- HbA_{1c}
- Fasting plasma glucose (FPG)
- Fasting insulin
- Fasting C-peptide
- Fasting glucagon

Lipids (all fasting):

- Total cholesterol
- LDL-cholesterol
- VLDL-cholesterol
- HDL-cholesterol
- Triglycerides
- Free fatty acids

8.3.2 Body measurements

Body weight

Body weight should be measured without shoes and only wearing light clothing. It should be recorded with one decimal and using the same set of scales throughout the trial (i.e., kg or lb)

Height

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

Waist circumference

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

Three consecutive measurements of waist circumference should be performed and recorded in the eCRF. The waist circumferences will be measured using a non-stretchable measuring tape. It should be recorded to the nearest ½ cm or ¼ inch using the same measuring tape throughout the trial.

The subject should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject should be standing with arms down their side and feet together. 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.

BMI

BMI will be captured in the eCRF using the equation:

BMI = Body weight (kg)/(Height (m) x Height (m)) [kg/m^2 = lb/in^2 x 703]

8.3.3 Patient reported outcomes

The PRO questionnaire used in this trial is SF-36v2™.

The questionnaire should be completed by the subject as specified in the flow chart, see Section 2, preferably before any other trial-related activities. It takes approximately ten minutes to complete the questionnaire.

The questionnaire is checked by the investigator for completion and unreported AEs (see Section 8.1.11). The investigator or site staff must date and sign the document and enter the results in the eCRF.

The SF-36v2™ questionnaire will be used to assess subjects overall Health related Quality of Life and can also be used to estimate Quality-Adjusted Life Year which is used in cost effectiveness calculations. This instrument contains 36 items and measures the individual overall health related quality of life on eight domains: physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health.

8.4 Assessments for safety

8.4.1 Hypoglycaemic episodes

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

All plasma glucose values:
- ≤ 3.9 mmol/L (70 mg/dL) or
- > 3.9 mmol/L (70 mg/dL) when they occur in conjunction with hypoglycaemic symptoms,

should be recorded by the subject in the diary. These must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from Visit 1-12.

The record should include the following information:
- Date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available)
- Whether the episode was symptomatic
- Whether the subject was able to treat him/herself
- Date and time of last trial product administration prior to episode
- Type of last trial product prior to episode
- Date and time of last main meal prior to episode
- Whether the episode occurred in relation to increased physical activity

The answer to the question: "Was subject able to treat him/herself?" must be answered "No" if oral carbohydrates, glucagon or IV glucose had to be administered to the subject by another person. Oral carbohydrates should not be given if the subject is unconscious.

A hypoglycaemic episode form must be filled in for each hypoglycaemic episode. If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and an electronic safety information form (eSIF) must also be filled in (see Section 12.2)

For all FPG values measured by central laboratory that meet the definition of a hypoglycaemic episode, a hypoglycaemic episode form must be completed in the eCRF.

8.4.2 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:
- Differential count (basophils, eosinophils, lymphocytes, monocytes and neutrophils)

- Erythrocytes
- Haematocrit
- Haemoglobin
- Leucocytes
- Thrombocytes

Biochemistry:
- Alanine aminotransferase
- Albumin
- Alkaline phosphatase
- Amylase
- Aspartate aminotransferase
- Bilirubin, total
- Calcium, total
- Calcium, albumin corrected (ionized)
- Creatine kinase
- Creatinine
- Lipase
- Potassium
- Sodium
- Urea

Hormone:
- Calcitonin (see Section 8.4.11)

Pregnancy test:
- Serum or plasma human chorionic gonadotropin (hCG)

8.4.3 Pregnancy test

Females of childbearing potential will have a serum pregnancy test (i.e., beta-hCG) performed as specified in Section 2 or as required by local law.

Pregnancy testing will not be required (unless required by local law) for subjects who are post-menopausal (defined as women who have undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation or for women above the age of 50, who have been without menstrual period for at least 1 year).

8.4.4 Urinalysis

Subjects will be asked to bring first morning urine during the trial (see Section 2). The urine samples will be analysed at the central laboratory to determine levels of the following safety laboratory parameters:

- Urinary albumin to creatinine ratio
- Urinalysis by urine dip-stick: erythrocytes, protein, glucose and ketones, pH

8.4.5 Antibodies

Blood samples will be drawn during the trial and analysed at specialised laboratory for determination of serum antibodies to semaglutide, including cross reactivity to endogenous GLP-1 (see flow chart, section 2). Samples positive for antibodies against semaglutide will be further characterised for *in vitro* neutralising effect towards semaglutide. In addition, samples positive for antibodies cross-reacting with endogenous GLP-1 will be analysed for *in vitro* neutralising effect towards endogenous 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 assessment must be done pre-dose.

8.4.6 Vital signs

The method for measuring systolic and diastolic blood pressure needs to follow the standard clinical practice at site but as a minimum; the following guideline must be adhered to: Avoid caffeine, smoking and exercise at least 30 minutes prior to measuring the blood pressure. The blood pressure should be measured in a sitting position, with the legs uncrossed, the back and arms supported and positioned at heart level. Subjects should be sitting for at least five minutes before the first measurement is taken. The subject should not talk during the measurement. Pulse (beats per minute) should be measured after resting for five minutes in a sitting position. Results are recorded in the eCRF.

In case of an “abnormal, clinically significant finding”, the investigator must record the finding on the medical history or concomitant illness form if present at screening.

Any new abnormal, clinically significant finding during the trial and any clinically significant worsening from baseline must be reported as an AE.

8.4.7 Electrocardiogram – 12-lead

12-lead ECG will be performed during the trial (see Section 2). All ECGs will undergo central assessment.

Sites will be informed of the central ECG evaluation in case this evaluation reveals an abnormal ECG reading. If the abnormality represents an unreported AE, SAE or MESI, such findings must be reported if the investigator finds the abnormality clinically significant (see Section 8.1.11).

Additional ECG recordings can be performed at the investigators site at the investigator's discretion at other visits than the planned ECG visits. All such ECGs will undergo central assessment.

An ECG performed for any reason unrelated to the trial within 30 days prior to the randomisation visit is acceptable as Visit 2 data, provided no clinical symptoms suggestive of cardiac disease has occurred in the meantime.

If the ECG 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.

For electronic central ECG evaluation vendor details, see Attachment I.

8.4.8 Fundoscopy/fundus photography

Fundoscopy/fundus photography will be performed at randomisation by the investigator or according to local practice. Results of the fundoscopy/fundus photography will be reviewed, signed and dated by the investigator (see Section 8.1.11). Dilation is not a requirement.

If fundoscopy/fundus photography has been performed within 90 days before the screening visit, the procedure does not need to be repeated unless worsening of visual function since the last examination. A subject cannot be randomised without results confirming there is not retinopathy or maculopathy requiring acute treatment.

If the 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.

8.4.9 Physical examination

A physical examination will be performed by the investigator according to local procedures, see Section 2).

A physical examination must include:

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

The results are recorded as described in Section 8.1.11.

8.4.10 Pharmacokinetics

Blood samples for the population PK will be drawn from all subjects for bioanalysis of the plasma concentrations of semaglutide at Visits 3-11 (see flow chart, Section 2). The investigator must record the exact time for drawing the blood samples in the laboratory requisition form and transcribe the data to the eCRF.

Subjects on oral treatment will also have PK measured pre-dose and post-dose (trough and peak) at three visits (see Section 2). At the visits for trough and peak PK measurements, the investigator needs to ensure that the subjects on oral treatment follow these procedures:

- Attend the visit fasting
- Have the IMP administered at the visit (i.e., subjects must not self-administrate the tablet on the day of the visit)
- Ingest tablet at site
- Eat a meal 30-60 minutes after IMP administration
- Have an extra blood sample drawn 60-90 minutes after IMP administration

The exact time points of trial drug administration, start of meal and blood sampling must be recorded in the eCRF by the investigator.

For the oral treatments, the date and time of the latest trial drug administration must be recorded by the subject in the subject diary and transcribed to the eCRF by the investigator.

For the s.c. semaglutide arm, the date, time, dose and injection site of the two latest trial drug administrations must be transcribed to the eCRF by the investigator based on the subject's diary.

8.4.11 Calcitonin

Blood samples for the measurement of calcitonin concentration will be drawn as per flow chart (see Section 2). Calcitonin values ≥20 ng/L will be submitted to an independent committee of thyroid experts. The Calcitonin Monitoring Committee (CMC) will provide guidance to the investigator with regards to treatment and further investigations. It is recommended that screening failure subjects with a calcitonin value ≥10 ng/L are referred to a thyroid expert for further evaluation. For details please refer to Appendix A.

8.5 Laboratory assessments

The laboratory analyses will mainly be performed by a central laboratory. For analyses of anti-semaglutide antibodies (see Section 8.4.5) and semaglutide plasma concentrations (see Section 8.4.10) a special laboratory will be used. Also, in the situation described in Section 8.6.2.1 a special laboratory will be used. Laboratory samples comprise both urine and blood samples. Descriptions of assay methods, laboratory supplies and procedures for collecting, handling, storing and shipping samples and information regarding who will perform the assessments will be described in the laboratory manual provided by the central laboratory (for central and special laboratory details, see Attachment I).

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

Laboratory samples not collected on the day of the actual visit should preferably be collected on another day within the visit window as 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 collected during the trial, subjects must attend the relevant site visits fasting (fasting is defined in Section 8.1.3).

At three visits (see Section 2), the subjects on oral treatment must attend the relevant site without having taken the trial product the same day to have PK measured pre-dose and post-dose (trough and peak), see Section 8.4.10.

The central laboratory will provide laboratory results to the investigator on an on-going basis and the investigator must review all laboratory results for concomitant illnesses and AEs and report these according to Section 12.2.

An exception to this is that 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).

All laboratory samples will be destroyed at the latest at the completion of the CTR, except samples obtained for anti-semaglutide antibody analysis which may be kept up to ten years or stored until

approval by health authorities. Antibody samples will only be analysed if requested by the health authorities or for safety.

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 must be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

8.6 Other assessments

8.6.1 Subject diary

The subject must be provided with diaries at all visits until the End-of-treatment visit. Entries in the diary are only to be made by the subject.

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

- For all subjects:
  - date and time of first IMP administration
  - hypoglycaemic episodes
  - concomitant medication
  - AEs
- For subjects treated with oral semaglutide:
  - date and time of last IMP administration prior to each visit
  - post-dose fasting routines during the trial and recorded at the End-of-treatment visit
- For subjects treated with s.c. semaglutide:
  - date, time, dose and injection site of the last two IMP administrations before each visit

The diaries should be collected at the following visit. The recordings must be reviewed as described in Section 8.1.11.

8.6.2 Additional safety assessments

8.6.2.1 Thyroidectomy, tissue sample and genetic testing

Thyroidectomy pathology slides

In case a subject undergoes a thyroidectomy (partial or total) for any reason during the trial the subject will be asked to inform the investigator prior to the operation.

In addition to the review of the thyroid tissue routinely made by the hospital pathology laboratory, the pathology slides of the thyroid tissue will be sent centrally for a second review by a pathologist with expertise in thyroid and C-cell pathology. The central pathologist will be blinded to both

randomised treatment and the diagnosis from the hospital pathology laboratory. Both the hospital pathology report and the central pathology report will be reviewed by an independent Event Adjudication Committee (EAC) (see Section 12.7.2). Once the samples are re-examined they will be sent back to the hospital pathology laboratory.

The investigator will be informed of the results of central pathology report and if C-cell pathology is confirmed by the EAC, the CMC will provide guidance to the investigator with regards to treatment and further investigations.

Thyroid tissue sample collection in case of thyroidectomy (not applicable for Israel)

If C-cell pathology is confirmed (i.e., hyperplastic or neoplastic thyroid C-cells) the subject will be asked to consent to have a sample of the removed thyroid tissue tested for RET Y1062 phosphorylation in the thyroid C-cells, if allowed by local law. The tissue sample will be destroyed after examination.

Blood sample for genetic testing in case of confirmed C-cell pathology (not applicable for Israel)

In addition, the subject will also be asked to consent to be tested (blood sample) to identify germline RET gene mutations associated with MEN2 syndrome. This RET gene mutation detection will only be conducted if the EAC has confirmed C-cell abnormality (medullary carcinoma or C-cell hyperplasia). The genetic testing will only be performed if allowed by local law.

The blood sample should be collected at the first visit to the clinic after the confirmation of C-cell pathology. The extraction of DNA will be performed by the central laboratory whereas the identification of gene mutations will be performed by a specialised laboratory. The blood sample will be destroyed as soon as the genetic analysis is complete.

8.6.2.2 Assessments in case of suspicion of acute pancreatitis

In case of acute, severe persistent abdominal pain characteristic of acute pancreatitis, the IMP must promptly be interrupted until pancreatitis is excluded (see Section 6.5.2). Appropriate additional examinations should be performed according to local practice. If acute pancreatitis is not confirmed trial product should be re-initiated.

If pancreatitis is confirmed (as a minimum 2 of 3):

- characteristic abdominal pain
- blood amylase and/or lipase >3x upper normal range (UNR)
- characteristic findings on ultrasound/CT/MRI

appropriate treatment and careful monitoring of the subject should be initiated. Trial product should not be re-initiated but subject should remain in the trial. The event should be reported as a MESI and will undergo assessment by the EAC (see Section 12.7.2).

8.6.2.3 Assessments in case of suspicion of severe hypersensitivity

If a severe immediate hypersensitivity reaction to the IMP is suspected, blood sampling for assessment of anti-semaglutide IgE antibodies and anti-semaglutide binding antibodies should be collected after a suitable washout period (minimum 5 weeks). In these cases, it is also recommended to test for tryptase (total and/or mature tryptase) within three hours of the reaction.

Furthermore, a tryptase sample should be taken at the same time as the IgE sample is obtained. Tryptase concentrations (if measured) as well as results of anti-semaglutide antibody and IgE-isotype anti-semaglutide antibodies should be sent to Novo Nordisk.

8.7 Subject compliance

Subject 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 IMPs. The investigator must assess the amount of IMPs returned compared to what was dispensed at the last dispensing visit and, in case of discrepancies, question the subject.

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

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.

For injectable products, the trial product must not be used if:

- it does not appear clear and colourless
- it has been frozen
- it has been exposed to excessive heat or direct sunlight

9.1 Trial products

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

Table 9–1 Trial products (IMP)

Active substance	Strength	Dosage form
Semaglutide	2.5 mg	tablet
Semaglutide	5.0 mg	tablet
Semaglutide	10 mg	tablet
Semaglutide	20 mg	tablet
Semaglutide	40 mg	tablet
Placebo	N/A	tablet
Semaglutide	1.34 mg/mL	solution for injection, 1.5 mL pre-filled PDS290 pen-injector

N/A: not applicable

The IMPs for oral use will be packed in 15 mL Duma containers (lid with desiccant). Each container will include ten tablets. Subjects in the oral treatment arms will be instructed in how to ingest the tablets following the condition rules. All tablets containing semaglutide or placebo are identical with regards to visual appearance, taste and smell.

The semaglutide, solution for injection will be delivered open-label with the pre-filled PDS290 pen-injector. The direction for use of the pen-injector will be given to each subject in the s.c. treatment arm at each dispensing visit.

For further details, please see the current edition of the IB (Oral Administration of Semaglutide (NN9924) Edition 5[6] and any updates hereof.

Metformin may be used at the discretion of the investigator. Metformin will not be supplied by Novo Nordisk. However, metformin will be reimbursed if required by the country's Health Authority or independent ethics committee/Institutional Review Board (IEC/IRB).

9.2 Labelling

Labelling of the trial products will be in accordance with Annex 13[12], local regulations and trial requirements.

Each investigator site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IV/WRS. Dispensing unit numbers (DUNs) will be distributed to the sites according to enrolment and randomisation.

The investigator or delegate must document that direction for use of the device is handed out at each dispensing visit. This could be by signature in the subject's medical record.

9.3 Storage

Tablets containing the SNAC enhancer are susceptible to degradation in humid environment. It is important to protect the tablets by following the storage conditions in Table 9–2. Before opening the Duma container for the first time, the container must acclimatise for 1 hour at room temperature due to risk of condensation.

Table 9–2 Storage conditions for trial products

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
Semaglutide and placebo tablets	• Must be stored in a refrigerator (2ºC to 8ºC) / (36ºF to 46ºF) • Do not freeze • Protect from light and humidity	• Store below 30°C / 86ºF • Do not refrigerate • Do not freeze • Protect from light and humidity • Container must be stored with lid tightly closed at all times	Use within 4 weeks
Semaglutide, solution for injection	• Must be stored in a refrigerator (2°C to 8°C) / (36ºF to 46ºF) • Do not freeze • Protect from light	• Store below 30°C / 86ºF • Do not refrigerate • Do not freeze • Protect from light	Use within 1 month
Semaglutide placebo, solution for injection (test pen)	• Must be stored in a refrigerator (2°C to 8°C) / (36ºF to 46ºF) • Do not freeze • Protect from light	• For single use only	For single use only

* In-use time starts when first dose is taken.

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

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

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator.

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.

The trial products will be dispensed to each subject as required according to treatment group. The IV/WRS will allocate trial product to the subject at each dispensing visit. The correct dispensing unit number(s) (DUN(s)) must be dispensed to the subject.

The investigator or delegated person is responsible for ensuring that:
- Trial products are not dispensed to any person not included in the trial
- Drug accountability is performed using the IV/WRS drug accountability module
- Subjects are instructed to return all used, partly used and unused trial product including empty packaging material at every visit
- Returned trial product(s) (used, partially used or unused including empty packaging material) is kept and stored separately from non-allocated trial products

Destruction will be done according to local procedures after accountability is finalised and verified by the monitor. Destruction of products must be documented.

9.5 Auxiliary supplies

Auxiliary supplies provided by Novo Nordisk:
- Blood glucose meters, including lancets, plasma-calibrated test strips and control solutions.
- Direction for use for devices (only subjects on s.c. semaglutide)
- Needles for pre-filled pen systems (only subjects on s.c. semaglutide)
- Test pens containing semaglutide placebo (only subjects on s.c. semaglutide)

Test pens containing semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen-injector will be supplied at the randomisation visit to subjects randomised to injection treatment. Training with the test pen is optional and recommended for subjects without prior injection experience to ensure the subject's willingness and ability to self-inject. The test pen should be administered once and the training be performed at the clinical site. The subjects must not take the test pens home.

Details of the auxiliary supplies are provided in the TMM.

10 Interactive voice/web response system

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

IV/WRS is used for:

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

IV/WRS user manuals will be provided to each trial site.

During the trial, only DUNs allocated by the IV/WRS are allowed to be dispensed to a subject. This will ensure that:

- needed stock is available at a site for the subjects
- no allocation of IMP that will expire before the next dispensing contact
- drug accountability can be made in IV/WRS

If a subject needs IMP between dispensing visits, the investigator must make an additional dispensing session in the IV/WRS.

11 Randomisation procedure and breaking of blinded codes

The trial is partially blinded. The oral semaglutide arms and the oral placebo arm are double-blind whereas the s.c. semaglutide active comparator arm is open-label.

The randomisation is stratified according to one stratification factor with two strata: Treatment with metformin at screening (yes/no).

11.1 Breaking of blinded codes

If the trial site needs to break the code, Novo Nordisk should, if possible, be contacted before the code is broken. The IV/WRS 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 IV/WRS, 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 IV/WRS is not accessible at the time of code break the monitor should be contacted and if monitor cannot get access the IV/WRS vendor helpdesk should be contacted. Contact details are listed in Attachment I.

If the code has been broken, the subject should be discontinued from trial product but be asked to continue in the trial (see Section 8.1.9).

If the subject is withdrawn after the code has been broken, a treatment discontinuation session should be completed in IV/WRS.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

Adverse event

An **adverse event** 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 8.4.1)

The following definitions are used when assessing an AE:

- **Severity assessment:**
  - **Mild** – no or transient symptoms, no interference with the subject's daily activities, acceptable
  - **Moderate –** marked symptoms, moderate interference with the subject's daily activities, but still acceptable
  - **Severe** – considerable interference with the subject's daily activities; unacceptable

- **Causality assessment**
  The following terms and definitions are used when assessing the 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 of an AE**
  - **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** – This term is only applicable if the subject has completed the trial or has died from another AE. The condition is improving and the subject is expected to recover from the event.
  - **Recovered/resolved with sequelae** – The subject has recovered/resolved 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 at the time of reporting.
  - **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

A **serious adverse event** 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 this definition of SAE[d]. Suspicion of transmission of infectious agents via 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 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.

Non-serious adverse event

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

Medical event of special interest

A medical event of special interest (MESI) is an event which, in the evaluation of safety, has a special focus. A MESI is an AE (SAE or non-serious AE) which fulfils one or more of the below defined MESI criteria.

1. Fatal Events (All events with fatal outcome) (A)
2. Acute Coronary Syndrome (Myocardial Infarction, Hospitalization for Unstable Angina) (A)
3. Cerebrovascular Events (Stroke, Transient Ischemic Attack) (A)
4. Coronary Revascularization Procedure (A)
5. Heart Failure requiring Hospital Admission (A)
6. Pancreatitis or clinical suspicion of pancreatitis (A)
7. Neoplasms (A)
8. Thyroid Disease ((A) if thyroidectomy is required)
9. Medication errors concerning trial products:
    - Administration of wrong drug
    - Wrong route of administration
    - Administration of a high dose with the intention to cause harm (e.g., suicide attempt)
    - Administration of a lower or higher dose than intended (e.g., taking more than the planned number of tablets); 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 not necessarily did happen

MESIs marked with an '(A)' in the list above will undergo adjudication by an independent EAC (see Section 12.7.2).

Any event confirmed or suspected to be a MESI must be reported. In case the sponsor identifies potentially missed MESIs through predefined review of available data, the investigator will be asked to reconsider if this is a MESI. However, MESIs should not be reported for screening failures.

For further information regarding definitions of MESIs and an overview of which events that should undergo adjudication, please refer to Appendix C.

When reporting a MESI the following forms must be completed: AE form, eSIF, specific MESI follow-up questions (MESI form) and if applicable, the Event Adjudication Document Collection Form (only events for adjudication) in the eCRF.

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., leakage, cracks, rubber membrane issues or errors in labelling text)
- Problems related to devices (e.g., to the injection mechanism, dose setting mechanism, glucose measurement, push button or interface between the pen and the needle)

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. 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 reported by the subject, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference document: IB (Oral Administration of Semaglutide (NN9924)), Edition 5[6] 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, an eSIF must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

MESIs, regardless of seriousness, must be reported using both the AE form, the safety information form and a MESI form. The MESI form is an electronic form tailored to collect specific information related to the individual MESIs. For MESIs qualifying for event adjudication, an Event Adjudication Document Collection Form will also have to be completed in the eCRF. The Event Adjudication Document Collection Form is a check list of clinical data to be provided from the site.

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

Timelines for initial reporting of AEs:

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

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

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

- **SAEs fulfilling the MESI criteria**: In addition to above, the MESI form **within 14 calendar days** of the investigator's first knowledge of the AE
- **Non-serious AE fulfilling the MESI criteria**: The AE form, and safety information form and MESI form **within 14 calendar days** of the investigator's first knowledge of the event.

If a MESI fulfils the Event Adjudication criteria the investigator must complete the Event Adjudication Document Collection Form within 14 calendar days of the investigator's first knowledge of the adverse event.

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 re-enter the information on the appropriate forms in the eCRF.

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

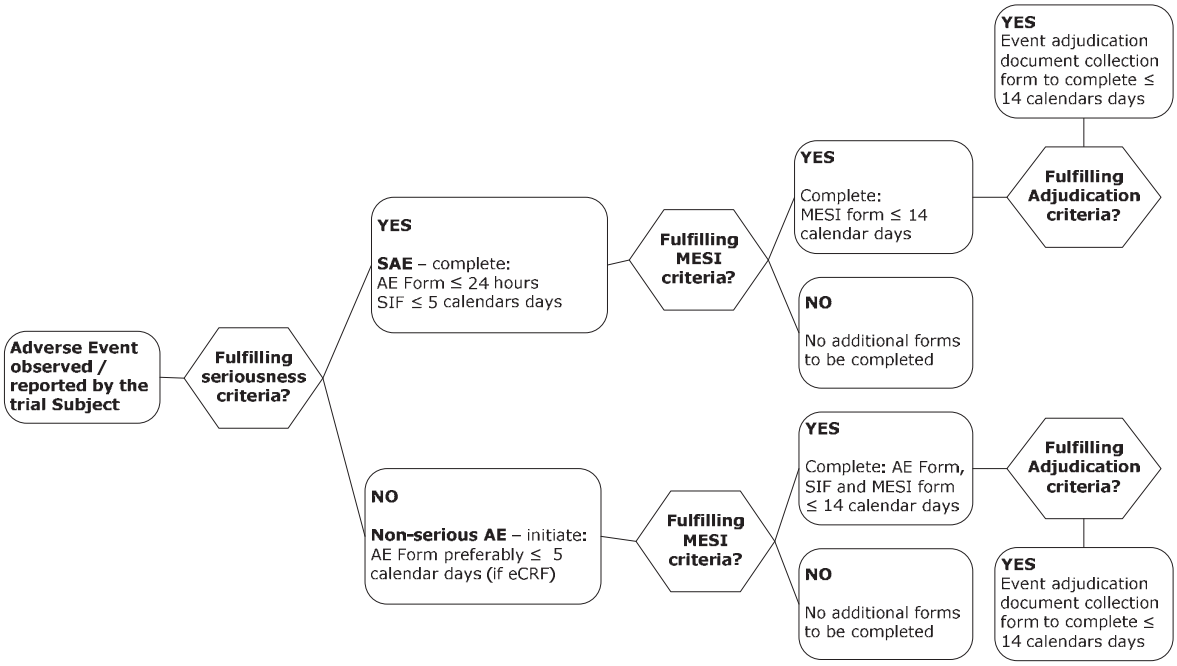

Figure 12–1 Initial reporting of AEs

Reporting of trial product-related SUSARs by the sponsor:

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 to 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.

12.3 Follow-up of adverse events

During and following a subject's participation in the trial, the investigator should ensure that adequate medical care is provided to the subject for any AE, including significant laboratory values related to the trial. The investigator should inform the subject when medical care is needed for AE(s) of which the investigator becomes aware.

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

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

- **SAEs:** All SAEs must be followed up 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. The applicable forms must be signed within 7 calendar days from the date the new information was entered in the eCRF.

- **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.

- **Non-serious AE fulfilling the MESI criteria:** Follow-up information on MESIs should only include new (e.g., corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently fulfil the MESI criteria.

The investigator must record follow-up information on non-serious AEs by updating the AE form in the eCRF.

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 tablets
- Placebo tablets
- Semaglutide for s.c. injection, solution for injection, 1.5 mL pre-filled PDS290 pen injector
- Semaglutide placebo for s.c. injection, solution for injection, 1.5 mL pre-filled PDS290 pen-injector (test pen)
- Novo Nordisk needles

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 the investigator's trial file.

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

Technical complaints must be reported on a separate technical complaint form for each product listed. If the technical complaint involves more than one code number, lot number or DUN, a technical complaint form for each code number, lot number or 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.

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 the investigator's trial file) and ensure that the sample is sent as soon as possible. A print of the technical complaint form must be sent with the sample.

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

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

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (see Section 9).

12.5 Pregnancies

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

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

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

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

1. **Reporting of pregnancy information**
   Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on Maternal Form 1A and 1B, respectively.
   When the pregnancy outcome is abnormal (i.e., congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

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

2. Reporting of AE information

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

Forms and timelines for reporting AEs:

Non-serious AEs:

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

* 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 confirmed hypoglycaemia include: hunger, slight headache, nausea, light-headedness, palpitations and sweating. Major hypoglycaemia (severe) may produce loss of consciousness. Symptoms of confirmed and not major hypoglycaemia should be treated by ingestion of carbohydrates.

Major 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 with SNAC was reported in the NN9924-3692 trial in a subject treated with 20 mg semaglutide with 300 mg SNAC. The subject accidentally took the trial product [redacted] on Day [redacted] of the trial. No AEs were reported at the 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 treated subjects. The case classified as moderate in severity and considered to be probably related to semaglutide was reported by a subject enrolled in 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 [redacted] felt nauseated, vomited and had a headache. The subject was instructed to drink copious amounts of fluids. [redacted] and the subject wished to continue in the trial. Blood glucose levels, blood pressure and pulse were monitored during the following five 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 (Oral Administration of Semaglutide (NN9924) Edition 5[6] and any updates hereof.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal Oral GLP-1 safety committee to perform on-going safety surveillance. The Oral GLP-1 safety committee may recommend un-blinding of any data for further analysis, and in this case an independent ad hoc safety group will be established in order to maintain the blinding of the trial personnel.

12.7.2 Event adjudication committee

An external event adjudication committee (EAC) is established to perform qualitative or quantitative validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical data related to the specific AE.

The events are reviewed by the EAC in an independent and blinded manner.

The EAC is composed of permanent members covering required medical specialities. EAC members must disclose potential conflicts of interest and must be independent of Novo Nordisk. The role of the EAC is solely to adjudicate events in a blinded manner. The EAC will have no authorisations to impact on trial conduct, trial protocol or amendments.

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

The events will be adjudicated according to FDA requirements and the adjudication vendor will ensure that the EAC gets access to all the documents provided by the investigator. The EAC will initiate the review and may ask for additional information that the investigator needs to provide if it is available.

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication packages (e.g., X-ray images, ECGs, ultrasound images, discharge summaries, pathology reports and death certificates). The investigator must provide medical documentation within 4 weeks of event identification.

The assessments made by the EAC will be included in the CTR 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 outcomes of adjudication will be kept in the clinical trial database.

The following AEs will be adjudicated in this trial:

- Fatal Events (All events with fatal outcome)
- Acute Coronary Syndrome (Myocardial Infarction, Hospitalization for Unstable Angina)
- Cerebrovascular Events (Stroke, Transient Ischemic Attack)
- Coronary Revascularization Procedure
- Heart Failure requiring Hospital Admission
- Pancreatitis or clinical suspicion of pancreatitis
- Neoplasms
- Thyroid Disease (if thyroidectomy is required)

Event adjudication will not be performed for AEs in screening failures.

There are two processes for capturing AEs for adjudication: Direct reporting of MESIs by the investigator and by potential missed MESI process.

Direct reporting of MESI by investigator: For each AE reported in the eCRF, the investigator must complete whether the event in his/her opinion is a MESI (yes/no).

By ticking YES:

- The investigator must specify the type of MESI event being reported
- The investigator must complete the event adjudication document collection form (‘adjudication form’) in the eCRF according to the timeline specified in Section 12.2. This form indicates the data/documents required for adjudication

- For each required document the investigator should specify/indicate when/if the data/document will be available. If a document is unobtainable this needs to be specified. The investigator must provide medical documentation within 4 weeks of event identification

By ticking NO:
All NOs within the relevant MESI category are screened for being potential missed MESI.

- If needed, the investigator will be asked to provide an explanation of why the event is not reported as a MESI (alternative etiology)
- The vendor or EAC can evaluate an event not initially reported as a MESI for adjudication to be adjudicated. In this case the investigator must provide data/documents required for adjudication as soon as possible when receiving a request from Novo Nordisk or the vendor

A site manual will be provided to each site detailing the specifics surrounding the medical documentation that must be provided by site to the adjudication vendor including how this documentation should be provided.

12.7.3 Calcitonin monitoring committee

The CMC will provide recommendations to the investigators with regards to further investigation and treatment of the individual subject (see Appendix A).

13 Case report forms

Novo Nordisk will provide a system for the eCRF. This system and support services to the system will be supplied by a vendor.

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

The following will be provided as paper CRFs:

- Pregnancy forms

In addition paper AE forms, SIF and technical complaint forms will be provided. These must be used when access to the eCRF is revoked (i.e., EDC system not available).

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

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

13.1 Corrections to case report forms

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

If corrections are made by the investigator's authorised 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 are recorded in the eCRF as soon as possible after the visit, preferably within 5 days. Once data have been entered, they 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, preferably within 3 days after the last subject's last visit 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.

13.3 Paper case report forms

The pregnancy forms are paper based CRFs. Also, the SIF, technical complaint form and AE form will be provided in paper but are only to be used if for any reason the eCRF is unavailable.

The investigator must ensure that data are recorded in these forms as soon as possible after the visit and ensure that Novo Nordisk receives these forms within the required timelines (see Sections 12.2, 12.4.1 and 12.5).

Corrections to the data in the CRFs may only be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that were crossed out. Each correction must be initialled, dated and explained (if necessary) by the investigator or the investigator's authorised staff.

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 and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 4 weeks during the recruitment period (i.e., from FSFV to last subject first visit (LSFV)). After LSFV the monitoring visit intervals will not exceed 8 weeks.

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 eCRF (except for BMI).

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.

For screening failures the monitor will ensure that relevant eCRF pages and other trial-related forms containing data from screening failures are completed. For screening failures the following data should be source verified: informed consent, reason for screening failure and AEs, if any.

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 completed diaries will be collected from the subject at each site visit and must be kept as source data at the site. The investigator/delegate must transcribe the data into the eCRF.

The monitor will ensure that the eCRFs are completed on an ongoing basis and within agreed timelines.

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 eCRF. If discrepancies are found, the investigator must be questioned about these.

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

15 Data management

Data management is always the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to an external contract research organisation (CRO).

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

Data from central laboratories will be transferred electronically from the laboratory performing the analyses. In cases where laboratory data are 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 identification number. 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

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.

Results from the statistical analysis will generally be presented by two-sided confidence intervals with a confidence level of 95% including a p-value for test of no difference between treatments.

The stratification variable referred to in the following is defined as the two level factor of treatment with metformin (yes/no).

The "planned comparisons between treatment arms" referred to in this section covers the following comparisons: a) between each of the oral semaglutide treatment arms and placebo, b) between the s.c. semaglutide arm and placebo, c) between each of the oral semaglutide treatment arms and s.c. semaglutide, and d) between the three treatment arms with an end dose of 40 mg.

A standard mixed model for repeated measurements (MMRM) will be used in the analysis of the primary and continuous secondary endpoints. The model will include treatment, country and the stratification variable as fixed factors, and the corresponding baseline value as covariate. All factors and the covariate will be nested within visit. Unless otherwise stated, the estimated differences with corresponding two sided p-values and 95% confidence intervals at 26 weeks will be presented for the planned comparisons between treatment arms.

In order to describe the dose-response relation of oral semaglutide and estimate the relative potency vs. s.c. semaglutide with regards to selected key endpoints, an explorative analysis will be conducted. In this model data from oral semaglutide arms using the standard titration scheme will be included. One or both of the treatment arms with an end dose of 40 mg using an alternative titration scheme may be included and pooled with the oral semaglutide arm with an end dose of 40 mg and using the standard titration scheme, if deemed appropriate based on the planned pairwise comparisons between the arms. Data from the placebo arm (corresponding to a dose of zero mg) could be included if deemed appropriate. The model will developed ad hoc after unblinding and aim for a suitable fit of the dose-response relation using e.g. a linear or a four-parameter logistic relation of the endpoint of interest vs. the logarithm of the dose.

17.1 Sample size calculation

The primary endpoint, change from baseline to end of treatment (i.e., after 26 weeks of treatment) in HbA1c, will be analysed by the standard MMRM.

In order to demonstrate efficacy of oral semaglutide the sample size is based on an initial comparison of change from baseline to end of treatment (i.e., after 26 weeks of treatment) in HbA_{1c}

between a) the pool of the two treatment arms using standard and fast escalation regimens, respectively, to an end dose of 40 mg and b) placebo.

A standard deviation (SD) of 1.2% for change from baseline in HbA_{1c} is chosen as assumption for the sample size calculation. The SD observed in several phase 3 trials of 26 weeks duration with s.c. liraglutide suggests a standard deviation less than 1.1%. However, as it is uncertain if the added variation in exposure compared to s.c. liraglutide will transfer to an added variation in the therapeutic response, a SD of 1.2% is assumed.

In trial NN9535-1821 the withdrawal rate for the doses 0.2 mg-0.8 mg was 16%-24%. In the present trial, GI events are mitigated by dose escalation and based on this the drop-out rate is expected to be 20%, equally distributed among treatment arms. For completers the treatment difference between the pooled 40 mg arm and placebo is expected to be at least 0.64% whereas for dropouts the treatment difference is set conservatively to 0.32%, thus leading to a detectable mean difference of 0.58%. With these assumptions, and using a two-sided t-test with a significance level of 5%, 134 subjects should be randomised to the pooled 40 mg treatment arm and 67 to placebo in order to have 90% power to demonstrate superiority of the pooled 40 mg treatment arm versus placebo. For similarity between the treatment arms, 67 subjects should be randomised in each of the nine treatment arms.

In total, 603 subjects are to be randomised.

17.2 Definition of analysis sets

Full Analysis Set (FAS): includes all randomised subjects who have received at least one dose and have any post randomisation data. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation “as randomised”.

Safety Analysis Set (SAS): includes all subjects exposed to at least one dose of randomised liraglutide or liraglutide placebo. Subjects in the SAS will contribute to the evaluation “as treated”.

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

17.3 Primary endpoint

The primary endpoint, change from baseline to end of treatment (i.e., after 26 weeks of treatment) in HbA1c, will be analysed by the standard MMRM.

In order to confirm efficacy of oral semaglutide without risk of inflation of the type 1 error an initial comparison of the primary endpoint between a) the pool of the two treatment arms using standard and fast escalation regimens to an end dose of 40 mg and b) placebo. The comparison will be made using the MMRM by estimating the difference between the mean of means in the two 40 mg arms and the mean in placebo. The estimated difference with corresponding two sided p-value and 95% confidence interval at 26 weeks will be presented, and efficacy of oral semaglutide will be considered confirmed if the upper limit of the confidence interval is strictly less than zero.

If efficacy of oral semaglutide is confirmed the planned comparisons between the nine original treatment arms will be evaluated.

Subjects in the FAS and only measurements taken before treatment discontinuation or initiation of rescue therapy will be included in the analysis.

Due to the uncertainty in relation to if the added variation in the exposure in the oral semaglutide arms compared to s.c. liraglutide will transfer to an added variation in the therapeutic response, a sensitivity analysis allowing the within subject unstructured covariance matrix to be fitted separately for each treatment arm will be conducted.

Furthermore, the following sensitivity analyses will be conducted in order to investigate the sensitivity of the results due to the impact of missing values:

- An MMRM similar to the primary analysis but including all data recorded after randomisation regardless of the data being obtained when the subjects have received rescue therapy or have discontinued randomised treatment.
- An analysis of covariance (ANCOVA) model including subjects in the FAS and using imputation of missing values according to the last observation carried forward (LOCF) method. The model will include fixed factors for treatment, country and the stratification variable and the baseline value as covariate. In accordance with the LOCF method, the dependent variable will be the last available value obtained within the 26 weeks period of the study.
- A completer analysis, i.e. an ANCOVA similar to the one above including only data obtained at 26 weeks from subjects who:
  - did not discontinue treatment prematurely
  - did not receive rescue therapy
  - had a valid HbA_{1c} assessment at baseline and after 26 weeks of treatment

17.4 Supportive secondary endpoints

17.4.1 Efficacy endpoints

The FAS will be used in all analyses of the supportive secondary efficacy endpoints.

Subjects who, after 26 weeks of treatment, achieve (yes/no) HbA_{1c} <7% (53 mmol/mol)

The binary endpoint will be analysed by a logistic regression model which will include fixed factors for treatment and the stratification variable and baseline HbA_{1c} as a covariate. Estimated odds ratios with corresponding two sided p-values and 95% confidence intervals at 26 weeks will be presented for the planned comparisons between treatment arms. Missing response data at 26 weeks will be imputed from the MMRM used for the primary analysis of HbA_{1c}.

Change from baseline to week 26 in body weight, waist circumference and fasting plasma glucose.

These endpoints will be analysed by the standard MMRM.

Change from baseline to week 26 in C-peptide, fasting insulin, glucagon, HOMA-IR, HOMA-B, total cholesterol, LDL-cholesterol, HDL-cholesterol, VLDL-cholesterol, triglycerides and free fatty acids.

For each endpoint, the assessments at every week will be log-transformed and subsequently analysed by the standard MMRM. The estimated differences and corresponding 95% confidence intervals at 26 weeks will be back transformed and presented as ratios together with the two sided p-values.

The fasting HOMA endpoints (i.e., fasting HOMA-B and HOMA-IR) will be calculated based on fasting insulin and FPG as follows:

1. Fasting HOMA-B (%) = 20 x fasting insulin [µU/ml]/(FPG[mmol/L]-3.5)
2. Fasting HOMA-IR (%) = fasting insulin [µU/ml] x FPG [mmol/L]/22.5

PRO outcomes

The outcomes from the SF-36 in terms of total scores overall and within each domain will be calculated and each of these scores will be analysed by the standard MMRM.

17.4.2 Safety endpoints

All safety endpoints will be summarised and analysed using the safety analysis set. Unless otherwise specified safety endpoints will be analysed by descriptive statistics only.

Adverse events

All AEs will be coded using the most recent version of the Medical Dictionary for regulatory Activities (MedDRA) coding. A TEAE is defined as an event that has onset date (or increase in severity) on or after the first day of exposure to randomised treatment and no later than the follow-up visit. TEAEs are summarised descriptively, whereas non-treatment emergent AEs are presented in listings.

Number of confirmed treatment emergent hypoglycaemic episodes

A hypoglycaemic episode will be defined as *treatment emergent* if the onset of the episode occurs on or after the first day of trial product administration and no later than the follow-up visit.

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of confirmed hypoglycaemia and the ADA classification of hypoglycaemia (see Figure 17–1).

Confirmed hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)[13]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of confirmed hypoglycaemia.

Confirmed hypoglycaemic episodes are defined as episodes that are:

- severe (i.e., an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) and/or
- biochemically confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia

ADA classification of hypoglycaemia

- *Severe hypoglycaemia:* An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
- *Asymptomatic hypoglycaemia:* An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL)
- *Documented symptomatic hypoglycaemia:* An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- *Relative hypoglycaemia:* An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia, and interprets those as indicative of hypoglycaemia, but with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL).
- *Probable symptomatic hypoglycaemia:* An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L [70 mg/dL]).

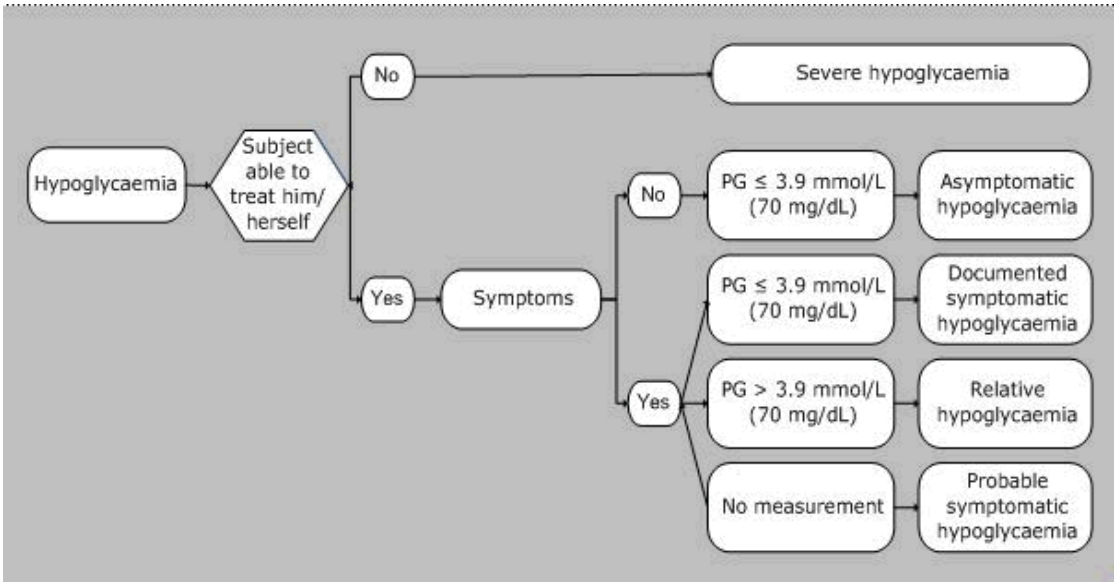

Figure 17–1 ADA classification of hypoglycaemia

Data on treatment emergent hypoglycaemic episodes will be summarised descriptively using the above definitions.

The number of confirmed treatment emergent hypoglycaemic episodes during 26 weeks treatment will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which an occurrence of a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment, country and stratification variable as fixed factors and baseline HbA_{1c} as covariate. Estimated rate ratios with corresponding two sided p-values and 95% confidence intervals at 26 weeks will be presented for the planned comparisons between treatment arms.

Change in pulse, systolic- and diastolic blood pressure from baseline to after 26 weeks of treatment

These endpoints will be analysed by the standard MMRM.

Change in amylase and lipase from baseline to after 26 weeks of treatment

For each endpoint, the assessments at every week will be log-transformed and subsequently analysed by the standard MMRM. The estimated differences and corresponding 95% confidence intervals at 26 weeks will be back transformed and presented as ratios together with the two sided p-values.

Change from baseline to after 26 weeks of treatment in electrocardiogram (ECG), physical examination, laboratory safety variables (haematology, biochemistry, hormone and urinalysis) other than amylase and lipase

These endpoints will be summarised by descriptive statistics.

Endpoints related to occurrence of anti-semaglutide antibodies during 26 weeks of treatment: Antibody level during 26 weeks of treatment, anti-semaglutide antibodies (positive/negative), anti-semaglutide antibodies with *in vitro* neutralising effect (positive/negative), anti-semaglutide antibodies cross reacting with endogenous GLP-1 (positive/negative), cross reacting antibodies with *in vitro* neutralising effect to endogenous GLP-1 (positive/negative)

These endpoints will be summarised by descriptive statistics and correlated to PK and PD.

17.4.3 Pharmacokinetics and/or pharmacodynamics modelling

If relevant, population PK and PK/PD modelling will be used to evaluate semaglutide exposure and exposure-response relationship after oral and subcutaneous administration in subjects with T2D to inform dose selection in future trials.

The objectives of these exploratory analyses are to:

- assess the dose-dependence of semaglutide exposure in plasma
- explore the effects of covariates on semaglutide exposure
- explore the relationship between semaglutide exposure and response variables of interest

The modelling will be performed by Quantitative Clinical Pharmacology at Novo Nordisk A/S and will be reported separately from the CTR.

18 Ethics

The trial will be conducted in compliance with ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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. Subjects will be treated within a regimen anticipated to be better than or equal to the treatment they receive at the time of entry into the trial. However, they will have to spend some extra time, as additional assessments and visits to the clinic are required. It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2013, Standards of Medical Care in Diabetes[14], or any updates thereof.

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile of semaglutide generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of once-daily oral doses of 2.5-40 mg semaglutide or once-weekly doses of 1.0 mg semaglutide in accordance with the planned clinical trial. Furthermore, a rescue strategy is implemented in this trial to ensure the safety of subjects experiencing deterioration of glycaemic control during the course of the trial to address the concern regarding the placebo arm and the inclusion of patients with an HbA_{1c} up to 9.5%. It is concluded that the risk to the subjects in this trial is low and acceptable in view of the benefits a GLP-1 analogue in a tablet formulation would provide to people with T2D.

The trial products may be associated with AEs, but relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation in the trial. These precautions include thorough information regarding the correct administration of the trial products and gradual dose adjustment. Furthermore, subjects are fully informed about possible AEs and inconveniences and will be instructed to contact the investigator in case of any concerns regarding the trial participation.

18.1 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 subject is allowed to bring a companion when the oral information is provided.

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 form will be obtained from the subject before any trial-related activity.

The responsibility for seeking informed consent must remain with the investigator, but the task may be delegated by the investigator 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.

18.2 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 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 and national requirements

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

18.3 Premature termination of the trial and/or trial site

Novo Nordisk, the investigator, 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 should also promptly inform the IRBs/IECs and provide a detailed written explanation. The relevant regulatory authorities should be informed.

If, after the termination of the trial, the risk/benefit analysis changes, the new evaluation should 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 does have an impact, the actions needed to inform and protect the subjects should be described.

An interim analysis to allow for premature discontinuation of the trial has not been planned.

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 all protocol deviations must be kept in the investigator's trial file and Novo Nordisk 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 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 substantial 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
- Curricula vitae of the investigator and sub-investigator(s) (current, dated and signed – must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure
- Signed and dated agreement on the final protocol
- Signed and dated agreement on any substantial protocol amendment, if applicable
- Financial agreement(s)
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Signed and dated Investigator Agreement
- Financial disclosure form for all investigators
- 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 each investigator

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

FDA form 1572 (for sites outside the US):

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.

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 making 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 should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties. The investigator should 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's trial file. The documents should be kept in a secure locked facility, so no unauthorized persons can get access to the data. The subject ID list should be kept securely and separate from the personal 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.

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

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

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

Novo Nordisk will be responsible for the preparation of the protocol, eCRF, supply of trial products and stated equipment, monitoring, data management, statistics and the CTR as documented by Novo Nordisk procedures and internal specific agreements as well as the current GCP guidelines[1].

Novo Nordisk will provide a system for EDC. This system and support services to the system will be supplied by a vendor. The activities of the vendor will be under the direction and supervision of Novo Nordisk. Furthermore, Novo Nordisk will be responsible for the IV/WRS.

A central laboratory will be responsible for providing all lab supplies for the analysis of all blood and urine samples taken during the trial. All results are received as paper copies at the sites as well as electronic transfer to Novo Nordisk clinical database.

The name of the central laboratories is listed in protocol attachment I.

23 Reports and publications

The information obtained during the conduct of this trial is considered confidential, and may be used by Novo Nordisk for regulatory purposes and 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.

The CTR will be reviewed and signed by one or more investigator(s) (signatory investigator) appointed by Novo Nordisk based on their experience in clinical research and input during the analysis phase.

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.

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

At the end of the trial, one or more public disclosures 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.

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

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 support 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 principal 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 the Novo Nordisk trial manager 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 (sometimes referred to as the Vancouver Criteria[15]).

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

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

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

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission for publication of such primary policy 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 participants' 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 site. If the Novo Nordisk provided data (e.g., the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy, as 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 investigator site/institution must be retained for 15 years after the completion of the trial, or longer if required by national regulations. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biospecimens

Serum samples (3-4 mL) of antibodies to semaglutide will be stored at the CRO after finalisation of the CTR (see Section 8.5). The retained antibody samples will only be used for further characterisation of antibodies against semaglutide if required by health authorities or for safety. The samples will remain anonymous (no personal data will be received).

Samples will be stored for up to ten years or until approval by health authorities. They may be transferred from the CRO to Novo Nordisk. Only Novo Nordisk and the CRO/laboratory will have access to the samples.

There are no potential consequences for the subjects or their relatives on the potential use of the antibody samples stored.

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 sponsor, 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, substantial protocol amendments, non-substantial 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 risk/benefit 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.

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 should be filed in the investigator's trial file and copies must be sent to Novo Nordisk.

Regulatory Authorities

Regulatory authorities will receive the clinical trial application (CTA) or clinical trial notification, protocol amendments, reports on SAEs and the CTR according to national requirements.

26 Indemnity statement

Novo Nordisk carries product liability for its products, and liability is 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 by the clinics 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 Germany: Drug Law dated August 24, 1976 last amended by Second Law for Changes in Regulations on Drugs and Other Issues dated October 19, 2012.
- For Spain: Royal decree 223/2004, of 6th February, establishing the requisites concerning clinical trials.

27 References

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Appendix A

Semaglutide, NN9924-3790

Monitoring of calcitonin

Table of Contents

Page

1 Background

Semaglutide treatment is associated with thyroid C-cell changes in rodents but not in the non-human primate. The proliferative C-cell changes in rodents are a known effect following GLP-1 receptor activation by GLP-1 receptor agonists and 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 can become challenging.

There are several known confounding factors affecting calcitonin levels, namely renal dysfunction, smoking, autoimmune thyroiditis and 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 and C-cell abnormalities – evaluation and follow-up

Subjects with a personal or family history of medullar thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2) or with a screening calcitonin ≥ 50 ng/L will be excluded from the trial.

A blood sample will be drawn at pre-specified trial visits for measurement of calcitonin. In case a subject has an increased calcitonin value ≥ 10 ng/L the algorithm outlined below should be followed. The algorithm applies for all calcitonin values including screening values.

All calcitonin values ≥20 ng/L will be submitted to an independent Calcitonin Monitoring Committee (CMC) of thyroid experts, together with relevant supplementary data, i.e. subject's demographics, diabetes history, concomitant medical history, concomitant medications, smoking status as well as information about relevant adverse events reported during the trial.

The CMC will provide recommendations to the investigators with regards to further investigation and treatment of the individual subject. The CMC will be blinded to trial treatment.

The summary for the rationale for the use of specific calcitonin values to trigger medical evaluation and an overview of the algorithm is provided below:

2.1 CT ≥ 100 ng/L

The value will be submitted to the CMC and the subject should be discontinued from trial product. If the value is a screening value the subject can not be randomised and the subject must be referred to a thyroid specialist.

These values were found in 0.15% of the population published by Constante et al[1] and in one subject (on active comparator) in the liraglutide development program. For a calcitonin value of ≥100 ng/L, the subject should be assumed to have significant C-cell disease and a high likelihood of having medullary carcinoma of the thyroid. Diagnostic evaluation should consist of thyroid ultrasound, fine needle aspiration of any nodules >1 cm and potentially surgery with neck dissection. Family history of MTC or MEN2 should be evoked and a RET proto-oncogene analysis should be performed.

2.2 CT ≥ 50 and < 100 ng/L

The value will be submitted to the CMC and the investigator will receive guidance from the CMC with regards to continuation of trial product. If the value is a screening value the subject can not be randomised and the subject should be referred to a thyroid specialist.

These values were found in 0.18% of a population with thyroid nodular disease published by Constante et al[1] Diagnostic evaluation will likely include ultrasound examination and if available and if there is no contraindication, subjects should undergo a pentagastrin stimulation test (Europe). Subjects with positive pentagastrin stimulation tests will be considered to undergo surgery. In the US where pentagastrin is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information informing the need for surgery.

2.3 CT ≥ 20 and <50 ng/L

The value will be submitted to the CMC. If the subject is a screen failure the subject should be referred to a thyroid specialist for further evaluation.

These values are expected to be found in up to 1% of subjects. Based on data from Constante et al[1], the predictive value of calcitonin levels ≥ 20 and < 50 ng/L clinically significant C-cell disease begins to fall. However, up to 25% of these subjects had a positive pentagastrin stimulation test. The likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.

2.4 CT ≥ 10 and < 20 ng/L

Confounding factors should be evaluated. If drugs potentially affecting calcitonin can be discontinued safely, calcitonin can be repeated after a washout period. Gastrin levels return to the normal range by ~10 days after stopping proton pump inhibitors (PPIs). No further actions are needed during the trial if the next calcitonin values remain below 20 ng/L.

If the subject is a screening failure or if the value is the last one taken in the trial, the subject should preferably be referred to a thyroid specialist for further evaluation.

These values may be found in ~2.5 to 4% of the trial population. Costante et al[1] had 216 patients in this category. 1/216 had a subsequent basal (unstimulated) calcitonin of 33 ng/L, and had C-cell hyperplasia at surgery, a lesion of unknown clinical significance. Two other studies used a cutoff of CT > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT >10 and <20 ng/L to allow conclusions[2, 3].

3 References

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

2 Scheuba C, Kaserer K, Moritz A, Drosten R, Vierhapper H, Bieglmayer C et al. Sporadic hypercalcitoninemia: clinical and therapeutic consequences. Endocr Relat Cancer 2009; 16(1):243-253.

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

Appendix B

Questionnaires SF36v2™

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix C

NN9924-3790

Multiple dose trial examining dose range, escalation and efficacy of oral semaglutide in subjects with type 2 diabetes

Medical events of special interest (MESI)

	Event Title	Definition	Rationale
1	Fatal events	All cause mortality: 1. Cardiovascular death, 2. Non-cardiovascular death, 3. Undetermined cause of death	An FDA guidance document requests that sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes, in order to ensure that the new therapy does not increase the cardiovascular risk to an unacceptable extend.
2	Acute coronary syndrome: • Myocardial Infarction • Hospitalisation for unstable angina	All types of myocardial infarction (MI) must be reported: • Spontaneous MI (including re-infraction and MI associated with stent thrombosis) • Percutaneous coronary intervention (PCI) related MI • Coronary artery bypass graft surgery (CABG) related MI • Silent MI All events with symptoms of myocardial ischemia requiring hospitalisation must be reported.	An FDA guidance document requests that sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes, in order to ensure that the new therapy does not increase the cardiovascular risk to an unacceptable extend.

	Event Title	Definition	Rationale
3	Cerebrovascular event (stroke or transient ischemic attack)	Transient ischemic attack: Transient ischemic attack (TIA) is defined as a transient (<24 hours) episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. Stroke (ischemic, haemorrhagic, undetermined): Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.	An FDA guidance document requests that sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes, in order to ensure that the new therapy does not increase the cardiovascular risk to an unacceptable extend.
4	Coronary Revascularisation Procedure	Coronary Revascularization Procedure: • Coronary Artery Bypass Graft Surgery • Percutaneous Coronary Intervention A coronary revascularization procedure is a catheter-based or open surgical procedure designed to improve myocardial blood flow.	An FDA guidance document requests that sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes, in order to ensure that the new therapy does not increase the cardiovascular risk to an unacceptable extend.

	Event Title	Definition	Rationale
5	Heart failure requiring hospital admission[3]	Clinical manifestations of a new episode or worsening of an existing heart failure.	An FDA guidance document requests that sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes, in order to ensure that the new therapy does not increase the cardiovascular risk to an unacceptable extend.
6	Pancreatitis or clinical symptoms leading to suspicion of pancreatitis	Two of the following diagnostic criteria fulfilling the diagnosis of acute pancreatitis: 1. severe acute abdominal pain 2. elevated blood levels of pancreatic enzymes (lipase, amylase) > 3xUNR 3. characteristic imaging finding (ultrasound, computerised axial tomography (CT), magnetic resonance imaging (MRI)) Chronic pancreatitis will be defined by characteristic imaging finding (ultrasound, CT, MRI) with abnormal pancreatic function tests or characteristic histological findings.	Treatment with GLP-1 agonists has been associated with acute pancreatitis and Novo Nordisk therefore monitors these events closely.

	Event Title	**Definition**	**Rationale**
7	Neoplasm (excluding thyroid neoplasms)	All types of neoplasms must be reported including: • Malign neoplasm • In situ neoplasm • Benign neoplasm • Neoplasms of uncertain or unknown behaviour	Neoplasm is an event Novo Nordisk follows closely for GLP-1 analogues due to non-clinical findings in rats and mice treated with GLP-1 agonists.
8	Thyroid disease (including thyroid neoplasms)	All disorders of thyroid gland must be reported	Thyroid C-cells carcinogenicity has been reported in rats and mice treated with GLP-1 agonists in non-clinical studies
9	Medication errors concerning trial products	1. Administration of wrong drug or use of wrong device 2. Wrong route of administration, such as intramuscular instead of subcutaneous 3. Administration of a high dose with the intention to cause harm, e.g. suicide attempt 4. Administration of an accidental overdose, i.e. a) a pre-defined threshold is exceeded OR b) a dose which may lead to significant health consequences, as judged by the investigator, irrespective of whether the SAE criteria are fulfilled or not.	Standard MESI in all Novo Nordisk clinical trials. Medication errors are captured to collect information which may be used to improve the design, name or packaging of the product and/or information which may have an impact on product labelling (for example information about substantial overdoses).

Attachment I

Global list of key staff and relevant departments and vendors of clinical relevance

Attachment versioning is independent of the protocol.

For CDP trials: To be completed and maintained by the International Trial Manager or Clinical Pharmacologist.

Mandatory for Japan: The responsibilities for each person/ vendors of clinical relevance must be described.

Sponsor:	Name:	Novo Nordisk
	Address:	
Sponsor's global medical expert:	Name:	
	Title:	
	Address:	
	Tel:	
	Email	

If multinational trial or clinical pharmacology CDP trial:

International Trial Manager(s):	*Name:*	
	Address:	
	Tel:	
	Fax:	
	Tel:	
	E-mail:	
Customer Complaint Center, Recipient of technical complaint samples:	Name:	Novo Nordisk A/S Att: Customer Complaint Center
	Address:	

List laboratory(ies), and other medical and/or technical department(s), and/or institutions involved in the trial that are of clinical relevance. If multiple labs are used, describe what each lab analyses and/or responsibility. Also include which lab provides the lab kit.

Laboratory(ies): *Name:*

Address:

Tel:

Fax:

Mobile:

E-mail:

For eCRF, IV/WRS etc include each vendor:

eCRF vendor: *Name:*

Address:

Tel:

Fax:

Mobile:

E-mail:

IV/WRS vendor: *Name:*

Address:

Tel:

Fax:

Mobile:

E-mail:

Attachment II

Insert name of country
Consider to include country code in header

It is mandatory to obtain the information listed in attachment II, but the information can be captured and updated elsewhere (eg in local regulatory documents). Attachments I and II may be integrated into one document if convenient (eg for single centre trials).

List of key staff and relevant departments

To be completed and maintained for each country

If monitored by a CRO:

Monitor:	Name:
	Address:
	Tel of the CRO:

List for each trial site:

For countries in EU/EEA, state the National Coordinating Investigator

National Coordinating Investigator:	Name:	
	Title /qualification:	(Medical qualification [eg MD, DMD] of the investigator must be stated)
	Address:	
	Tel:	
	Fax:	
	E-mail:	
Investigator:	Name:	
	Title:	
	Address:	
	Tel:	

If the investigator is not a qualified physician, state responsible physician:

Responsible physician: Name:

Title/qualifications:

Address: (If different from above)

Tel:

Fax:

Mobile:

E-mail:

Mandatory if name(s) and address(es) of the laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial are not included in the protocol:

Local laboratory(ies): Name:

Address:

Tel:

Other medical and/or technical department(s) and/or institution(s):

Name:

Address:

Tel:

Protocol Amendment

no 1
to Protocol, Final Version 1.0
dated 25 June 2013

Trial ID:NN9924-3790

Multiple dose trial examining dose range, escalation and efficacy of oral semaglutide in subjects with type 2 diabetes

Trial phase: 2

Applicable to Sweden

Amendment originator:
[redacted]

Table of contents

Page

1 Introduction including rationale for the protocol amendment

This local substantial amendment for Sweden implements the requirement for a changed definition on adequate contraceptive measures for patients participating in the trial in Sweden as requested by the Medical Products Agency (MPA).

In this protocol amendment:

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

2 Changes

2.1. Section 6.3 Exclusion criteria

The following text will be changed under exclusion criteria No 3:

~~*Sweden: Adequate contraceptive measures are hormonal intrauterine devices, hormonal oral contraceptives, hormonal implants or injections, double barrier (a condom or diaphragm) with spermicide, sexual abstinence or vasectomised partner.*~~

is re-written according to the explicit request by the MPA to:

Sweden: Oral (except low-dose gestagen (lynestrenol and norestisteron)), injectable, or implanted hormonal contraceptives, intrauterine device, intrauterine system (for example, progestin-releasing coil), vasectomized male (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

Protocol Amendment

no 2
to Protocol, final version 1.0
dated 25 June 2013
including all amendments

Trial ID: NN9924-3790

Multiple dose trial examining dose range, escalation and efficacy of oral semaglutide in subjects with type 2 diabetes

Trial phase: 2

Applicable to all countries

Amendment originator:

[redacted]

Table of contents

1 Introduction including rationale for the protocol amendment

The HbA_{1c} criterion will be removed as part of the rescue criteria during the treatment period. It has been judged that there is a risk of having an inappropriately high proportion of the subjects requiring rescue due to high HbA_{1c} levels during the trial. Hence it has been decided to only assess the need for rescue medication based on confirmed fasting plasma glucose levels. As described in the statistical section, subjects on rescue medication will not be included in the primary analysis (only data up to the point of rescue) meaning that a high number of subjects on rescue medication could potentially invalidate the data and trial results. The investigator can at anytime during the trial decide to discontinue trial product and initiate other treatment if any safety issues are seen, consequently this change is not assessed to have any safety risks for the subjects.

The process of reporting central ECG evaluation back to investigator has been changed. Only clinically significant abnormal findings as evaluated by the central reader will be sent to the investigator. The investigators will do their own assessment at site, hence it is not relevant to inform the investigator of all findings as this would increase the workload significantly at the site without adding value with regards to the safety of the subject.

The ADA classification of hypoglycaemia has recently been updated. The protocol has been updated to be aligned with the new definition. Furthermore, the section on IRB and IEC has been updated to comply with the recent update of the Declaration of Helsinki.

The definition of thyroid events for adjudication has been updated to add clarity and to be aligned with the Event Adjudication Charter. Thyroid events must be reported for adjudication both in case of thyroid neoplasm AND in case of thyroidectomies regardless of indication.

In addition, minor inconsistencies and errors have been corrected.

In this protocol amendment:

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

2 Changes

2.1 Section 2.1 Flow chart foot notes

x[6]: Trough and peak PK sampling is only applicable for subjects in the oral treatment arms *and replaces the regular PK sampling for these subjects at visits 4, 8 and 11*. Subjects must attend the visit without having taken the tablet on the same day (see Section 8.4.10)

x[8]: Fasting *for lab sampling* is defined as having consumed only water since midnight. For the Follow-up visit (V12) attending fasting is defined as having consumed only water for at least the preceding 2 hours. *For the trough and peak PK sampling visits (V4, 8, 11) the fasting is outlined in section 5.3.1.*

2.2 Section 5.2 Rationale for trial design

Parallel treatment groups and a randomised partially-blinded, controlled design have been chosen in accordance with the trial objectives. To avoid bias in the assessment of the different doses of oral semaglutide, the eight oral treatment arms are double-blind. The doses are escalated in standard four week intervals to limit gastrointestinal AEs. Escalation intervals of two weeks and ~~six~~ *eight* weeks are also being explored to investigate effect on onset of action and overall AEs.

2.3 Section 6.4 Rescue criteria

~~Subjects with unacceptable hyperglycaemia should be offered treatment intensification (rescue medication) according to local label at the discretion of the investigator as add-on to randomised treatment and should continue to follow the protocol-specified visit schedule. Rescue medication should exclude other incretin-based therapies such as other GLP-1 receptor agonists, DPP-4 inhibitors and amylin analogues.~~

~~Unacceptable hyperglycaemia in this trial is defined as:~~

- ~~FPG >15 mmol/L (270 mg/dL) from baseline to week 6~~
- ~~FPG >13.3 mmol/L (240 mg/dL) from week 6 to week 12~~
- ~~FPG >11.1 mmol/L (200 mg/dL) or HbA_{1c} > 8.0% (64 mmol/mol) from week 12 to end of trial~~

If any of the FPG values exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified the subject should be offered treatment intensification (rescue medication):

- 15.0 mmol/L (270 mg/dL) from randomisation to end of Week 5
- 13.3 mmol/L (240 mg/dL) from Week 6 to end of Week 11
- 11.1 mmol/L (200 mg/dL) from Week 12 to end of trial

A confirmatory FPG should be obtained by central laboratory if related to a scheduled visit or by local laboratory if not related to scheduled visits. If the confirmatory FPG exceeds the values described above the subject should be offered treatment intensification (rescue medication) at the discretion of the investigator and in accordance with ADA/European Association for the Study of Diabetes[a] (preferably excluding GLP-receptor agonists, DPP-4 inhibitors and amylin analogues). Rescue medication (intensification of existing background medication and/or initiation of new medication) and any changes to this should be captured on the concomitant medication form in the eCRF. Rescue medication should be prescribed as add-on to randomised treatment and subjects should continue to follow the protocol-specified visit schedule.

Reference a added see section 2.14

2.4 Section 8.4.7 Electrocardiogram – 12-lead

Sites will be informed of the central ECG evaluation in case this evaluation reveals an abnormal*, clinically significant* ECG reading. If the abnormality represents an unreported AE, SAE or MESI, such findings must be reported if the investigator finds the abnormality clinically significant (see Section 8.1.11).

2.5 Section 8.4.10 Pharmacokinetics

For subjects on oral treatment, three of the PK sampling assessments will be pre-dose and post-dose (trough and peak) only ~~Subjects on oral treatment will also have PK measured pre-dose and post-dose (trough and peak) at three visits~~ (see Section 2). At the visits for trough and peak PK measurements, the investigator needs to ensure that the subjects on oral treatment follow these procedures:

2.6 Section 12.1 Definitions

Medical event of special interest
A medical event of special interest (MESI) is an event which, in the evaluation of safety, has a special focus. A MESI is an AE (SAE or non-serious AE) which fulfils one or more of the below defined MESI criteria.

8. Thyroid Disease ~~((A) if thyroidectomy is required)~~*((A) if thyroid neoplasm or resulting in thyroidectomy)*

2.7 Section 12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from *when* ~~the first trial-related activity after~~ the subject has signed the informed consent until the end of the post-treatment follow-up period. The events must be recorded in the applicable eCRF forms in a timely manner (see timelines below and Figure 12–1).

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

following reference document: IB (Oral Administration of Semaglutide (NN9924)) *section 6.2.6.1 Reference safety information*, Edition 5[6] and any updates hereof.

2.8 Section 12.7.2 Event adjudication committee

- Thyroid Disease (~~if thyroidectomy is required~~*if thyroid neoplasm or resulting in thyroidectomy)*)

2.9 Section 17.1 Sample size calculation

A standard deviation (SD) of 1.2% for change from baseline in HbA1c is chosen as assumption for the sample size calculation. The SD observed in several phase 3 trials of 26 weeks duration with s.c. liraglutide suggests a standard deviation less than 1.1%. However, as it is uncertain if the added variation in exposure compared to s.c. ~~liraglutide~~*semaglutide* will transfer to an added variation in the therapeutic response, a SD of 1.2% is assumed.

2.10 Section 17.2 Definition of analysis sets

Safety Analysis Set (SAS): includes all subjects exposed to at least one dose of randomised ~~liraglutide~~*semaglutide* or ~~liraglutide~~*semaglutide* placebo. Subjects in the SAS will contribute to the evaluation "as treated".

2.11 Section 17.3 Primary endpoint

Due to the uncertainty in relation to if the added variation in the exposure in the oral semaglutide arms compared to s.c. ~~liraglutide~~ *semaglutide* will transfer to an added variation in the therapeutic response, a sensitivity analysis allowing the within subject unstructured covariance matrix to be fitted separately for each treatment arm will be conducted.

2.12 Section 17.4.2 Safety endpoints

Confirmed hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1mmol/L (56 mg/dL)[13]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of confirmed hypoglycaemia.

Confirmed hypoglycaemic episodes are defined as episodes that are:

- severe ~~(i.e., an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions)~~*according to the ADA classification below* and/or
- biochemically confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia

ADA classification[b] of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, *or take other corrective actions.* ~~other resuscitative~~

~~actions.~~ *Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose back to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.*

- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL)
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- ~~Relative~~*Pseudo*-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia~~, and interprets those as indicative of hypoglycaemia, but~~ with a measured plasma glucose 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 plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L ~~(70 mg/dL)~~).

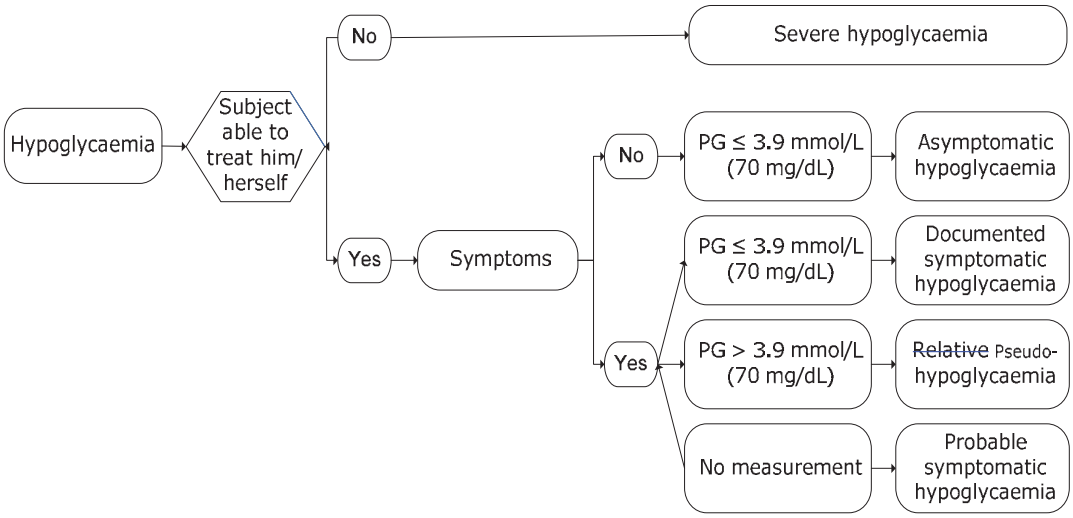

Figure 17–1 ADA classification of hypoglycaemia

Reference b added see section 2.14

2.13 Section 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 sponsor, 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, ~~substantial protocol amendments, non-substantial~~ 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 risk/benefit 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.

2.14 Section 27 References

2 World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. ~~59th WMA General Assembly, Seoul. 1 Oct 2008~~. *Last amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013*

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

b Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L et al: Hypoglycemia and Diabetes: A report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 36: 1384-1395, 2013

Protocol Amendment

no 3
to Protocol, final version 1.0
dated 25 June 2013
including all amendments

Trial ID: NN9924-3790

Multiple dose trial examining dose range, escalation and efficacy of oral semaglutide in subjects with type 2 diabetes

Trial phase: 2

Applicable to Germany

Amendment originator:

[redacted]

Table of contents

1 Introduction including rationale for the protocol amendment

According to the deficiency letter from [redacted] from 28-Feb-2014, the global substantial Amendment no 2 to Protocol, final version 1.0 dated 25 June 2013, final version 1.0, dated 16 January 2014 will be amended by this document for [redacted].

The HbA1c criterion will be removed as part of the rescue criteria during the treatment period. It has been judged that there is a risk of having an inappropriately high proportion of the subjects requiring rescue due to high HbA1c levels during the trial. Hence it has been decided to only assess the need for rescue medication based on confirmed fasting plasma glucose levels. As described in the statistical section, subjects on rescue medication will not be included in the primary analysis (only data up to the point of rescue) meaning that a high number of subjects on rescue medication could potentially invalidate the data and trial results. The investigator can at any time during the trial decide to discontinue trial product and initiate other treatment if any safety issues are seen, consequently this change is not assessed to have any safety risks for the subjects.
To ensure proper treatment respectively treatment intensification of subjects, the rescue FPG criteria will be lowered from 200 mg/dl to 180 mg/dl from week 12 and onwards.

In this protocol amendment:

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

2 Changes

2.1 Section 6.4 Rescue criteria

~~Subjects with unacceptable hyperglycaemia should be offered treatment intensification (rescue medication) according to local label at the discretion of the investigator as add-on to randomised treatment and should continue to follow the protocol-specified visit schedule. Rescue medication should exclude other incretin-based therapies such as other GLP-1 receptor agonists, DPP-4 inhibitors and amylin analogues.~~

~~Unacceptable hyperglycaemia in this trial is defined as:~~

- ~~FPG >15 mmol/L (270 mg/dL) from baseline to week 6~~
- ~~FPG >13.3 mmol/L (240 mg/dL) from week 6 to week 12~~
- ~~FPG >11.1 mmol/L (200 mg/dL) or HbA_{1c} > 8.0% (64 mmol/mol) from week 12 to end of trial~~

If any of the FPG values exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified the subject should be offered treatment intensification (rescue medication):

- 15.0 mmol/L (270 mg/dL) from randomisation to end of Week 5
- 13.3 mmol/L (240 mg/dL) from Week 6 to end of Week 11
- ~~11.1 mmol/L (200 mg/dL)~~ *10.0 mmol/L (180 mg/dL)* from Week 12 to end of trial

A confirmatory FPG should be obtained by central laboratory if related to a scheduled visit or by local laboratory if not related to scheduled visits. If the confirmatory FPG exceeds the values described above the subject should be offered treatment intensification (rescue medication) at the discretion of the investigator and in accordance with ADA/European Association for the Study of Diabetes[a] (preferably excluding GLP-receptor agonists, DPP-4 inhibitors and amylin analogues). Rescue medication (intensification of existing background medication and/or initiation of new medication) and any changes to this should be captured on the concomitant medication form in the eCRF. Rescue medication should be prescribed as add-on to randomised treatment and subjects should continue to follow the protocol-specified visit schedule.