Cover Page for Protocol

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Official title of study:	Investigation of safety and efficacy of once-daily semaglutide in obese subjects without diabetes mellitus
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16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

Trial ID: NN9536-4153

Investigation of safety and efficacy of once-daily semaglutide in obese subjects without diabetes mellitus

A 52-week, randomised, double-blind, placebo-controlled, nine-armed, parallel group, multi-centre, multinational trial with liraglutide 3.0 mg as active comparator

Trial phase: 2

Protocol originator

[redacted]

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	Alanine aminotransaminase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
BMR	basal metabolic rate
CPK	creatine phosphokinase
C-SSRS	Columbia Suicidality Severity Rating Scale
CRF	case report form
CTR	clinical trial report
DPP-4	dipeptidyl peptidase 4
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FPFV	first patient first visit
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA_{1c}	glycosylated haemoglobin
HRQoL	health-related quality of life
hsCRP	High-sensitivity C reactive protein
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee

IRB	institutional review board
IWRS	interactive web response system
IWQoL-Lite	Impact of Weight on Quality of Life Lite
LDL	low density lipoprotein
LPLV	last patient last visit
MAR	missing at random
MESI	medical event of special interest
MHP	mental health professional
MMRM	mixed model for repeated measurements
NRS	numeric rating scale
PD	pharmacodynamic
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic
PRO	patient reported outcome
RET	re-arranged during transfection
SAE	serious adverse event
s.c.	subcutaneous(ly)
SF-36	Short Form-36
SMBG	self-measured blood glucose
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
TEE	total energy expenditure
TMM	Trial Materials Manual
TSH	thyroid-stimulating hormone
UTN	Universal Trial Number

1 Summary

Primary objective
To assess and compare the dose-response of five doses of once-daily semaglutide versus placebo in inducing and maintaining weight loss after 52 weeks in obese subjects without diabetes mellitus

Primary endpoint
Relative change from baseline in body weight (%) at 52 weeks

Key secondary objectives

To compare the effect of once-daily semaglutide versus once-daily liraglutide 3.0 mg in inducing and maintaining weight loss after 52 weeks in obese subjects without diabetes mellitus

To compare the effects of once-daily semaglutide to placebo and once-daily liraglutide 3.0 mg on:
- Glucose metabolism parameters

Key secondary endpoints

- Proportion (%) of subjects with weight loss of ≥ 5% of baseline body weight at 52 weeks
- Proportion (%) of subjects with weight loss of ≥ 10% of baseline body weight at 52 weeks

Change from baseline to 52 weeks in:
- Other parameters of weight loss
  - Body weight (kg)
- Glucose metabolism parameters:
  - Glycosylated haemoglobin (HbA_{1c})
  - Fasting plasma glucose (FPG)

Trial design

This is a 52-week, randomised, double-blind, placebo-controlled, nine-armed, parallel group, multi-centre, multinational trial comparing once-daily subcutaneous administration of semaglutide in five different doses (ranging from 0.05 mg/day to 0.4 mg/day) with placebo in obese subjects without diabetes mellitus. Liraglutide 3.0 mg/day is included as an active comparator. The trial is double-blinded between active and placebo treatment. The total trial duration for the individual subject will be approximately 60 weeks.

To ensure a sufficiently large sample of men, an upper limit will be implemented, allowing no more than 70% of the trial population to be women and the randomisation will be stratified according to sex.

Subjects will be randomised in a balanced manner (6:1 active:placebo) for each of the 8 active treatment arms. The placebo arms are considered as one, giving a total of 9 arms. The treatment arms are:

- semaglutide at randomised target dose 0.05, 0.1, 0.2, 0.3, or 0.4 mg (for dose levels above 0.05 mg, dose escalation will take place every fourth week)
- semaglutide at randomised target dose 0.3 or 0.4 mg (starting dose 0.05 mg with dose escalation every second week)
- liraglutide 3.0 mg (starting dose 0.6 mg with dose escalation every week)
- placebo (matching each of the active treatment arms)

Subjects in all treatment arms including placebo will receive nutritional counselling and a calorie-reduced diet by a dietician or equivalent qualified delegate as well as physical activity counselling by a qualified person on a monthly basis beginning at the randomisation visit.

Trial population:

A total of 935 subjects is planned to be randomised and this will not exceed 963 randomised subjects. Based on an assumption of a 30% screening failure rate, 1,336 subjects are planned to be screened.

Key inclusion criteria:

- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
- Male or female, age ≥ 18 years at the time of signing inform consent
- Body mass index (BMI) ≥ 30.0 kg/m^2 at the screening visit
- At least one unsuccessful weight loss attempt per investigator judgement

Key exclusion criteria:

- A HbA_{1c} ≥ 6.5% at screening or diagnosed with type 1 or type 2 diabetes mellitus
- Treatment with glucose lowering agent(s) within 90 days before screening
- Screening calcitonin ≥ 50 ng/L (pg/mL)
- Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
- History of pancreatitis (acute or chronic)
- Obesity induced by endocrine disorders (e.g. Cushing Syndrome)
- Treatment with any medication within 90 days before screening that based on investigator's judgement may cause significant weight change

- Previous surgical treatment for obesity (liposuction and/or abdominoplasty performed > 1 year before screening is allowed)
- History of major depressive disorder within 2 years before randomisation
- Any lifetime history of a suicidal attempt
- Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice)

Assessments:

Efficacy
- Body measurements (body weight in kg)
- Glucose metabolism (HbA_{1c}, FPG)

Safety
- Adverse events
- Pulse
- Mental health
- Biochemistry and haematology
- Antibodies against semaglutide

Trial products:

The following trial products will be supplied by Novo Nordisk A/S, Denmark:
- Semaglutide 1.0 mg/ml, solution for injection, 3.0 ml cartridge, for NovoPen® 4
- Semaglutide placebo, solution for injection, 3.0 ml cartridge, for NovoPen® 4
- Liraglutide 6.0 mg/ml, solution for injection, 3.0 ml pre-filled PDS290 pen-injector
- Liraglutide placebo, solution for injection, 3.0 ml pre-filled PDS290 pen-injector

2 Flow chart

	Screening	Randomi-sation	Dose escalation / Maintenance								Maintenance period									EOT	FU	Trial product discontinuation 52-week FU[1]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22x
Weeks in relation to visit 2	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	59	52
Visit window, days	+3 to -7		± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	- 5	± 5
SUBJECTS																						
Informed consent (18.2)	X																					
In/exclusion criteria (6.2, 6.3)	X	X																				
Discontinuation of trial product criteria (6.4, 8.1.4)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Demography (8.2.1)	X																					
Medical history/concomitant illness (8.2.2)	X																					
History of concomitant cardiovascular disease (8.2.2.1)	X																					
History of gallbladder disease (8.2.2.2)	X																					
History of psychiatric disorders (8.2.2.3)	X																					
History of breast neoplasms[2] (8.2.2.4)	X																					
History of colon neoplasms (8.2.2.5)	X																					
Concomitant medications (8.2.2)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Evaluation of antihypertensive and lipid-lowering treatment(8.2.3.1)										X				X			X			X		
Tobacco use (8.2.4)	X																					
EFFICACY																						
Body weight (8.4.1.1)	X	X[3]	X	X[3]	X	X	X	X	X	X[3]	X	X	X	X[3]	X	X	X[3]	X	X	X[3]	X	X
Height (8.4.1.2)	X																					
Waist and hip circumference (8.4.1.4)	X	X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	
Systolic and diastolic blood pressure, sitting (8.4.2)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA_{1c} (8.4.3)	X	X		X						X				X			X			X		
Fasting plasma glucose (8.4.3)		X		X						X				X			X			X		
hsCRP (8.4.3)		X												X						X		
Lipids (8.4.3)		X		X						X				X			X			X		

	Screening	Randomi-sation	Dose escalation / Maintenance								Maintenance period									EOT	FU	Trial product discontinuation 52-week FU[1]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22x
Weeks in relation to visit 2	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	59	52
Visit window, days	+3 to -7		± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	- 5	± 5
Nutritional compliance (8.6.3)				X		X		X		X		X	X	X	X	X	X	X	X	X	-	
IWQoL-Lite for Clinical Trials[4] (8.4.4)		X												X					X	X		
SF-36 questionnaire[4] (8.4.4)		X												X						X		
Patients' global impression of change[4] (8.4.4)														X						X		
SAFETY																						
Physical examination (8.5.1)	X																			X		
ECG (8.5.2)		X												X						X		
Pulse, sitting (8.5.3)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Breast neoplasms follow-up[2] (8.5.4)																				X		X
Colon neoplasms follow-up (8.5.5)																				X		X
Mental health questionnaires (8.5.6)	X	X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	
Adverse Events[5] (8.5.7)	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
Technical complaints (12.4)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Haematology (8.5.11)	X	X		X						X				X			X			X		
Biochemistry (8.5.11)	X	X		X						X				X			X			X		
Calcitonin (8.5.11, 12.7.3)	X	X		X						X				X			X			X		
Pregnancy test[6] (8.5.12)	X	X		X		X[7]		X[7]		X		X[7]	X[7]	X	X[7]	X[7]	X	X[7]	X[7]	X	X	
Anti-semaglutide antibodies[8, 9] (8.5.13)		X		X		X				X				X			X			X	X	
OTHER ASSESSEMENTS																						
Semaglutide plasma concentration[9] (8.6.1)				X	X	X		X		X				X			X			X	X	
Nutritional and physical activity counselling (8.6.3, 8.6.4		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	
TRIAL MATERIAL																						
Dispensing of trial product (9.4)		X				X				X				X			X					
Drug Accountability (9.4)						X				X				X			X			X		
IWRS session (10)	X	X				X				X				X			X			X		
REMINDERS																						

	Screening	Randomi-sation	Dose escalation / Maintenance								Maintenance period									EOT	FU	Trial product discontinuation 52-week FU[1]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22x
Weeks in relation to visit 2	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	59	52
Visit window, days	+3 to -7		± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	- 5	± 5
Handout ID card (8.1.1)	X																					
Training in trial product and pen handling (8.1.6, 9.1)		X																				
Dispense dosing diary (8.6.2)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Collect dosing diary and record in eCRF (8.6.2)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Attend visit fasting (8.1.2)		X		X						X				X			X			X	X[10]	

Abbreviations: ECG = Electrocardiogram, EOT = end-of-treatment, FU = follow-up, HbA_{1c} = glycosylated hemoglobin, hsCRP = high-sensitivity C reactive protein, IWRS = interactive web response system, IWQoL-Lite = Impact of Weight on Quality Of Life Lite, SF-36 = Short Form-36

[1]) Only applicable for subjects who discontinue trial product before visit 20. Subjects discontinued from trial product should be encouraged to come for the EOT visit and FU visit and have the Trial product discontinuation 52-week FU visit scheduled 52 weeks (± 5 days) after randomisation
[2]) History of breast neoplasms and breast neoplasms follow-up should only be performed for female subjects
[3]) Fasting body weight
[4]) Will only be done in the US. The questionnaires must be completed by the subject and should preferably be completed after conclusion of all fasting-related activities, but before any other visit-related activities
[5]) If the subject experienced nausea within 24 hours before a visit, use the nausea questionnaire (see section 8.5.8). If a hypoglycaemic episode is reported, please refer to section 8.5.9.
[6] For women of childbearing potential: Pregnancy testing will be performed on a monthly basis throughout the trial. Urine pregnancy test should be performed at any time during the trial if a mentrual period is missed, or as required by local law
[7]) At these visits, urine pregnancy testing will be performed
[8]) Subjects must be instructed to withhold their trial product dose in the morning until blood sampling has been performed at the visit.. This is not applicable for subjects that have discontinued trial product. Samples taken at the follow-up visit (visit 21) must be taken fasting (as a minimum by only having consumed water for at least 2 hours).
[9]) Anti-semaglutide antibodies and semaglutide plasma concentrations must only be drawn for subjects in the semaglutide treatment arms or the matching placebo arms.
[10]) The subject should be fasting for a minimum of 2 hours (only water consumption allowed) prior to the anti-semaglutide antibody sampling at visit 21

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 Background information

Obesity is one of the most significant public health challenges globally. It's impact is considerable in the Western world but it is now also an emerging epidemic in developing countries [3]. Lately the American Medical Association, the National Institutes of Health, The Obesity Society and the American Association for Clinical Endocrinology have recognised the seriousness of obesity and the related comorbidities by classifying obesity as a disease[4]. Obesity can lead to serious health consequences including hypertension, atherosclerosis, hyperglycaemia, dyslipidaemia, certain types of cancer and obstructive sleep apnoea (OSA)[5,6].

Although not all people with obesity develop health problems, the risk of obesity-related complications and comorbidities increases with increasing BMI, and even a moderate weight loss of 5–10% has been shown to have significant health benefits in terms of improving glycaemic control, reducing progression to type 2 diabetes mellitus (T2DM) and improving other weight-related comorbidities, as well as physical symptoms and quality of life[7-9].

3.1.1 Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the L-cells in the small intestine. GLP-1 has a glucose-dependent stimulatory effect on insulin and inhibitory effect on glucagon secretion from the pancreatic islets (i.e. when plasma glucose levels are above normal)[10,11]. Furthermore, GLP-1 is a physiological regulator of appetite and food intake and GLP-1 receptors are present in several areas of the brain involved in appetite regulation. Physiologically, GLP-1 has a pronounced inhibitory effect on gastric emptying; however this effect seems to diminish upon chronic exposure[12-14]. Endogenous GLP-1 has a very short elimination half-life of <1.5 minutes after intravenous administration due to rapid degradation by ubiquitous dipeptidyl peptidase (DPP-4)[15]. Development of a GLP-1 receptor agonist (GLP-1 RA) with longer half-life has been necessary to enable effective treatment option for T2DM and obesity.

3.1.2 Semaglutide

Semaglutide is a potent human GLP-1 RA with a half-life of approximately 160 hours, suitable for both once daily (subcutaneous (s.c.) and oral) and once weekly s.c. administration. It is structurally similar to liraglutide (Victoza® and Saxenda®), a once daily GLP-1 RA developed by Novo Nordisk and approved in several countries for the treatment of T2DM and weight management, respectively.

For the semaglutide molecule the principal mechanism of protraction is albumin binding facilitated by a large fatty acid derived chemical moiety attached to the lysine in position 26. *In vitro* receptor studies have shown that semaglutide is a potent and selective GLP-1 RA, and animal studies using non-diabetic rats, non-diabetic pigs and diabetic mice have shown lowering of blood glucose and inhibition of food intake.

3.1.3 Liraglutide

Liraglutide is a long-acting once daily GLP-1 analogue. Liraglutide 3.0 mg (Saxenda®) has recently been submitted to various Health Authorities worldwide and is approved in USA, Canada, and EU for the indication of weight management[16]. Liraglutide 1.2 and 1.8 mg (Victoza®) is approved in multiple countries for the treatment of T2DM. Compared to human GLP-1, liraglutide has a C16 fatty (palmitic) acid chain attached at position 26 (lysine) of the peptide, and has lysine at position 34 replaced by arginine. *In vitro* receptor studies have shown that liraglutide is a selective, potent and full agonist of the cloned human GLP-1 receptor. In animal studies, peripheral administration of liraglutide, led to specific activation of the GLP-1 receptors in the hypothalamus, which increased key satiety and decreased key hunger signals, thereby leading to lowering of body weight. In humans, liraglutide lowers body weight primarily through loss of fat mass with relative reduction in visceral fat being greater than subcutaneous fat[17].

A total of 52 clinical trials with liraglutide for T2DM and weight management have been completed (including doses up to 3.0 mg). The trials were conducted world-wide. Out of more than 11,000 subjects, more than 7,500 subjects were exposed to liraglutide for up to three years. In the weight management programme, subjects treated with liraglutide 3.0 mg experienced a dose-dependent weight loss ranging between 5.7% and 9.2% (6.0-8.8 kg) depending on the trial, whereas subjects treated with placebo (on diet and exercise alone) had a mean weight loss between 0.2% and 3.1% (0.2-3.0 kg). In addition to weight-lowering, for subjects treated with liraglutide 3.0 mg there was a decrease in systolic blood pressure and the prevalence of pre-diabetes was significantly reduced compared to subjects treated with placebo. The safety evaluation was favourable with the main tolerability finding being gastrointestinal adverse events. Cases of gallstones (cholelithiasis) and inflammation of the gallbladder (cholecystitis) were reported more commonly in adult subjects treated with liraglutide 3.0 mg compared to placebo.

3.1.4 Nonclinical data

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

Thyroid C-cell tumours in rodents

Treatment-related non-genotoxic proliferative changes in the thyroid C-cells of mice and rats were observed in 2-year carcinogenicity studies with semaglutide; thyroid hyperplasia was preceded by an increase in serum calcitonin. C-cell changes have not been observed in long-term studies in non-human primate. The observed pattern of effects in mice and rats (thyroid C-cell hyperplasia 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 RAs, including liraglutide. According to this mechanism, C-cell hyperplasia is mediated by the GLP-1 receptor and is not associated with RET (re-arranged during transfection) activation, and rodents appear to be particularly sensitive, whereas humans are not. The relevance for human subjects is currently unknown, but considered to be low. In the present trial, calcitonin will be measured on a regular basis and guidance to investigators of further evaluation and action on elevated plasma calcitonin concentrations will be carried out by an independent group of thyroid experts, the calcitonin monitoring committee (see Appendix A). This will ensure appropriate and consistent handling of elevated calcitonin levels across trials.

Teratogenicity in rats

Semaglutide caused embryo-foetal malformations in the rat through a GLP-1 receptor mediated effect on the inverted yolk sac placenta leading to impaired nutrient supply to the developing embryo. Primates do not have an inverted yolk sac placenta which makes this mechanism unlikely to be of relevance to humans and cynomolgus monkeys. In the developmental toxicity studies in cynomolgus monkey, a marked pharmacology mediated maternal body weight loss coincided with increased early foetal loss; however, there was no indication of a teratogenic potential of semaglutide in this species. As a precaution female subjects who are pregnant, breast-feeding or intend to become pregnant will not be included in the trial. Likewise, females of childbearing potential not using an adequate contraceptive method throughout the trial including the 7-week follow-up period are not eligible for treatment with trial product. During the trial, pregnancy tests will be done at site visits.

3.1.5 Clinical data

Semaglutide is currently being investigated in the T2DM clinical development programme (NN9535). Currently no dedicated data in obese subjects without T2DM exist. Doses up to 1.6 mg with weekly dosing have been tested and doses up to 0.4 mg with daily dosing are planned in dedicated trials. As of 20 December 2014, 6 clinical pharmacology trials (trials NN9535-1820, NN9535-3679, NN9535-3633, NN9535-3616, NN9535-3819, and NN9535-4010) and 1 phase 2 trial (trial NN9535-1821) have been completed with semaglutide. In the completed trials, 553 subjects have been exposed to semaglutide. Thereof, 192 were healthy subjects (both single and multiple dosing), 313 were subjects with T2DM and 48 were subjects with varying degrees of renal impairment (4 with T2DM). In addition, 22 healthy subjects have been exposed to semaglutide

(s.c.) in the oral administration semaglutide project (NN9924). A total of 8 therapeutic confirmatory trials with nearly 8000 subjects enrolled were ongoing (as of 20 December 2014) including a 104-week trial comparing the long-term safety (including cardiovascular risk) and efficacy of semaglutide versus placebo as add on to standard-of-care treatment. In parallel, 10 clinical pharmacology trials are ongoing to investigate the metabolism of semaglutide, the impact of hepatic impairment on the PK-profile of semaglutide and the effect of semaglutide on several aspects of glycaemic control, appetite regulation, QTc-prolongation and drug-drug interaction with selected oral drugs. These investigations are being performed in different populations including healthy subjects, subjects with T2DM, obese subjects and subjects with hepatic impairment.

Efficacy

As of 20 December 2014, the efficacy of semaglutide in subjects with T2DM 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 T2DM received once weekly s.c. injection of 1 of 5 semaglutide dose levels (0.1-1.6 mg), once-daily s.c. injection of open-label liraglutide (1.2 mg or 1.8 mg) or once-weekly s.c. injection of placebo. No diet and exercise intervention was instituted in trial NN9535-1821. Statistically significant weight loss was observed in the semaglutide groups (including doses of 0.8 mg and above) of up to 4.82 kg compared to 1.18 kg in the placebo group. Glycosylated haemoglobin (HbA_{1c}) was significantly decreased up to -1.19% (placebo adjusted estimated treatment difference). Dose-dependency was established both for weight loss and glycaemic parameters.

Safety

Consistent with findings with other GLP-1 RAs, the most frequent adverse events (AEs) were gastrointestinal disorders (nausea and vomiting); most of the events were mild in intensity and transient in nature. Hypoglycaemia has been observed 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 RAs. The implications of this increase are currently unknown.

As is the case with all protein-based pharmaceuticals, subjects treated with semaglutide may develop immunogenic and allergic reactions. Few allergic reactions have been reported in connection with semaglutide treatment. These have mainly been mild and transient. More generalised reactions, including urticaria, rash, pruritus and a single case of angioedema have also been observed. Few injection site reactions have been reported. These have mainly been mild and transient in nature.

Please refer to the current versions of the semaglutide s.c. (project NN9535), T2DM, Investigator's Brochure and liraglutide (project NN8022) weight management, Investigator's Brochure for further details.

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

3.2 Rationale for the trial

Semaglutide is a long-acting GLP-1 RA currently under development for treatment of T2DM. Based on results from studies with semaglutide and liraglutide and supported by scientific literature on GLP-1 RAs, semaglutide is expected to lower body weight primarily by reducing energy intake, and not by affecting energy expenditure as semaglutide is known to enter specific areas of the brain relevant for reduction of energy intake[18].

The semaglutide phase 2 dose-finding trial (NN9535-1821) in subjects with T2DM without nutritional and physical activity counselling supports the effect of semaglutide in lowering body weight, as semaglutide 1.6 mg/week provided an absolute weight loss of 4.8 kg (baseline body weight of 84.9 kg). The trial showed a clear dose-dependent response on weight loss over 12 weeks of treatment, indicating that higher weight losses could be expected with even higher doses than those previously investigated. Based on the mode of action of semaglutide, it is hypothesised that semaglutide at doses up to 0.4 mg/day may provide even greater weight loss.

Clinical trials in the liraglutide weight management development programme (NN8022) have shown that liraglutide 3.0 mg provides a clinically meaningful weight loss; the weight loss ranged between 5.7 and 9.2% (placebo ranged between 0.2 and 3.1%) in the individual trials. However, based on early clinical data and the different molecular properties of semaglutide compared to liraglutide, superior weight loss is expected with semaglutide.

The purpose of the present trial is to investigate the potential of semaglutide at five dose levels to induce weight loss in obese subjects without diabetes mellitus compared to placebo and liraglutide 3.0 mg. Furthermore, a fast escalation regimen will be investigated balancing time to reach target dose with tolerability. Safety and tolerability including the formation of anti-semaglutide antibodies will be investigated.

4 Objectives and endpoints

4.1 Objectives

Primary objective

- To assess and compare the dose-response of five doses of once-daily semaglutide versus placebo in inducing and maintaining weight loss after 52 weeks in obese subjects without diabetes mellitus

Secondary objectives

- To compare the effect of once-daily semaglutide versus once-daily liraglutide 3.0 mg in inducing and maintaining weight loss after 52 weeks in obese subjects without diabetes mellitus
- To compare the effects of once-daily semaglutide to placebo and once-daily liraglutide 3.0 mg on:
  - Glucose metabolism
  - Cardiovascular risk factors
  - Change in antihypertensive and lipid-lowering medical treatment
  - Compliance with dietary counselling
  - Patient reported weight-related quality of life and general health status
- To compare the safety and tolerability of five dose levels of once-daily semaglutide with placebo and once-daily liraglutide 3.0 mg in obese subjects without diabetes mellitus
- To compare efficacy of dose escalation every 2 weeks versus that of dose escalation every 4 weeks for two dose levels of once-daily semaglutide after 52 weeks in obese subjects without diabetes mellitus
- To compare tolerability of dose escalation every 2 weeks versus that of dose escalation every 4 weeks for two dose levels of once-daily semaglutide in obese subjects without diabetes mellitus
- To examine criteria for identifying early responders that predict weight loss after 52 weeks

4.2 Endpoints

4.2.1 Primary endpoint

- Relative change from baseline in body weight (%) at 52 weeks

4.2.2 Secondary endpoints

Supportive secondary efficacy endpoints

- Proportion (%) of subjects with weight loss of ≥ 5% of baseline body weight at 52 weeks*
- Proportion (%) of subjects with weight loss of ≥ 10% of baseline body weight at 52 weeks*

- Change from baseline to 52 weeks in:
  Other parameters of weight loss:
  - Body weight (kg)*
  - Waist circumference (cm)
  - Waist to hip circumference ratio (waist(cm)/hip(cm))
  - BMI (kg/m^2)

  Glucose metabolism:
  - HbA_{1c}*
  - FPG*
  - Shift in glycaemic category (normoglycaemia, pre-diabetes, T2DM)

  Cardiovascular risk factors:
  - Systolic and diastolic blood pressure
  - Lipids (total cholesterol [TC], low density lipoprotein cholesterol [LDL cholesterol], high density lipoprotein cholesterol [HDL cholesterol], very low density lipoprotein cholesterol [VLDL cholesterol], triglycerides [TG], free fatty acids [FFA])
  - Cardiovascular biomarker (high sensitivity C reactive protein [hsCRP])

  Patient reported weight-related quality of life and general health status:
  - Impact of Weight on Quality of Life-Lite (IWQoL-Lite) for Clinical Trials: Total score and scores on the individual sub-domains
  - Short form-36 (SF-36): Physical and mental component summary scores and scores on the individual sub-domains: Physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health

  Proportion of subjects with change (decrease, no change, increase) in concomitant medications:
  - Antihypertensive medications
  - Lipid-lowering medications
- Compliance with nutritional counselling

Supportive secondary safety endpoints

- Number of treatment-emergent AEs during the trial
- Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during the trial
- Number of new and ongoing treatment-emergent nausea, vomiting, diarrhoea and constipation events by week
- Nausea:
  - Individual scores of nausea questionnaire
  - Severity by numeric rating scale (NRS) score

- Change from baseline to 52 weeks in:
  - ECG
  - Pulse
  - Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential count)
  - Biochemistry (creatinine, CPK, urea, albumin, bilirubin [total], alanine aminotransaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, sodium, potassium, calcium [total], amylase, lipase, calcitonin, TSH)
  - Mental health assessed by Columbia Suicidality Severity Rating Scale (C-SSRS) and Patient Health Questionnaire-9 (PHQ-9)
- Anti-semaglutide antibodies during and after treatment

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

5 Trial design

5.1 Type of trial

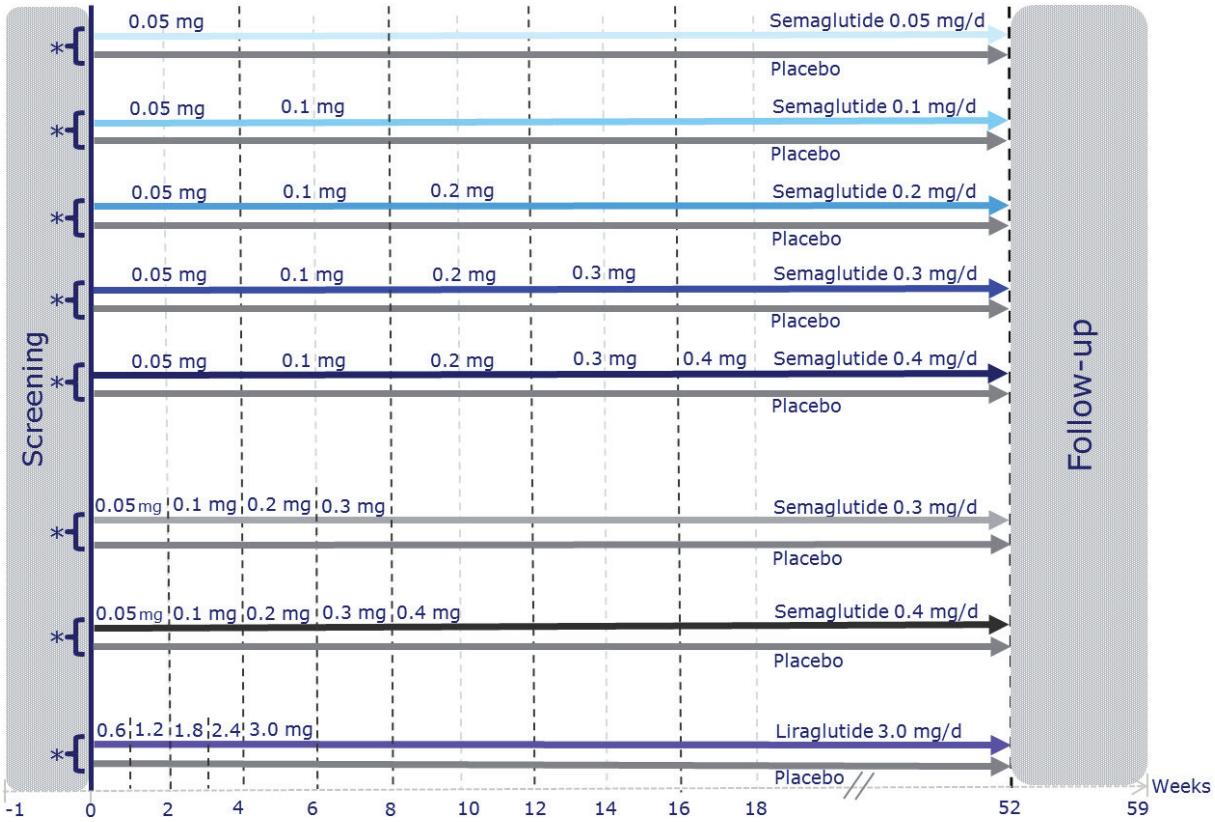
This is a 52-week, randomised, double-blind, placebo-controlled, nine-armed, parallel group, multi-centre, multinational trial comparing once-daily subcutaneous administration of semaglutide in five different doses (ranging from 0.05 mg/day to 0.4 mg/day) with placebo in obese subjects without diabetes mellitus. Once-daily administration of two doses of semaglutide (0.3 mg/day and 0.4 mg/day) will be tested in a fast escalation regimen to investigate the effect of a different regimen on efficacy, safety and tolerability. Additionally, liraglutide 3.0 mg/day is included as an active comparator. The total trial duration for the individual subjects will be approximately 60 weeks. The trial includes a 1-week screening period, followed by a 52-week treatment period and a follow-up visit after 7 weeks.

A total of 935 subjects is planned to be randomised and this will not exceed 963 randomised subjects. Based on an assumption of a 30% screening failure rate, 1,336 subjects are planned to be screened. Subjects will be randomised in a balanced manner (6:1 active:placebo) to receive a daily target dose of (for details see Figure 5–1):

- semaglutide 0.05, 0.1, 0.2, 0.3, or 0.4 mg (dose escalation every fourth week)
- semaglutide 0.3 or 0.4 mg (dose escalation every second week)
- liraglutide 3.0 mg (dose escalation every week)
- placebo (matching each of the active treatment arms)

The placebo group will be subdivided into eight arms with different injection volumes corresponding to the different dose levels of semaglutide and liraglutide 3.0 mg.

Subjects in all treatment arms including placebo will receive nutritional counselling and a calorie-reduced diet by a dietician or equivalent qualified delegate as well as physical activity counselling by a qualified person on a monthly basis beginning at the randomisation visit.



* Each active treatment arm is blinded towards placebo with matching injection volumes, but not towards the other treatment arms.

Figure 5–1 Trial design

5.2 Rationale for trial design

It is broadly recognised that obesity is a chronic disease related to multiple serious co-morbidities[4]. This mandates chronic treatment and currently few effective and safe treatment options are available.

The present trial is a 52-week, randomised, double-blind, placebo-controlled, nine-armed, parallel group, multi-centre, multinational trial. To avoid bias in the assessment of the different semaglutide doses and the liraglutide dose, the trial will be double-blinded within treatment arm to placebo. The treatment arms will not be blinded towards each other because of different dose escalations, different pens, and different target doses.

A trial duration of 52 weeks is considered adequate in terms of establishing a clinically meaningful weight loss and is in accordance with regulatory guidelines[19,20]. Furthermore, a 52-week trial period is considered to be sufficient to characterise the semaglutide safety and tolerability profile.

It is known from other trials in weight management[4,21] including the majority of the liraglutide weight management trials that the trial population mainly consist of women (up to 80%). To ensure a sufficiently large sample of men, an upper limit will be implemented, allowing no more than 70% of the trial population to be women and the randomisation will be stratified according to sex.

As the high doses of semaglutide require a long time to reach the target dose, a fast escalation regimen is investigated in order to decrease the time-to-target dose.

As gastrointestinal AE rates are anticipated to increase with higher doses and with large excursions in the semaglutide plasma concentration, semaglutide is dosed once daily to ensure less variability in concentrations. Dose escalation every fourth week is chosen to reach steady state at each dose level before increasing the dose. This could potentially reduce gastrointestinal AEs. However, for the higher doses, the time before target dose is reached is prolonged and this could mean that the maximisation of weight loss early in the treatment period might be missed. Therefore a fast escalation regimen (for two doses) is being investigated with dose escalation every second week.

5.3 Treatment of subjects

5.3.1 Semaglutide treatment

The dosing of semaglutide will be once daily with dose escalation to the next dose every fourth week or every second week until the randomised target dose is reached (see Figure 5–1). For all semaglutide arms, the dosing will start at 0.05 mg/day, and then increase to 0.1 mg/day followed by increments of 0.1 mg/day until the target dose is reached. Once the target dose is reached, the dose level should be maintained. The dose changes will be recorded in the eCRF

Duration of the dose escalation period for the semaglutide treatment arms are listed in Table 5–1.

Table 5–1 Duration of dose escalation period for semaglutide treament arms

Treatment arm	Projected duration of dose escalation to reach target dose
Dose escalation every fourth week	
Semaglutide 0.05 mg/day	0 weeks
Semaglutide 0.1 mg/day	4 weeks
Semaglutide 0.2 mg/day	8 weeks
Semaglutide 0.3 mg/day	12 weeks
Semaglutide 0.4 mg/day	16 weeks
Dose escalation every second week	
Semaglutide 0.3 mg/day	6 weeks
Semaglutide 0.4 mg/day	8 weeks

The escalation regimen should be followed. In case of intolerable gastrointestinal adverse events as judged by the investigator, dose escalation can be postponed:

- Dose escalation every fourth week:
  - can be postponed up to 7 days
  - maximum allowed duration on each dose step is 5 weeks
- Dose escalation every second week:
  - can be postponed up to 4 days
  - maximum allowed duration on each dose step is 2 weeks + 4 days

If intolerable gastrointestinal adverse events persist, the subject should be evaluated against discontinuation of trial product criteria (see section 6.4).

5.3.2 Liraglutide treatment

In order to reduce the level of gastrointestinal side effects, liraglutide is gradually escalated up to the maintenance dose. The dose will gradually be escalated to 3.0 mg starting with 0.6 mg/day and with a dose level increment of 0.6 mg every 7 days. If subjects do not tolerate an increase in dose during dose escalation, the investigator has the option to individualise the dose escalation with a total delay of up to 7 days. All subjects must reach the target dose of 3.0 mg liraglutide no later than 5 weeks after randomisation (see Figure 5–1). If this is not possible, the subject should be evaluated against discontinuation of trial product criteria (see section 6.4). Once the target dose is reached the dose level should be maintained.

5.3.3 Missed dose

If a subject forgets to inject a dose, the dose can be administered as soon as the subject remembers. However, if it is more than 12 hours since the subject should have administered the dose, they should skip the missed dose. Then take the next dose as usual on the following day.

5.3.4 Nutritional and physical activity counselling

All subjects will receive nutritional and physical activity counselling starting at visit 2 (randomisation) and monthly at the site visits.

The subjects will be counselled to a hypocaloric diet with an energy deficit of approximately 500 kcal/day and an increase in physical activity (recommended minimum 150 minutes/week). Please refer to section 8.6.3 and 8.6.4 for description of counselling and procedures.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products the investigator should discuss potential weight management options with the subject.

5.5 Rationale for treatment

Subjects are enrolled for a treatment period of one year in order to be able to evaluate the full effect of treatment on the primary and secondary endpoints as well as to be able to make a reasonable safety assessment. This is further based on the knowledge from liraglutide 3.0 mg trials where the maximum effect on weight loss occurs around 40 weeks (36 weeks on target dose) and the regulatory authorities' guidelines on trials in weight management stating that duration of at least 1 year is deemed appropriate to evaluate efficacy and safety and tolerability[19,20].

The comparators in the trial are placebo and liraglutide 3.0 mg. Placebo is used in order to evaluate the absolute safety and efficacy of once-daily semaglutide and to reduce the sample size. All subjects including those treated with comparator will receive nutritional and physical activity counselling. Liraglutide is included to compare to an approved once daily weight management treatment.

The semaglutide doses of 0.05 mg/day to 0.4 mg/day have been chosen to carefully investigate the optimal semaglutide dose with a satisfactory balance of efficacy and safety for the majority of subjects.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 1,336
Number of subjects planned to be randomised: 935 (30% screen failure rate)
Number of subjects expected to complete the trial: 561 (40% trial product discontinuation rate)

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age ≥ 18 years at the time of signing informed consent
3. Body Mass Index (BMI) ≥ 30.0 kg/m^2 at the screening visit
4. Stable body weight i.e. less than 5 kg self-reported change within 90 days before screening
5. At least one unsuccessful weight loss attempt per investigator judgement

6.3 Exclusion criteria

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

1. A HbA_{1c} ≥ 6.5% at screening or diagnosed with type 1 or type 2 diabetes mellitus
2. Hypothyroidism/hyperthyroidism defined as TSH > 6 mIU/L or < 0.4 mIU/L
3. Treatment with glucose lowering agent(s) within 90 days before screening
4. Screening calcitonin ≥ 50 ng/L (pg/mL)
5. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
6. History of pancreatitis (acute or chronic)
7. Obesity induced by an endocrinologic disorder (e.g. Cushing Syndrome)
8. Treatment with any medication within 90 days before screening that based on investigator's opinion may cause significant weight change
9. Diet attempts using herbal supplements or over-the-counter medications within 90 days before screening
10. Participation in an organised weight reduction program (e.g. WeightWatchers®) within 90 days before screening
11. Treatment with orlistat, zonisamide, topiramate, phentermine, lorcaserin, bupropion, naltrexone, GLP-1 RAs alone or in combination prescribed for weight loss or any other medication that could promote weight loss in the opinion of the investigator within 90 days before screening
12. Previous surgical treatment for obesity (liposuction and/or abdominoplasty is allowed if performed > 1 year before screening)

13. History of major depressive disorder within 2 years before randomisation
14. History of other severe psychiatric disorders (e.g. schizophrenia, bipolar disorder)
15. A Patient Health Questionaire-9 (PHQ-9) score of ≥ 15 at screening or randomisation
16. Any lifetime history of a suicidal attempt
17. Any suicidal behaviour within 30 days before randomisation
18. Any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or randomisation
19. Surgery scheduled for the trial duration period, except for minor surgical procedures, in the opinion of the investigator
20. Systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg at screening
21. History or presence of malignant neoplasms within the last 5 years before screening (except basal and squamous cell skin cancer, polyps and in-situ carcinomas)
22. Known or suspected abuse of alcohol or narcotics
23. Language barrier, mental incapacity, unwillingness or inability to adequately understand or comply with study procedures
24. Known or suspected hypersensitivity to trial product(s) or related products
25. Previous participation in this trial. Participation is defined as signed informed consent
26. Subjects from the same household participating in the trial
27. Participation in another clinical trial within 90 days before screening
28. Any condition which, in the investigator's opinion might jeopardise subject's safety or compliance with the protocol
29. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice)

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

    FOR UNITED KINGDOM ONLY: Adequate contraceptive measures are defined as established use of oral, injected or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository), female sterilisation, male sterilisation (where partner is sole partner of subject), or true abstinence (when in line with preferred and usual lifestyle).

6.4 Discontinuation of trial product criteria and withdrawal of informed consent

If any of the below trial product discontinuation or withdrawal criteria apply, the subject must be discontinued from trial product and the procedures in section 8.1.4 (and section 8.1.5, if relevant) should be performed.

Trial product discontinuation criteria

The subject must discontinue from trial product if the following applies:

1. Due to a safety concern at the discretion of the investigator
2. Non-compliance with trial procedures at the discretion of the investigator
3. Included in the trial in violation of the inclusion and/or exclusion criteria
4. Pregnancy
5. Intention of becoming pregnant
6. Participation in another clinical trial throughout the trial
7. In case of code break (see section 11.1)
8. If the target treatment dose of the randomised trial product is not tolerated by the subject
9. Diagnosis of T2DM and treated with other medication(s) than metformin (see section 8.7.1)
10. Diagnosis of acute pancreatitis (as described in section 8.7.3)
11. Diagnosis of medullary thyroid carcinoma
12. Lifestyle changes that contradicts the protocol or advices from site
13. Surgical treatment for obesity
14. Treatment with orlistat, zonisamide, topiramate, lorcaserin, phenteremine, bupropion, naltrexone, GLP-1 RAs alone or in combination prescribed for weight loss or any medication that could provide weight change in the opinion of the investigator
15. Inadequate psychotherapy and/or pharmacotherapeutic treatment of a subject's psychiatric disorder (see section 8.5.6.1)
16. The subject refuses mental health professional referral and, in investigator's opinion, it is unsafe for the subject to continue (see section 8.5.6.1)

Withdrawal of informed consent

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

Please see section 8.1.5 for procedures to be performed in case of subject withdrawal.

Subjects who are withdrawn will not be replaced.

6.5 Rationale for trial population

The trial population will consist of obese subjects without diabetes mellitus. Obese subjects represent a clinically relevant population to treat for weight loss as they are likely to benefit from weight reduction. Subjects with diabetes mellitus have been excluded from the trial, as there may be a confounding effect of improvements in glycaemic control on weight loss and as subjects with T2DM may have different safety concerns. Control of potential hypo- and hyperglycaemia and background medication for treatment of T2DM would be more appropriately handled in a dedicated trial investigating subjects with T2DM.

As first line treatment for obesity should always be lifestyle modification through healthier nutrition and increased physical activity[22], only subjects who have tried but failed this type of weight loss intervention should be included.

7 Milestones

Planned duration of recruitment period: 20 weeks

End of trial is defined as LPLV.

Recruitment

The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation can be randomised.

To ensure a sufficiently large sample of men, an upper limit will be implemented, allowing no more than 70% of the trial population to be women and the randomisation will be stratified according to sex. All investigators should aim to include at least 30% males. All investigators will be notified with instructions before the upper limit of women is reached.

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[23], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[24], the Food and Drug Administration Amendment Act (FDAAA)[25], European Commission Requirements[26,27] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

The following sections describe the assessments and procedures that must be performed during this trial. The overview of when they must be performed is included in the flow chart (section 2).

8.1 Visit procedures

8.1.1 Screening, re-screening and screening failures

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.

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

Screening failures

For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial. Serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up of serious adverse events (SAEs) must be carried out according to section 12. A screening failure session must be made in the IWRS. The case book must be signed.

Re-screening

Re-screening is not allowed.

8.1.2 Fasting visits

At visits 2, 4, 10, 14, 17, and 20 the subjects must attend the visits fasting (see section 2).

Fasting is defined as at least eight hours without food or liquids, except for water. Trial product and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood sampling and body weight measurements have been performed. If the subject is not fasting as required, the subject should be called in for a new visit within the visit window to have the fasting procedures done. Fasting procedures include body weight and blood sampling of FPG and lipids.

At visit 21, the subject must be fasting for two hours prior to the anti-semaglutide antibody sampling (see section 8.5.13).

8.1.3 Missed visits

If an entire visit is missed and it is not possible to re-schedule the visit within the time window, every effort should be made to re-schedule the visit at the earliest possible date before the next visit.

8.1.4 Discontinuation of trial product

If a subject is discontinued from trial product, the investigator must aim to undertake procedures similar to those for visit 20 (end of treatment) as soon as possible and the follow-up visit (visit 21) should be performed 7 weeks later. All female subjects using an adequate contraceptive method should be reminded to continue this for 7 weeks after discontinuation of trial product.

Furthermore, subjects discontinued from trial product must be asked to attend an additional visit (visit 22x) taking place 52 weeks (± 5 days) after their randomisation date. The purpose of this visit is to record body weight, blood pressure and any AEs since discontinuation of trial product.

If the subject is not willing to attend one or more of the above mentioned visits, it should be documented in the subject's medical record that the subject has refused to attend the visit and why.

For subjects discontinued from trial product, final drug accountability must be performed and a treatment discontinuation session must be made in the IWRS. The reason for discontinuation of trial product must be recorded in subject's medical records and the eCRF.

8.1.5 Withdrawn subjects

If a subject is withdrawn from the trial, the investigator must aim to undertake procedures similar to those for visit 20 (end of treatment) as soon as possible and the follow-up visit (visit 21) should be performed 7 weeks later.

For withdrawn subjects, the end-of-trial form must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be made in the IWRS. The case book must be signed.

Although a subject is not obliged to give his/her reason(s) for withdrawing from a trial, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for not completing the trial must be specified on the end-of-trial form in the eCRF.

8.1.6 Subject training

Dosing diary (see section 8.6.2)
The subject must be provided with diaries at the specified visits (section 2). The investigator should instruct the subjects in filling in the diary according to the provided diary instructions (see section 8.6.2). The diaries dispensed to subjects should be collected at the specified visits (section 2).

Trial product
Trial product must be dispensed to subjects at the specified visits (2). Trial product will be dispensed to the subject by the site, hospital pharmacy or equivalent. At the randomisation visit, the subjects will be instructed in the handling of trial product and trained in the use of the pen-injector and in the administration of s.c. injection of trial product. The first dose of trial product must be injected by the subject at the site.

Nausea and hypoglycaemic episodes recognition
The investigator or delegate will train the subjects in symptom recognition and handling of hypoglycaemia and nausea.

Suspected pregnancy
Female subjects must be instructed to contact site if a menstrual period is missed between site visits so they can come in for urine pregnancy test.

8.1.7 Investigator's assessment

It is the responsibility of the investigator or delegated staff to review laboratory reports, electrocardiograms (ECGs), mental health questionnaires, diaries, patient reported outcome questionnaires (PROs), and blood pressure and pulse measurements during the trial.

Review of diaries must be documented either on the documents and/or in the subject's medical record. If clarification of entries or discrepancies in the diary 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.

For laboratory report values outside the reference range, the investigator must specify whether the value is clinically significant or not. All laboratory report printouts must be signed and dated by the investigator or delegate. The evaluation of screening results must be dated and signed prior to visit 2 (randomisation), for the subsequent visits preferably on the day of evaluation.

Review of ECGs must be documented as described in section 8.5.2.

It is the responsibility of the investigator or delegated staff to review the mental health and PRO questionnaires and to report possible AEs immediately following completion. The review must be documented.

8.2 Subject related information

8.2.1 Demography

The following information must be recorded in the subject's medical record and eCRF:

- Date of birth (according to local regulation)

- Sex
- Race (according to local regulation)
- Ethnicity (according to local regulation)

8.2.2 Concomitant illness and medical history

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

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.

Medical history is a medical event that the subject has experienced in the past (i.e. prior to visit 1). Only relevant and significant medical history as judged by the investigator should be recorded. Findings of specific medical history described below should only be entered on the specific forms.

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

8.2.2.1 History of concomitant cardiovascular disease

Information related to concomitant cardiovascular disease (i.e., myocardial infarction, disorders of rhythm or conduction, heart failure incl. New York Heart Association functional classification, ischemic heart disease incl. type, percutaneous coronary intervention and coronary artery bypass graft surgery, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, hypertension, ischemic stroke, transient ischemic attack, haemorrhagic stroke, intracranial artery stenosis, carotid artery stenosis, peripheral arterial disease including > 50% stenosis on angiography or other imaging) must be recorded.

8.2.2.2 History of gallbladder disease

Information related to gallbladder disease (i.e., pancreatitis, gallstone disease and cholecystitis) must be recorded.

8.2.2.3 History of psychiatric disorders

Information related to psychiatric disorders (specifically history of depression, substance and alcohol abuse, suicidal behaviour, anxiety, mood disorders, insomnia, or sleep disorders) must be recorded.

8.2.2.4 History of breast neoplasms

Information related to history of breast neoplasms must be recorded for all female subjects. Information regarding menopausal status, previous mammograms and outcome, first degree relatives with breast cancer and predisposing factors (alcohol intake above recommended local

guidelines, hormone replacement therapy, age of menarche, number of births, maternal age at first birth, and if the subject ever breastfed) should be recorded.

8.2.2.5 History of colon neoplasms

Information related to history of colon neoplasms, previous endoscopic examination(s) of the colon, history of inflammatory bowel disease, and first degree relatives with colon neoplasms must be recorded.

8.2.3 Concomitant medication

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

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

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation.

If a change is due to an AE, then this must be reported according to section 12.2. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.2.3.1 Evaluation of antihypertensive and lipid-lowering treatment

Any antihypertensive and/or lipid-lowering medications must be recorded as concomitant medication described above. For any changes from baseline in antihypertensive and/or lipid-lowering treatment, the investigator must evaluate if the change should be considered as an increase, a decrease or no change in treatment at the visits specified (section 2).

8.2.4 Tobacco use

Details of tobacco use must be recorded at the first visit. Tobacco use is defined as smoking at least one cigarette, cigar or pipe daily in average. The collected information should include whether or not the subject smokes or has smoked.

8.3 Laboratory assessments

The laboratory analyses will be performed by a central laboratory except for analysis of anti-semaglutide antibodies and semaglutide plasma concentration analysis which will be performed at a specialised laboratory. The central laboratory may utilise subcontractors.

Descriptions of laboratory supplies, procedures for obtaining samples, handling, storage and shipments of samples, will be given in the trial-specific laboratory manual provided by the central laboratory.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

Laboratory samples may be drawn on another day than the day of the actual visit, as long as it is within the visit window outlined in the flow chart (see section 2). For some of the samples drawn during the trial, it is required that the subject is fasting. If a subject is not fasting at these visits, the fasting blood sampling (8.1.2) must, as a minimum, be re-scheduled within the visit window.

Laboratory results will be sent by the central laboratory to the investigator on an on-going basis except for the anti-semaglutide antibody results and the results of the plasma concentration analysis. Anti-semaglutide antibody results and the results of the plasma concentration analysis will not be provided to the investigator, as these results will not be used for any clinical evaluation during the trial and would potentially unblind the treatment.

Samples, including samples for genetic testing and specific safety assessments, will be destroyed on an on-going basis or at the latest at the completion of the clinical trial report (CTR).

Antibody samples may be retained until drug approval by U.S. Food and Drug Administration (FDA) and/or European Medicines Agency (EMA). The retained antibody samples may be used for further characterisation for antibody responses towards drug if required by health authorities or for safety reasons, see section 24.2.

8.4 Assessments for efficacy

8.4.1 Body Measurements

8.4.1.1 Body weight

The body weight should be measured at all visits with an empty bladder, without shoes and only wearing light clothing. It should be recorded with one decimal (kg or lb) and preferably using the same digital scale throughout the trial. The scale must be calibrated according to the directions for use and as a minimum once a year.

Body weight must be measured in fasting state at the fasting visits, and in non-fasting state, at the non-fasting visits, see flowchart (section 2). If the subject is not fasting as required, the subject should be called in for a new visit within the visit window to have the fasting body weight measured.

8.4.1.2 Height

Height is measured at screening without shoes in centimetres or inches (one decimal).

8.4.1.3 Body mass index

Body mass index will be calculated by the eCRF from visit 1 data and must be in accordance with inclusion criterion 3.

8.4.1.4 Waist and hip circumference

The waist circumference will be measured at the specified visits (section 2) and is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest.

The hip circumference is defined as the widest circumference around the buttocks.

Three consecutive waist and hip measurements must be performed and are measured in the horizontal plane and rounded to the nearest 0.5 cm or 0.2 inches using a non-stretchable measuring tape. The same measuring tape should be used throughout the trial.

The subject should be measured in a standing position with an empty bladder and wearing light clothing. The subject should be standing, feet together with arms at the side and waist and hip accessible. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally and the measurement should be performed in the following order: hip, waist, hip, waist, hip and waist.

8.4.2 Systolic and diastolic blood pressure

For blood pressure at visit 1, three measurements must be performed. The mean value is calculated by the eCRF and must be used to evaluate eligibility of the subject in relation to exclusion criterion 20. For subsequent visits, one measurement of blood pressure must be performed.

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
- Blood pressure should be measured in a sitting position, with the legs uncrossed, the back and arms supported
- The subject should be sitting for five minutes before the first measurement is taken
- The same arm and an appropriate cuff size should be used for blood pressure measurements at all visits

8.4.3 Blood samples

Biochemistry

- HbA_{1c}
- FPG
- hsCRP (cardiovascular biomarker)
- Lipids (total cholesterol [TC], low density lipoprotein cholesterol [LDL cholesterol], high density lipoprotein cholesterol [HDL cholesterol], very low density lipoprotein cholesterol [VLDL cholesterol], triglycerides [TG], free fatty acids [FFA])

8.4.4 Patient reported outcome questionnaires

Patient reported outcome (PRO) questionnaires will only be used for subjects enrolled in the U.S. speaking English at a sufficient level of fluency, as judged be the investigator (this information will be recorded in the eCRF). The trial aims at including approximately 200 subjects filling in the questionnaire in English. The PRO questionnaires will be collected at the specified visits (section 2).

A modified version of the IWQoL-Lite, the Short Form 36 (SF-36) and a few question regarding Patients' global impression of change assessing subjects' perceptions of change in their health-related quality of life (HRQoL) during the trial will be used to investigate the impact of weight loss on HRQoL and patient functioning.

All three questionnaires will be available on a tablet computer in a linguistically validated version. The questionnaires must be completed by the subject and should preferably be completed after conclusion of all fasting-related activities, but before any other visit-related activities. Subjects should be given the opportunity to complete the questionnaires by themselves without interruption.

IWQoL-Lite for Clinical Trials

The modified IWQoL-Lite (named IWQoL-Lite for Clinical Trials) is a 23-item instrument designed to assess weight-related quality of life. Based on FDA guidance[28], there is a need to re-evaluate and modify this instrument for use as a clinical outcome assessment to support a secondary endpoint in clinical trials of obese adults. Please see Appendix B for a clarification of the questions. To make the re-evaluation of the IWQoL-Lite instrument, SF-36 and patients' global impression of change is used for validation.

SF-36

SF-36 measures the individual's overall HRQoL on 8 domains: physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health[29].

Patients' global impression of change

A few questions assessing patients' impression of change during the clinical trial in both their overall HRQoL and the specific dimensions of HRQoL addressed in the modified IWQoL-Lite must be collected. See Appendix C for clarification of questions.

8.5 Assessments for safety

8.5.1 Physical Examination

Physical examination will be performed at the specified visits (section 2) according to local procedure. Physical examination should include general appearance, thyroid gland, respiratory system, cardiovascular system, gastrointestinal system including mouth, musculoskeletal system, central and peripheral nervous system, skin, lymph node palpation, and head, ears, eyes, nose, throat and neck, and must be recorded in the subject's medical record and eCRF. Any abnormal, clinically significant findings at screening visit 1 must be recorded as a concomitant illness (see section 8.2.2).

8.5.2 ECG

A 12-lead ECG will be performed at the visits specified in the flow chart (2). The investigator or delegate must sign, date and interpret the ECG by using the following categories:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

All ECGs will in addition undergo central assessment. Sites will be informed of the central ECG evaluation in case this evaluation reveals an abnormal ECG reading. If the abnormality, in the opinion of the investigator, represents an unreported AE, such finding must be reported by the investigator (see section 12.2).

Additional unscheduled ECG recordings can be performed at the investigator's discretion at other visits than the planned ECG visits. If unscheduled ECGs are recorded and submitted for central assessment the reason should be documented and an AE reported (if applicable).

8.5.3 Pulse

Pulse (beat/min) will be recorded in a sitting position after resting for five minutes at the specified visits (section 2).

8.5.4 Breast neoplasms follow-up

For all female subjects, information whether any new mammograms have been performed since screening must be recorded at the visit as specified in the flow chart (section 2). If yes, reason and diagnosis should be recorded to the extent possible.

8.5.5 Colon neoplasms follow-up

Information whether any new endoscopic examination(s) of the colon have been performed since screening must be recorded at the visit specified in the flow chart (2). If yes, reason and diagnosis should be recorded to the extent possible.

8.5.6 Mental health questionnaires

The mental health of subjects will be assessed by using the C-SSRS[30] and PHQ-9[31] questionnaires to meet the regulatory requirements[32]. The questionnaires will be available on a tablet computer in a linguistically validated version and will be filled in at the specified visits (section 2).

The C-SSRS is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation. The questionnaire will be administered as an interview by the investigator or a qualified delegate. Prior to administering the C-SSRS questionnaire, the investigator or qualified delegate must complete sufficient training.

Two versions of the scale will be used: a 'baseline' version (lifetime assessment, used at screening) and a 'since last visit' version (used at all subsequent visits).

The PHQ-9 is the 9-item depression module of the patient health questionnaire, which is a self-administered diagnostic tool used for assessment of mental disorders[31]. The questionnaire takes approximately 10 minutes to complete.

8.5.6.1 Referral to a mental health professional

If a subject has a PHQ-9 score of 10-14 both inclusive the subject should be referred to a mental health professional (MHP) if judged relevant by the investigator. If referral is not deemed relevant this along with the reason why must be documented in the subject's medical records.

A subject must be referred to a MHP if:

- the subject has a PHQ-9 score ≥15 or
- the subject has any suicidal behaviour or
- the subject has any suicidal ideation of type 4 or type 5 on any C-SSRS assessment
- in the opinion of the investigator, it is necessary for the safety of the subject

If one or more of the referral criteria are met, the investigator should explain to the subject why the referral and psychiatric evaluation by a MHP is needed. If the subject refuses to be referred to a

MHP, the subject's decision should be documented in subject's medical record and the investigator must assess if it is safe for the subject to continue in the trial or if the subject should be discontinued from trial product.

If a subject's psychiatric disorder can be adequately treated with psychotherapy and/or pharmacotherapeutic treatment, then the subject, at the discretion of the investigator (and in agreement with the MHP), may continue in the trial. Otherwise, the subject must be discontinued from trial product.

8.5.7 Adverse Events

AEs must be recorded at all visits in accordance with the procedures in sections 12.1 and 12.2.

8.5.8 Nausea questionnaire

All events of nausea must be documented as AEs according to section 12.2. If a subject experiences nausea within 24 hours prior to a site visit, the nausea questionnaire in Appendix D must be completed. One questionnaire for each event must be reported. The first part of the questionnaire will be administered as an interview by the investigator or a qualified delegate, and the second part will be completed by the subject.

8.5.9 Hypoglycaemic episodes

All subjects will at randomisation be instructed in symptom recognition and handling of hypoglycaemia.

Hypoglycaemic episodes may be identified by:

- Subject reporting of symptoms of hypoglycaemia or
- FPG values $\leq$ 3.9 mmol/L (70 mg/dL) from blood sampling at site visits

Since the laboratory results from blood sampling are not reported on the day of the site visit the investigator should follow up with the subject as soon as possible within a week from when the lab report is available and collect 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 and dose of last trial product prior to episode
- Date and time of last main meal prior to episode (breakfast, lunch or dinner)
- Whether the episode occurred in relation to physical activity
- Any sign of fever or other disease

- Whether the subject was asleep when the episode occurred
  - If yes, whether the symptoms of the episode woke up the subject

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

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

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

- Who assisted in the treatment of the hypoglycaemic episode (i.e. family/friend/co-worker or similar, paramedic, doctor or other, please specify)
- Where the treatment was administered (i.e. at home/at friends/at work or similar, in an ambulance, emergency room/hospital or other, please specify)
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other, please specify)
- Were symptoms alleviated by the administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet changed, medication error (i.e. overdose, mix-up between products), other factors not listed, please specify or none)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms?[34]
  - Autonomic: sweating, trembling, hunger or palpitations
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination
  - General malaise: headache or malaise
- Did the subject experience other symptoms? Please specify
- Description of the episode, if applicable

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 a safety information form must also be filled in, see section 12.2.

8.5.10 Adverse events requiring special forms in the eCRF

For some AEs the investigator must fill in a special form in the eCRF in addition to the AE reporting described in section 12. The AEs that require special forms in the eCRF are listed in Table 12–1 and in appendix E.

The below sections will describe which information should be collected for the different events.

Acute coronary syndrome

If an event of acute coronary syndrome is observed during the trial, this must be recorded as an AE and on a specific acute coronary syndrome form in the eCRF. The following information must be reported if available:

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

Coronary revascularisation procedures

If an event of coronary revascularisation is observed during the trial, this must be recorded as an AE and on a specific coronary revascularisation form in the eCRF. The following information should be obtained:

- Type of revascularisation performed
- Indication for the procedure

Cerebrovascular events (stroke or transient ischemic attack)

If a cerebrovascular event is observed during the trial, this must be recorded as an AE and on a specific cerebrovascular event form in the eCRF. The following information must be reported if available:

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

Heart failure requiring hospitalisation

If an event of heart failure requiring hospitalisation is observed during the trial, this must be recorded as an AE and in addition on a specific heart failure event form in the eCRF. The following information must be reported if available:

- Signs and symptoms of heart failure
- NYHA Class

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

Pancreatitis

If an event of pancreatitis is observed during the trial, this must be recorded as an AE and on a specific pancreatitis event form in the eCRF. The following information must be reported if available:

- Signs and symptoms of pancreatitis
- Specific laboratory test supporting a diagnosis of pancreatitis:
  - Amylase
  - Lipase
  - Alanine aminotransaminase (ALT) and aspartate aminotransferase (AST)
  - Bilirubin
  - Alkaline phosphatase (ALP)
- Imaging performed and consistency with pancreatic disease
- Treatment for and complications of the event
- Relevant risk factors for pancreatic disease including:
  - History of gallstones
  - History of pancreatitis
  - Family history of pancreatitis
  - Trauma

Acute gallbladder disease

If an event of acute gallstone disease or clinical suspicion of this is observed during the trial, this must be recorded as an AE and on a specific acute gallstone disease event form in the eCRF. The following information should be reported if available:

- Signs and symptoms of acute gallstone disease
- Specific laboratory test supporting a diagnosis of gallstone:
  - White blood cell count (WBC)
  - C-reactive protein (CRP)
  - Direct, indirect and total bilirubin
  - ALT and AST
  - Alkaline phosphatase (ALP)
  - Amylase
  - Lipase
- Imaging performed and consistency with gallstone disease
- Treatment given for the condition

- Relevant risk factors for acute gallstone disease including
  - History of gallstones
  - Family history of gallstones
  - Relevant surgery

Neoplasm (excluding thyroid neoplasms)

All events of neoplasms (excluding thyroid neoplasm) must be recorded as an AE and on a specific neoplasm event form in the eCRF. The following information should be obtained if available as part of standard of care:

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

Thyroid disease (including thyroid neoplasms)

If an event of thyroid disease, including any thyroid neoplasms observed during the trial, this must be recorded as an AE and on a specific thyroid disease event form in the eCRF. The following information must be reported if available:

- History of thyroid disease
- Signs and symptoms leading to investigations of thyroid disease
- Specific laboratory tests describing thyroid function including:
  - TSH
  - Total and free T3 and T4 and Free Thyroid Index
  - Calcitonin
  - Thyroid peroxidase antibodies
  - Thyroglobulin and thyroglobulin antibody
  - Thyroid Stimulating Hormone receptor antibody
- Diagnostic imaging performed and any prior imaging supporting the disease history
- Pathologic examinations
- Treatment given for the condition
- Risk factors identified
- Family history of thyroid disease

8.5.11 Blood samples

Blood samples for haematology and biochemistry must be collected at the specified visits (section 2).

Haematology

- Haemoglobin
- Haematocrit
- Thrombocytes
- Erythrocytes
- Leucocytes
- Differential count
  - Eosinophils
  - Neutrophils
  - Basophils
  - Monocytes
  - Lymphocytes

Biochemistry

- Creatinine
- Creatine phospokinase
- Urea
- Albumin
- Bilirubin, total
- Alanine aminotransaminase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase
- Amylase
- Lipase
- Sodium
- Potassium
- Calcium, total
- Calcitonin (please refer to Appendix A for actions to be taken if calcitonin is ≥ 10 ng/L)
- Tryptase, if hypersensitivity is suspected
- Thyroid-stimulating hormone (TSH)

8.5.12 Pregnancy test

Females of childbearing potential will have a human chorionic gonadotropin (hCG) serum pregnancy test performed at the specified visits in the flow chart (see section 2).

Urine pregnancy tests will be performed for females of childbearing potential at the visits specified in the flowchart (section 2). This will result in a monthly pregnancy testing. If a female subject misses a menstrual period, she should contact site to come in for a urine pregnancy test. Urine pregnancy kits will be supplied by the central laboratory. The test will be performed at the site.

Pregnancy testing will not be required for women who have undergone a hysterectomy or bilateral tubal ligation, or for women above the age of 50, who have been without menstrual periods for at least one year.

8.5.13 Anti-semaglutide antibodies

Blood samples will be drawn during the trial and analysed at a specialised laboratory for determination of serum antibodies against semaglutide, including cross reactivity to endogenous GLP-1 (see flow chart, section 2). Subjects must be instructed to withhold their trial product dose in the morning until blood sampling has been performed at the visit. Samples taken at the follow-up visit (visit 21) must be taken fasting (as a minimum by only having consumed water for at least 2 hours). Samples taken at the follow-up visit which are positive for anti-semaglutide antibodies will be further characterised for *in vitro* neutralising effect towards semaglutide. In addition, samples taken at the follow-up visit which are positive for cross-reactivity against endogenous GLP-1 will be analysed for *in vitro* neutralising effect towards endogenous GLP-1.

8.6 Other assessments

8.6.1 Semaglutide plasma concentration

For subjects receiving semaglutide or semaglutide placebo, a single blood sample for measurement of plasma semaglutide concentration will be drawn at selected visits (see section 2).

Subjects must be instructed to withhold their trial product dose in the morning until blood sampling is performed on the visit.

8.6.2 Dosing diary

All subjects must complete a dosing diary prior to each visit after randomisation until the end-of-treatment visit (section 2). The subject must record the date, time, dose and injection site of the injection on the day prior to the visit. Furthermore, the subject must fill in if any doses were not taken in the previous week. The dosing diaries will be collected at all visits until the end-of-treatment visit. The information will be transcribed to the eCRF by the investigator or delegate together with the exact date and time for blood sampling of plasma concentration, when applicable.

8.6.3 Nutritional counselling

From visit 2 and at all monthly visits (see section 2) subjects will receive nutritional counselling performed by a dietician or equivalent qualified delegate according to local standard. The

nutritional counselling will focus on healthier food choices and subjects will be put on a hypocaloric diet with an energy deficit of approximately 500 kcal/day compared to the subject's estimated total energy expenditure (TEE).

Calculation of estimated TEE

The TEE is calculated by multiplying the estimated Basal Metabolic Rate (BMR) (see Table 8–1) with a Physical Activity Level (PAL) value of 1.3[35]:

Table 8–1 Equation for estimating BMR

Sex	Age	BMR (kcal/day)
Men	18-30 years	15.057 x actual weight in kg + 692.2
	31-60 years	11.472 x actual weight in kg + 873.1
	> 60 years	11.711 x actual weight in kg + 587.7
Women	18-30 years	14.818 x actual weight in kg + 486.6
	31-60 years	8.126 x actual weight in kg + 845.6
	> 60 years	9.082 x actual weight in kg + 658.5

Maintenance diet

If a BMI $\leq$ 22 kg/m^2 is reached the recommended energy intake should be recalculated with no kcal deficit (maintenance diet) for the remainder of the trial.

Nutritional compliance

Healthy nutrition compliance must be evaluated from visit 4 and at monthly visits (see section 2) by the dietician or equivalent qualified delegate (as per local standard), using a numeric rating scale (NRS) with a value from 0 to 10, and results must be provided to the investigator. The investigator or delegate must record the NRS score into the eCRF.

8.6.4 Physical activity counselling

From visit 2 and at all monthly visits, subjects will receive counselling in physical activity by a qualified person. An increase in physical activity (recommended minimum 150 minutes/week) will be encouraged.

8.7 Specific safety assessments

8.7.1 Subjects developing type 2 diabetes mellitus

Subjects who develop T2DM during the trial should receive the best standard of care at the discretion of the investigator. If the investigator determines that medication(s) other than metformin

is the best treatment option, the subject must be discontinued from trial product. The medication prescribed by the investigator will not be provided nor reimbursed by Novo Nordisk.

8.7.2 Thyroidectomy

Subjects scheduled for thyroidectomy will be asked to inform the investigator prior to the operation.

Thyroidectomy pathology slides

In case a subject undergoes a thyroidectomy (partial or total) for any reason during the trial or after the trial secondary to an event reported during the trial, pathology slides of the thyroid tissue will be centrally reviewed in addition to the routine examination at the site level. A set of pathology slides, routinely made after thyroidectomies by the pathology laboratory of the hospital where the operation was performed, must be sent for a second reading with evaluation by a pathologist with expertise in thyroid and C-cell pathology, who will be blinded to both trial treatment and site diagnosis. Once the samples are re-examined they will be sent back to the site laboratory. Both the site pathology report and the central pathology report will be reviewed by an external independent event adjudication committee (EAC), see section 12.7.2. However, reports for thyroidectomies performed after the trial secondary to an event reported during the trial will not be reviewed by the EAC nor will the reports be part of the clinical trial database.

Thyroid tissue sample collection in case of thyroidectomy

Subjects to undergo thyroidectomy will in addition be asked to consent to have a small sample of the removed thyroid tissue collected for testing of RET Y1062 phosphorylation in the thyroid C-cells. This is only applicable if C-cell pathology is confirmed (i.e., hyperplastic or neoplastic thyroid C-cells) confirmed by the EAC, and only if allowed by local law. The tissue sample will be destroyed after examination.

FOR ISRAEL ONLY: The RET Y1062 phosphorylation and genetic testing will not be performed for subjects in Israel.

Genetic testing in case of a confirmed C-cell pathology

Subjects scheduled for thyroidectomy will be asked to consent to be tested (blood sample) to identify germline RET gene mutations associated with multiple endocrine neoplasia syndrome type 2 (MEN2). This RET gene mutation detection will be conducted in subjects with C-cell pathology (i.e., hyperplastic or neoplastic thyroid C-cells) confirmed by the EAC. Genetic testing will only be performed if allowed by local law and if the subject chooses to consent to it.

8.7.3 Suspicion of acute pancreatitis

In case of acute, severe persistent abdominal pain or other relevant symptoms leading to a suspicion of acute pancreatitis, the trial product should promptly be interrupted until pancreatitis is ruled out.

Appropriate additional examinations must be performed, including local measurement of amylase and lipase activity levels. If acute pancreatitis is ruled out, trial product should be re-initiated at the dose level the subject was at when trial product was interrupted. If acute pancreatitis is confirmed the subject must be discontinued from trial product (6.4). Appropriate treatment and careful monitoring of the subject should be initiated if pancreatitis is confirmed (as a minimum 2 of the 3):

- severe acute abdominal pain
- amylase and/or lipase activity levels >3x upper normal range (UNR)
- characteristic findings on relevant imaging e.g. computerised axial tomography (CT)/magnetic resonance imaging (MRI)/ultrasound

8.7.4 Suspicion of severe hypersensitivity

If a severe immediate hypersensitivity reaction to the trial products is suspected, blood sampling for assessment of anti-semaglutide/anti-liraglutide IgE antibodies and anti-semaglutide/anti-liraglutide binding antibodies should be collected after a suitable washout period (minimum 7 weeks for semaglutide and 2 weeks for liraglutide). In these cases, it is also recommended to test for tryptase (total and/or mature tryptase) within 3 hours of the hypersensitivity reaction. In case a tryptase sample was collected within 3 hours of the event of hypersensitivity reaction, a baseline tryptase sample should be taken at the same time as the IgE sample is obtained (after washout). Tryptase concentrations (if measured) as well as results of anti-semaglutide/anti-liraglutide antibody and IgE-isotype anti-semaglutide/anti-liraglutide antibodies will be collected by Novo Nordisk and included in the subject narratives.

8.7.5 Suspicion of immune complex disease

If immune complex disease is suspected, a blood sample for central assessment of complement levels (C3 and C4) should be drawn.

8.8 Subject compliance

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. If the subject continues to be non-compliant the investigator may discontinue the subject from trial product (see section 6.4).

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. Trial product must not be used, if it does not appear clear and almost colourless.

9.1 Trial products

The following trial products for subcutaneous injection will be manufactured and supplied by Novo Nordisk A/S, Denmark:

- Semaglutide 1.0 mg/ml, solution for injection, 3.0 ml cartridge, for NovoPen® 4
- Semaglutide placebo, solution for injection, 3.0 ml cartridge, for NovoPen® 4
- Liraglutide 6.0 mg/ml, solution for injection, 3.0 ml pre-filled PDS290 pen-injector
- Liraglutide placebo, solution for injection, 3.0 ml pre-filled PDS290 pen-injector

The placebo and active drug are visually identical for both trial products.
All trial products are considered investigational medicinal products (IMPs).

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS.

The investigator must document that direction for use (DFU) is given to the subject orally and in writing at the first dispensing visit (visit 2). At the later dispensing visits the investigator or delegate should ensure that subjects comply with injection procedures and re-dispense DFU, if needed.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[36], local regulations and trial requirements.

9.3 Storage

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

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

Table 9–1 Storage of trial product

Trial product	Storage conditions (not in-use)	In-use conditions	In-use time[1]
Semaglutide 1.0 mg/ml	Store in a refrigerator (2°C-8°C/36°F-46°F) Do not freeze Protect from light	Store below 30°C (86°F) Do not refrigerate Do not freeze Protect from light	Use within 30 days
Semaglutide placebo			
Liraglutide 6.0 mg/ml	Store in a refrigerator (2°C-8°C/36°F-46°F) Do not freeze Protect from light	Store below 30°C Do not freeze Protect from light **US:** Store at room temperature (59°F-86°F) or in refrigerator (36°F-46°F)	Use within 1 month **US:** Use within 30 days
Liraglutide placebo			

[1] In-use time starts when the pen is taken out of the subject's refrigerator.

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator.

The trial products will be dispensed to each subject as required according to treatment group. The IWRS will allocate trial product to the subject at randomisation and 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:

- Drug accountability is performed using the IWRS drug accountability module
- Subjects are instructed to return all used, partly used and unused trial product including empty packaging material at each dispensing visit and at end-of-treatment visit

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

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

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

- Needles for pre-filled and NovoPen® 4 pen systems (maximum length to be used is 8 mm)
- Direction for use for devices

10 Interactive web response system

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

In this trial, the IWRS is used for:

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

IWRS user manuals will be provided to each trial site.

Subject logs

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 the IWRS.

11 Randomisation procedure and breaking of blinded codes

A randomisation session will be carried out for all eligible subjects by using the IWRS.

At the randomisation visit (visit 2), eligible subjects will be randomised in a balanced manner (6:1 active:placebo) to receive daily dose of:

- semaglutide 0.05, 0.1, 0.2, 0.3, or 0.4 mg (dose escalation every fourth week)
- semaglutide 0.3 or 0.4 mg (dose escalation every second week)
- liraglutide 3.0 mg (dose escalation every week) or
- placebo (matching each of the active treatment arms)

Randomisation will be stratified based on the sex of the subject and will be controlled by the IWRS. An upper limit will be implemented, allowing no more than 70% of the trial population to be women. All investigators will be notified with instructions before the upper limit of women is reached.

11.1 Breaking of blinded codes

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

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

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

If the code has been broken the subject must be discontinued from trial product and a treatment discontinuation session must be completed in IWRS.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

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

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

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see section 8.5.9.

The following three definitions are used when assessing an AE:

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

- **Causality**

Relationship between an AE and the relevant trial product(s):

  - **Probable** - Good reason and sufficient documentation to assume a causal relationship.
  - **Possible** - A causal relationship is conceivable and cannot be dismissed.
  - **Unlikely** - The event is most likely related to aetiology other than the trial product.

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

Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

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

a. The term "life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

b. The term "hospitalisation" is used when a subject:
   - Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
   - Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

c. A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

d. For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasiasis or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

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

Medication error concerning trial product is considered a medical event of special interest (MESI). It is an event which, in the evaluation of safety, has a special focus. This MESI is an AE (SAE or non-serious AE) which fulfils one or more of the below defined criteria:

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

Adverse events with additional data collection

Adverse events with additional data collection are AEs defined as critical for the evaluation of product safety. Some of these events will furthermore be adjudicated by an external independent committee as described in section 12.7.2.

The AEs that require additional data collection can be seen in Table 12–1, including whether they will be sent for adjudication and whether the use of a specific event form in the eCRF is required. For further information regarding definitions and which data to collect for the events that require additional data collection, please see section 8.5.10 and Appendix E.

Table 12–1 Adverse events with additional data collection

Event	Event adjudication	Specific event form
Fatal events	Yes	No
Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)	Yes	Yes
Coronary revascularisation procedure	Yes	Yes
Cerebrovascular event (stroke or transient ischemic attack)	Yes	Yes
Heart failure requiring hospitalisation	Yes	Yes
Pancreatitis	Yes	Yes
Acute gallbladder disease	No	Yes
Neoplasm (excluding thyroid neoplasms)	Yes	Yes
Thyroid disease (including thyroid neoplasms)	Yes, (only events that require thyroidectomy)	Yes

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, 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 (visit 21). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

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

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

- Semaglutide T2DM (project NN9535): Investigator's Brochure[37], 10th edition, 2015 or any updates hereof
- Liraglutide weight management (project NN8022): Investigator's Brochure[38], 7th edition, 2015 or any updates hereof

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

For SAEs, a safety information form 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 and the safety information form and a medication error form. The medication error form is a form tailored to collect specific information related to the individual MESI.

For AEs requiring additional data collection, a specific event form must be completed in addition to the AE form.

The AE form for a non-serious AE not fulfilling the MESI criteria 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 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. For SAEs with additional data collection: in addition also the specific event form **within 14 calendar days** from the investigator's first knowledge of the AE.
- **SAEs fulfilling the MESI criteria:** In addition to above, the medication error 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 medication error form **within 14 calendar days** of the investigator's first knowledge of the event.
- Non-serious AE with additional data collection: The AE form and the additional data collection form **within 14 calendar days** of the investigator's first knowledge of the event

- **Events** for **Adjudication:** The Event Adjudication Document Collection Form must be initially completed **within 14 calendar days** of the investigator's first knowledge of the AE. Medical documentation of the event for adjudication should be provided within 4 weeks of event identification.

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

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

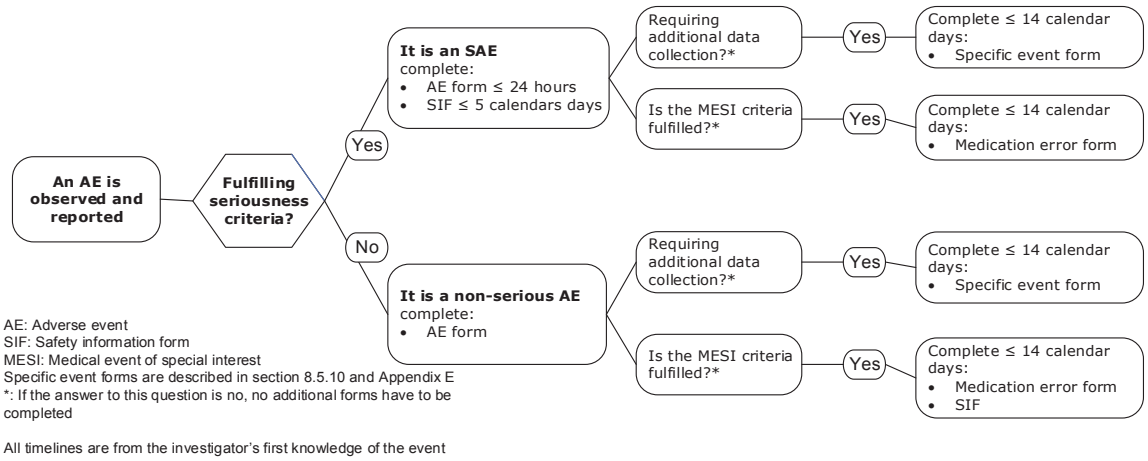


Figure 12–1 Initial reporting of AEs

Reporting of trial product-related SUSARs by Novo Nordisk:
Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and GCP.[1] In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

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

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

12.3 Follow-up of adverse events

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

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

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

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

- **Non-serious AE fulfilling the MESI criteria or non-serious AEs with additional data collection:** Non-serious AE fulfilling the MESI criteria or non-serious AEs with additional data collection must be followed as specified for non-serious AEs. Follow-up information on MESIs or non-serious AEs with additional data collection 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 reported non-serious AEs which subsequently fulfil the MESI criteria or the criteria for additional data collection.

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 1.0 mg/ml or placebo, 3.0 ml cartridge
- Liraglutide 6.0 mg/ml or placebo, 3.0 ml PDS290 pen-injector
- NovoPen® 4
- Needles for pre-filled pen systems

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

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

Technical complaints must be reported on a separate technical complaint form. A technical complaint form for each code or lot number or for each DUN must be completed.

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints **within 5 calendar days**

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A print or copy of the technical complaint form must be sent with the sample.

The investigator must ensure that the technical complaint sample contains the code or lot 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 9.3).

12.5 Pregnancies in female subjects

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

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

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

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

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

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

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

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

Semaglutide: Events of nausea, vomiting and headache have been reported in connection with accidental administration of semaglutide doses up to 4 mg. No symptoms of hypoglycaemia have been reported in connection with overdose of semaglutide. In the event of overdosage, appropriate supportive treatment should be initiated according to subject’s clinical signs and symptoms.

Liraglutide: From clinical trials and marketed use of liraglutide overdoses have been reported up to 24 times the recommended dose (72 mg). Events reported included severe nausea and severe vomiting. None of the reports included severe hypoglycaemia. All subjects recovered without complications. In the event of overdose, appropriate supportive treatment should be initiated according to the subject’s clinical signs and symptoms

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal semaglutide safety committee to perform ongoing safety surveillance. The semaglutide safety committee may recommend unblinding of any data for further

analysis, and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

12.7.2 Event adjudication committee

An independent external event adjudication committee 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 event adjudication committee in a blinded manner.

The AEs for adjudication are listed in Table 12–1 and defined in appendix E.

Event adjudication will be performed for AEs in randomised subjects including AEs with an onset date during the screening period. Event adjudication will not be performed for AEs in screening failures.

The EAC is composed of members covering required medical specialities. The EAC members must disclose potential conflicts of interest. The EAC will have no authorisation to impact trial conduct, trial protocol or protocol amendments.

AEs for adjudication must be reported according to section 12.2. Besides these events, all AEs not originally sent for adjudication will be screened as potential adjudication events. The adjudication vendor or the EAC can decide to have an AE adjudicated even if not initially sent for adjudication by the investigator. In this case, the investigator will be notified and should complete the adjudication form within 14 days and provide the data/documents as soon as possible.

The adjudication vendor will ensure that the EAC has access to all medical documents provided by the investigator. The EAC will initiate the review and may ask for additional information that the investigator needs to provide if available.

The evaluation made by the EAC and by the investigator will be included in the clinical trial report.

A site manual will be provided to each site detailing how the site should provide the relevant medical documentation for the adjudication vendor. The anonymisation requirements are also described in the site manual.

12.7.3 Calcitonin monitoring committee

The calcitonin monitoring committee will provide recommendations for all calcitonin values ≥20 ng/L (except for screening failures) to the investigators with regards to further investigation and treatment of the individual subject (see Appendix A).

13 Case report forms

For this trial a combination of electronic case report forms (eCRFs) and paper CRFs will be used.

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

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

The following will be provided as paper CRFs:

- Pregnancy forms
- Technical complaint forms (to be used as backup for electronic reporting or for technical complaints where the product has not been allocated to a subject yet)
- AE forms (only to be used as backup for electronic reporting)
- Safety information forms (only to be used as backup for electronic reporting)

The paper version of the technical complaint form, AE form, and safety information form must only be used to ensure timely reporting when/if the electronic CRF is unavailable.

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

If corrections are made by the investigator's delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.2 Case report form flow

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

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 Electronic collection of questionnaires

Novo Nordisk will use a tablet computer at sites for electronic recording of a series of questionnaires investigating mental health (see section 8.5.6) and quality of life (see section 8.4.4). The tablet computer and related support services will be supplied by an external vendor.

Subjects will be instructed in the use of the tablet computer before entering any data. The tablet computer will contain built-in edit checks, to ensure that all relevant questions are answered. The tablet computer is not intended to support the subsequent review and modification of completed entries. In case of need for corrections to the transferred data, a query flow must be initiated by the investigator or delegate. An audit trail will be maintained.

All data entered will be transferred automatically from the tablet computer to a database hosted by the supplier which is considered source data. Data entered on the devices will upon confirmation of successful backup be deleted from the devices.

Data in this database will be viewable to relevant site and Novo Nordisk personnel through a secure and password-protected web portal. Data will be transferred to the Novo Nordisk clinical database at defined intervals.

Site-specific electronic questionnaire data (in an electronic readable format) will be provided to the trial site before access to the supplier database is revoked. This data must be retained at the trial site.

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 FPFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the CRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks for trial sites with active subjects (defined as subjects in screening, treatment, or follow-up).

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

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

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 following data will be source data verified for screening failures:

- date for obtaining informed consent
- reason for screening failure
- serious adverse events (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 original diaries must not be removed from the trial site.

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

Monitors must review the subject's medical records and other source data (e.g. the diaries) 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. They should address any action to be taken.

15 Data management

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

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

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

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

16 Computerised systems

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

Investigators 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 and unblinding of the trial.

Results from the statistical analysis will generally be presented by treatment differences with two-sided 95% confidence intervals.

The full analysis set (FAS) will be used in the analysis of efficacy endpoints. For safety endpoints the safety analysis set will be used.

The 8 different placebo arms will be pooled into one placebo treatment arm in the main analyses. This pooling assumes that there is no substantial effect of different placebo volumes or different dose escalation on the efficacy and safety endpoints. The validity of this assumption will be checked for the primary endpoint by plotting mean data for the 8 placebo arms separately, and by evaluating summaries of treatment-emergent adverse events for each placebo arm. Should the placebo arms demonstrate substantial differences, appropriate sensitivity analysis will be included. The description of planned analysis given here assumes that all 8 placebo arms will be pooled into one placebo arm.

In general, the statistical analysis will be made by one statistical model estimation on the full dataset including all treatment arms. Statistical inference and data presentations will be separated into two parts. Part A concerns identifying the optimal dose and includes inference for the liraglutide arm, the semaglutide arms with dose escalation every fourth week, and the pool of the placebo arms. Part B concerns identifying the optimal dose escalation regime and includes inference for the semaglutide arms with dose escalation every second week, the corresponding semaglutide arms (with regards to dose) with dose escalation every fourth week, and the pool of the placebo arms.

The baseline value will be defined as the last measured and available value from visit 1 and 2.

In the case of missing data no general imputation will be performed for the analyses, unless otherwise specified.

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

17.1 Sample size calculation

The sample size calculation is based on the primary endpoint; change from baseline in body weight (%) at 52 weeks.

Part A is a dose-finding trial examining five doses of semaglutide and placebo, and an active comparator. The sample size calculation is based on the relative change after 52 weeks treatment in the primary endpoint, body weight. In the sample size calculations, it is presumed that the placebo groups will be pooled in the analysis, assuming no correlation between body weight change after 52 weeks and placebo-injected volume. By trial design we expect to have 135 subjects on placebo and 100 in each active group. In the unfortunate situation that we should not be able to pool all placebo arms but only be able to pool the (semaglutide) placebo arms with dose escalation every fourth week and (liraglutide) placebo, we will still expect to have at least 100 subjects in the relevant pool of placebo subjects. Hence the argumentation below only assumes 100 subjects in the placebo arm in a conservative manner and for simplicity. However, at time of analysis we plan to include all subjects on placebo as one group in the analysis as described above, if possible.

The following assume 100 subjects randomised in a balanced manner to receive each active treatment and being conservative at least 100 evaluable subjects in the placebo arm. In trial NN8022-1839, in obese subjects without T2DM a standard deviation of just below 7% was seen for observed weight loss (in %) in the liraglutide 3.0 mg arm. A conservative estimate of the dropout rate is 40%. A standard deviation of 7% and a sample size of 100 in each treatment arm will allow the 95% confidence interval for the estimated difference between two semaglutide doses, with 90% probability, to be contained within ±2.5% of the estimate, which is considered to be a sufficient precision for determining which doses to use for the continued development of semaglutide in the weight management indication.

For the primary endpoint change in body weight after 52 weeks of treatment, a difference (semaglutide minus placebo) of 9.5% is expected for completers in the optimal dose group. For the withdrawn subjects, who are anticipated to constitute up to 40% of the total trial population, the treatment difference (semaglutide minus placebo) is assumed to be 0% giving an overall expected treatment difference of 8.2%. The standard deviation will also be increased using the MI approach. The standard deviation in the final data is assumed to be up to 8.2%. A standard deviation of 8.2% together with an expected difference of 8.2% results in a power of more than 99%.

For part B, in total two times 100 subjects will be randomised to the dose escalation every second week. Combined with placebo and the two doses corresponding to the ‘every second week’ arms (i.e. 0.3 mg/day and 0.4 mg/day) we will have more than five hundred subjects for the inference of the dose escalation finding part of the trial. In trial NN8022-1839, nausea, vomiting, and constipation were the most common gastrointestinal AEs with incidences between 15% and 40% of all subjects on liraglutide 3.0 mg. These AEs are not expected to be less frequent with semaglutide. This part of the trial is exploratory in nature and is intended to evaluate the overall safety profile with respect to the different types of events and when they occur compared to the escalation steps and with a view towards the efficacy response as well. With the given number of subjects, we have a reasonable sample size to detect marked clinical relevant difference between the arms.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9[39] guidance:

- The full analysis set (FAS) will include all randomised subjects. Only in exceptional cases may subjects be excluded from the FAS. In such cases the reason for exclusion will be justified and documented. Subjects in the FAS will contribute to the evaluation 'as randomised'.
- The safety analysis set will include all subjects receiving at least one dose of randomised treatment. Subjects in the safety analysis set will contribute to the evaluation 'as treated'.

Any subjects or observations excluded from analysis, and the reason for exclusion will be described in the CTR.

17.3 Primary endpoint

The primary endpoint, relative change from baseline in body weight (%) at 52 weeks, will be investigated using the following main analysis to compare between the randomised treatment arms using a multiple imputation (MI) analysis. The main analysis of the primary endpoint will also be referred to as the primary analysis as opposed to the sensitivity analysis of the primary endpoint. Week 52 data from subjects discontinued from trial product that return for visit 22x will be included. In this pattern mixture model approach withdrawn subjects without visit 22x from all treatment arms are assumed to respond as if treated with placebo for the entire trial. Multiple copies (100 copies) of the full dataset will be generated by imputing missing values (change from baseline in body weight (%) at 52 weeks) based on estimated parameters for the placebo group. This will be done as follows:

- In the first step, 100 copies of the dataset will be generated
- In the second step, an enriched analysis of covariance model with treatment, region and sex as factors and baseline body weight, waist circumference, age and HbA_{1c} as covariates is fitted to the change from baseline in body weight (%) at 52 weeks for the completers only
- In the third step, for each of the 100 copies of the dataset the estimated parameters, and their variances, from this model are used to impute missing values at 52 weeks for subjects in all treatment arms, based on their region, sex, body weight, waist circumference, age and HbA_{1c} at baseline with treatment equal to placebo from the enriched model in step two
- For each of the 100 complete data sets, the change from baseline in body weight (%) at 52 weeks is analysed using an analysis of variance model with treatment, region, and sex as factors, and baseline body weight as a covariate
- The estimates and standard deviations for the 100 data sets are pooled into one estimate and associated standard deviation using Rubin's formula:

$$m_{MI} = \frac{1}{100}\sum_{i=1}^{100} m_{i,} \quad SD_{MI} = \sqrt{\frac{1}{100}\sum_{i=1}^{100} {SD_i}^2 + \left(1+\frac{1}{100}\right)\left(\frac{1}{100-1}\right)\sum_{i=1}^{100}(m_i - m_{MI})^2},$$

where m_i and SD_i are the estimated means and standard deviations

for the 100 copies of the dataset, and m_{MI}, SD_{MI} are the pooled estimates.

– From m_{MI} and SD_{MI}, the 95% confidence interval for the treatment differences and the associated p-value are calculated

Pairwise treatment differences between semaglutide doses and placebo, liraglutide and placebo, different semaglutide doses, and between semaglutide doses and liraglutide at week 52 will be estimated from the model and 95% confidence intervals will be calculated.

In part A, the comparisons of semaglutide doses vs. placebo will have the family wise type I error protected in the strong sense. This will be achieved by using Dunnett's method in which simultaneous confidence intervals will be calculated. A significance level of 5% will be applied. Further, the focus of this part of the trial is to examine the dose response relationship. In part B, no multiplicity adjustment will be performed.

The dose of semaglutide providing a weight loss corresponding to liraglutide 3.0 mg will be estimated by fitting a linear approximation to the log dose vs. estimated means for the semaglutide doses and compare this to the estimated mean for liraglutide 3.0 mg. This analysis will be based on the estimated means and the covariance matrix for the means obtained from the MI analysis. Fieller's method will be used to calculate 95% confidence limits for the estimated dose of semaglutide corresponding to liraglutide 3.0 mg. If a linear approximation does not describe the log(dose)-response relationship well, a different approximation (e.g. a sigmoidal curve) may be investigated.

The MI method does not assume missing at random. It assumes that withdrawn subjects and subjects with missing endpoint at week 52 in the placebo arm have a response similar to the completers in the placebo arm given similar baseline characteristics. In the active treatment arms, the assumption is that withdrawn subjects and subjects with missing endpoint at week 52 behave as if they have been in the placebo arm during entire trial regardless of the time of discontinuation. In this way the assumptions are differential and conservative for estimating the treatment effect. The estimate in the primary analysis can be said to be an intention to treat (ITT) estimand or an effectiveness estimand in all randomised subjects of the add-on effect of semaglutide to nutritional and physical activity counselling.

Based on previous trials in weight management the withdrawal rate from randomised treatment is expected to be up to 40%. Semaglutide treatment has in previous (T2DM) trials been effective with regard to weight loss, and this should reduce the number of withdrawals due to ineffective therapy. Based on previous experience, a higher rate of withdrawal of consent is expected in the placebo group compared to active treatment. This difference may be due to lack of efficacy with placebo treatment. A higher withdrawal rate due to gastrointestinal adverse events is expected in the high dose semaglutide treatment arms and the liraglutide 3.0 mg arm compared to placebo. Apart from this, missing data due to adverse events (AEs) is expected to be similar across groups. This

emphasises the validity of the primary analysis as a conservative analysis of the treatment effect of semaglutide.

The sensitivity of the results with regard to different assumptions for missing data from withdrawn subjects will be investigated by plotting weight loss data for withdrawn subjects and compare this with plots of weight loss data for subjects completing 52 weeks of treatment. Further, for subjects that discontinue treatment but provide data at the week 52 visit (22x) plots will compare weight loss at last visit on treatment with weight loss at visit 22x. In addition, several sensitivity analyses will be performed where different assumptions are made with regard to withdrawn subjects.

The following sensitivity analyses will be performed:

1. An analysis of covariance (ANCOVA) model comparing the change from baseline in body weight (%) at 52 weeks between treatments. Only on-treatment data will be included. Missing data at week 52 will be imputed from on-treatment data using the last observation carried forward (LOCF) method. The ANCOVA model will include treatment, region, and sex as factors, and baseline body weight as a covariate. This analysis corresponds to the primary analysis approach used in the liraglutide weight management development programme.

2. An analysis of covariance (ANCOVA) model comparing the change from baseline in body weight (%) at 52 weeks between treatments. All available data will be included. Missing data at week 52 will be imputed using the subject's baseline observed weight carried forward (BOCF). The ANCOVA model will include treatment, region, and sex as factors, and baseline body weight as a covariate. This is a conservative analysis which will underestimate the differences between semaglutide/liraglutide and placebo.

3. A mixed model for repeated measurements (MMRM) comparing the change from baseline in body weight (%) at 52 weeks between treatments. All post randomisation measurements at planned visits up to week 52 and obtained before withdrawal from treatment will be included in the model as dependent variables. Treatment, region, and sex will be included as fixed factors, and the baseline body weight will be included as a covariate. All factors and the covariate will be nested under the factor visit. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. Subjects without post randomisation measurements of weight will be excluded from the analysis.

4. The primary analysis model (the MI) will be applied to data from subjects attending the end-of-treatment visit in fasting state. Any non-fasting measurements will be treated as missing measurements.

5. An analysis of covariance (ANCOVA) model comparing the change from baseline in body weight (%) at 52 weeks between treatments including only subjects with data for week 52 on

treatment (a completer analysis). The ANCOVA model will include treatment, region, and sex as factors, and baseline body weight as a covariate.

6. The primary analysis model (MI) will be applied where data from all withdrawn subjects are imputed (i.e. data from visit 22x is disregarded).

Further sensitivity analysis may be added at time of reporting as deemed relevant.

The ANCOVA model with LOCF assumes that post treatment discontinuation, the body weight is on average stable in both treatment arms. This assumption can be evaluated over the 7 weeks follow-up period in withdrawn subjects and in completing subjects. If the assumption holds, the treatment effect (effectiveness estimand) in each arm and the treatment difference can be estimated from this analysis unbiased. If the withdrawal and the development in both arms are similar, the treatment difference can be estimated from this analysis unbiased. If the development in body weight after treatment discontinuations differs between active and placebo, this analysis might provide an optimistic or over-conservative estimate, depending on the actual circumstances. The analysis is included to be able to compare the results with legacy obesity programs, where this analysis was the main analysis of the primary endpoints.

The ANCOVA model with BOCF assumes that post treatment discontinuation subjects returns to a body weight in the proximity of their baseline body weight regardless of the timing of discontinuation. This analysis is expected to provide a conservative estimate (effectiveness estimand) of the treatment effect (in each arm). The impact of this assumption on the treatment difference depends on withdrawal pattern over time and development of body weight post treatment discontinuation and reason for withdrawal. The analysis is typically expected to provide a conservative estimate of the treatment difference (effectiveness estimand).

The MMRM model assumes that withdrawn subjects, had they completed the trial, would not have behaved differently than completing subjects from the same treatment arm with the same baseline characteristic and change in body weight at time of withdrawal. This analysis estimates the treatment effect and difference had all subjects stayed on the randomised treatment (efficacy estimand).

The MI model on fasting values examines the influence of not being fasting at the end-of-treatment visit. This analysis is expected to give similar treatment differences as the main analyses and estimate the same estimand.

The ANCOVA analysis in completers is expected to give more positive results than the primary analysis. However, this analysis has its own clinical interpretation and will serve as a benchmark and provide an estimate of the efficacy estimand in the population that tolerate the trial product and endure the diet and exercise counselling program.

The MI model disregarding visit 22x data examine the influence of data from withdrawn subjects returning at week 52 on the main analysis. It is difficult to postulate expectation on the results from this sensitivity analysis. The analysis estimates the same estimand as the primary analysis.

17.4 Secondary endpoints

For statistical analysis of secondary endpoints, when mentioned below, the analyses methods reproduce the main analysis of the primary endpoint by the same MI approach. The endpoint at baseline will replace body weight at baseline as covariate. The statistical methodology depends on the type of endpoint, but the model factors and covariates are similar to those specified for the primary analysis.

17.4.1 Efficacy endpoints

Endpoints addressing weight loss

- Proportion (%) of subjects with weight loss of ≥ 5% of baseline body weight at 52 weeks
- Proportion (%) of subjects with weight loss of ≥ 10% of baseline body weight at 52 weeks

These two dichotomous endpoints will be compared between the treatment arms using a MI approach as in the primary analysis based on a logistic regression. The datasets from the primary analysis will be reused for this analysis where imputed values for change in body weight will be used to generate the dichotome endpoints. Pairwise treatment differences between treatments will be estimated from the model and 95% confidence intervals will be calculated.

Change from baseline to 52 weeks in:

- Body weight (kg)
- Waist circumference (cm)
- Waist to hip circumference ratio (waist (cm)/hip (cm))
- BMI (kg/m^2)

These endpoints will be compared between treatments using the MI approach used for the main analysis of the primary endpoint (with the corresponding baseline value as covariate).

Endpoints addressing glucose metabolism

Change from baseline to 52 weeks in:

- HbA_{1c}
- FPG
- Shift in glycaemic category (normoglycaemia, pre-diabetes, T2DM)

The endpoints HbA1c and FPG will be compared between treatments using the MI approach used for the main analysis of the primary endpoint (with the corresponding baseline value as covariate). Shift in glycaemic category will be compared between treatments using the proportional odds

model (or ordinal logistic regression) and imputing missing measurements in the same fashion as used for the main analysis of the primary endpoint.

Glycaemic categories

Normoglycaemia:

- FPG < 5.6 mmol/L (100 mg/dL) **and** HbA_{1c} < 5.7%

Pre-diabetes:

- FPG 5.6-6.9 mmol/L (100-125 mg/dL) (both inclusive) **and** $HbA_{1c} \leq 6.4\%$

or

- FPG ≤ 6.9 mmol/L (125 mg/dL) **and** HbA_{1c} 5.7-6.4% (both inclusive)

T2DM:

- FPG ≥ 7.0 mmol/L (126 mg/dL) **and/or** $HbA_{1c} \geq 6.5\%$

Endpoints addressing cardiovascular risk factors

Change from baseline to 52 weeks in:

- Systolic and diastolic blood pressure
- Lipids (total cholesterol [TC], low density lipoprotein cholesterol [LDL cholesterol], high density lipoprotein cholesterol [HDL cholesterol], very low density lipoprotein cholesterol [VLDL cholesterol], triglycerides [TG], free fatty acids [FFA])
- Cardiovascular biomarker (high sensitivity C reactive protein [hsCRP])

These endpoints will be compared between treatments using the MI approach used for the main analysis of the primary endpoint (with the corresponding baseline value as covariate). For lipids and hsCRP a multiplicative model will be used, i.e. the ratio between post randomisation measurements and baseline will be calculated instead of differences, and both the dependent variable and covariate will be log-transformed. Estimates and CI will be presented as percentage change from baseline.

Endpoints addressing patient reported weight-related quality of life and general health status

Change from baseline to 52 weeks in:

- Impact of Weight on Quality of Life-Lite (IWQoL-Lite) for Clinical Trials: Total score and scores on the individual sub-domains
- Short form-36 (SF-36): Physical and mental component summary scores and scores on the individual sub-domains: Physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health

These endpoints will be compared between treatments using the MI approach used for the main analysis of the primary endpoint (with the baseline total score as covariate).

Endpoints addressing changes in antihypertensive and lipid-lowering medical treatment

Change from baseline to 52 weeks in:

- Proportion of subjects with change in concomitant medications:
  - Antihypertensive medications
  - Lipid-lowering medications

The endpoint is based on the evaluations made by the investigators and recorded according to the description in section 8.2.3.1.The proportion of subjects with any change (decrease/no change/increase) in dose and/or drug within the two above classes will be calculated and described. These endpoints will be compared between treatments using the proportional odds model (or ordinal logistic regression). Only on-treatment data will be considered. Subjects not using drugs within the specified categories will count as no-change. The model factors and covariates will be identical to the main analysis model.

Endpoint addressing nutritional compliance

Compliance with nutritional counselling will be summarised by week.

Analysis identifying early responders

- Predictability of weight loss of more than 5% at week 52 by early weight loss response (3%, 4%, and 5%) after 12, 16, and 20 weeks

The ability of early weight loss of 3%, 4%, and 5% at week 12, 16, 20 to predict long term weight loss (5% at week 52) will be described by sensitivity, specificity, positive predictive value, and negative predictive value. Receiver operating curve (ROC) will be presented for weight loss at week 12, 16 and 20. The analysis will be repeated seperately for each treatment arm.

17.4.2 Safety endpoints

The endpoint “Number of treatment-emergent adverse events during the trial” will be extensively described using descriptive statistics and listings.

All adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). An adverse event will be defined as treatment emergent if the onset of the adverse event is on or after the first day of trial product administration, and no later than whatever comes first of a) last drug date plus seven weeks or b) follow-up visit, or c) last study visit.

Treatment-emergent adverse events will be summarised by system organ class, preferred term, seriousness, severity and relation to trial product.

Endpoint addressing hypoglycaemic episodes:

The endpoint "Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic events" will be tabulated according to the definition below. The remainder of the low blood glucose events (asymptomatic hypoglycaemic events) will be tabulated as well.

Given that the trial population does not have T2DM at inclusion, the risk of developing hypoglycaemia is considered low and hence no blood glucose monitoring will be instituted. However, in case of severe hypoglycaemia where third party assistance is needed or in case of a low blood glucose value detected by scheduled blood sampling accompanied by relevant symptoms, the hypoglycaemic episode will qualify for the endpoint analysis.

Classification of hypoglycaemic events

Treatment-emergent: hypoglycaemic episodes 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 whatever comes first of a) last drug date plus seven weeks or b) follow-up visit, or c) last study visit.

The hypoglycaemic episodes will be categorised based on the ADA classification[33] of hypoglycaemia:

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

Safety endpoints continued

The endpoint "Number of new and ongoing treatment-emergent nausea, vomiting, diarrhoea and constipation events by week" will be summarised by week.

Nausea:

- Individual scores of nausea questionnaire
- Severity by numeric rating scale (NRS) score

Nausea questionnaire and NRS score will be summarised by week.

Changes from baseline to 52 weeks in:

- EGG
- Pulse
- Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential count)
- Biochemistry (creatinine, CPK, urea, albumin, bilirubin [total], ALT, AST, alkaline phosphatase, sodium, potassium, calcium [total], amylase, lipase, calcitonin, TSH)
- Mental health assessed by Columbia Suicidality Severity Rating Scale (C-SSRS) and Patient Health Questionnaire-9 (PHQ-9)

will be summarised and described for each treatment arm. Changes in pulse will be compared between treatments using an MMRM model as described under sensitivity analysis in section 17.3 (with the baseline pulse value as covariate) based on the safety analysis set. For amylase and lipase two statistical analyses will be applied, respectively. The relative change (100*value/baseline) will be analysed with an MMRM model as described under sensitivity analysis in section 17.3. The relative change and baseline values will be log-transformed prior to the analysis. Subjects having a measurement above >3x UNR anytime during treatment (yes/no) will be analysed using a logistic regression. For the evaluation of the response, all measurements obtained during treatment will be included and these measurements are defined as any scheduled or unscheduled measurements obtained from, but not including, baseline and until, and including, end of treatment. Separate analyses will be made for amylase and lipase. The results will be presented as odds ratios together with the associated 95% confidence intervals.

The endpoint “Anti-semaglutide antibodies during and after treatment” will be described by summarising the number and percentage of subjects with antibodies in the different treatment arms. Similarly, subjects with semaglutide antibodies with neutralising effect and with cross-reactivity against endogenous GLP-1 will be described by summaries. The primary endpoint will be summarised by anti-semaglutide antibody status (positive or negative) at follow-up.

17.5 Pharmacokinetic and pharmacodynamic modelling

Exploratory population PK and PK/PD modelling will be used to evaluate the semaglutide dose-exposure, the effects of pre-specified covariates on the exposure and the semaglutide exposure-response on selected efficacy and safety parameters. For the covariate analysis, covariates such as sex, body weight and age will be explored.

The population PK modelling will include data from all randomised subjects that were exposed to semaglutide, excluding data records with concentration values missing or below LLOQ, and data records with incomplete or ambiguous dosing information. Actual time points for dose administration and PK sampling will be used. PK/PD modelling will include data from subjects included in the population PK modelling, with relevant PD assessments available.

Results of the modelling analysis will be presented using criteria which will be pre-specified in a modelling analysis plan that is to be finalised before database lock (DBL). The modelling will be performed by Quantitative Clinical Pharmacology at Novo Nordisk A/S and will be reported separately from the CTR.

18 Ethics

18.1 Benefit-risk assessment of the trial

Risks and precautions for semaglutide

The sections below describe potential risks associated with semaglutide treatment, based on findings with other GLP-1 RAs and observations in nonclinical and clinical trials with semaglutide administered s.c. once weekly. For each of these risks, mitigating actions have been implemented to minimise the risks for subjects enrolled in this trial.

The nonclinical safety programme of semaglutide has revealed no identified safety issues for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity.

Thyroid C-cell tumour

The human relevance of the proliferative C-cell changes found in rodents is unknown, but data suggest that rodents are more sensitive to the mode of action for induction of C-cell tumours with GLP-1 RAs. However, as a precaution subjects with a family or personal history of Multiple Endocrine Neoplasia type 2 (MEN 2), familial medullary thyroid carcinoma (MTC), personal history of non-familial medullary thyroid carcinoma, and subjects with a screening calcitonin ≥50 ng/L will be excluded from trial. During the trial calcitonin will be measured on a regular basis and guidance for investigators of further evaluation and action on elevated plasma calcitonin concentrations will be carried out by an independent group of thyroid experts, the Calcitonin Monitoring Committee (CMC). This will ensure appropriate and consistent handling of elevated levels across trials.

Teratogenicity (nonclinical embryo-foetal toxicity)

Semaglutide has been concluded teratogenic in rats. This effect is regarded to be caused by impairment of nutrient supply to the embryo across the inverted yolk sac with placental function. As the yolk sac does not play such a role for nutrition of the embryo in humans, this effect is unlikely to be relevant for humans. However, as a precaution subjects fulfilling exclusion criterion 29 will be excluded from trial participation. Furthermore, female subjects included in the trial will have pregnancy testing performed on a monthly basis.

Gastrointestinal adverse events

Consistent with findings from other GLP-1 RAs, the most frequently reported AEs in the clinical trials with semaglutide thus far have been gastrointestinal (GI) disorders (nausea, vomiting, diarrhoea, dyspepsia and constipation). However, based on a completed clinical trial (NN9535-3819) where slower dose escalation substantially improved the GI tolerability profile, a 4-week dose escalation regimen has been developed and is used in ongoing clinical phase 3 programme for semaglutide s.c. administered once weekly as well as for most or the arms in this trial.

Allergic reactions and injection site reactions

As is the case with all protein based pharmaceuticals subjects treated with semaglutide risk developing immunogenic and allergic reactions. These may include localised injection site reactions or generalised reactions including urticaria, rash or pruritus. Severe allergic reactions such as anaphylactic reactions could potentially also pose a risk for subjects treated with semaglutide.

Hypoglycaemia

Based on current knowledge about the GLP-1 RA drug class, there is a risk of hypoglycaemic episodes. Hypoglycaemic episodes have mainly been observed when a GLP-1 RA is combined with sulphonylurea (SU) or insulin in patients with T2DM. The risk for development of hypoglycaemia specifically with semaglutide in combination with SU and insulin is unknown due to limited data.

Altered renal function and acute pancreatitis

Based on current knowledge about the GLP-1 RA drug class two potential risks have been found relevant:

Firstly, untoward effects of volume depletion, resulting from nausea, vomiting and dehydration, such as acute renal failure have been observed in subjects treated with other GLP-1 RAs. As a precaution serum creatinine is measured regularly.

Secondly, acute pancreatitis, including reports of severe necrotising and haemorrhagic forms, has been associated with other GLP-1 RAs. As a precaution patients with a history of acute or chronic pancreatitis will be excluded from the trial. Subjects will be monitored for elevated activity levels of amylase and lipase and be informed of the characteristic symptoms of acute pancreatitis.

Risks and precautions for liraglutide

In the liraglutide 3.0 mg weight management programme, the main tolerability finding was gastrointestinal AEs. Cases of gallstones (cholelithiasis) and inflammation of the gallbladder (cholecystitis) were reported more commonly in adult subjects treated with liraglutide 3.0 mg compared to placebo. From literature, it is well-known that obesity carries an increased risk of cholelithiasis and that an association between rapid/marked weight loss and the development of cholelithiasis is present. In overweight or obese subjects with and without T2DM, treatment with liraglutide doses up to 3.0 mg was generally well tolerated. Overweight and obese subjects have an increased risk of certain types of cancer. In the weight management programme, the reporting rate of neoplasm events confirmed by event adjudication was similar with liraglutide and placebo. A numerical imbalance was observed for events of breast neoplasms in females and colorectal adenomas in males. Based on the limited number of reports a causal relationship to liraglutide could neither be confirmed nor excluded. In conclusion: Liraglutide in doses up to 3.0 mg has a well-described and acceptable risk-benefit profile. The maximum liraglutide to be used in the current trial (3.0 mg) is therefore considered to be safe.

Benefits

Subjects will be treated within a regimen anticipated to be better than or equal to the weight management they receive at the time of entry into the trial.

Semaglutide has in a phase 2 trial (NN9535-1821) proven to have a clinical meaningful and dose-dependent effect on body weight. Doses ≥ 0.8 mg semaglutide provided a greater weight loss than liraglutide 1.8 mg. In clinical studies with liraglutide 3.0 mg (Saxenda®) approximately 2/3 of the subjects lost more than 5% of their initial body weight and approximately 1/3 lost more than 10% of their initial body weight. Even a moderate weight loss of 5% has been shown to have significant health benefits in terms of improving glycaemic control, reducing progression to T2DM and improving the other abovementioned comorbidities (see section 3.1)

Although subjects will have to spend time on site visits and procedures required by trial participation, it is expected that all subjects (including those subjects randomised to placebo) will benefit from participation through close contact with the trial site, with close follow-up of their obesity and a careful medical examination. All of which will most likely result in an intensified management of their obesity.

Conclusion

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 informed about possible AEs and inconveniences and will be instructed to contact the investigator in case of any concerns regarding the trial participation.

When treatment with trial products ends, the subject and investigator will decide on the best available treatment.

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 in T2DM has not revealed any safety issues that would prohibit administration of once weekly doses of 0.5 mg or 1.0 mg semaglutide. As the previously tested doses seem suboptimal for the weight management indication, higher doses are investigated in the present trial and based on the nature and frequency of the AEs in the T2DM trials it appears to be safe to investigate daily doses of up to 0.4 mg. However, as gastrointestinal AEs are expected and are likely to be dose-dependent, additional safety surveillance will be instituted in all treatment arms during the dose escalation period until 4 weeks after last target dose is reached (steady state). It is concluded that the risk to the subjects in this trial is low and acceptable in view of the benefits a long-acting GLP-1 analogue would provide to subjects with obesity.

18.2 Informed consent

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

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand. This includes the use of an impartial witness where required.

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

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

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

The responsibility for seeking informed consent must remain with the investigator, but the 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.

In case a subject undergoes a thyroidectomy a separate informed consent will be obtained for collection of thyroid tissue sample and genetic testing (see section 8.7.2).

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

18.3 Data handling

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

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

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

18.4 Information to subject during the trial

During the trial, the subjects may receive information that could include a “welcome to the trial letter”, newsletter(s) and a “thank you for your participation letter” after completion of the trial, if locally acceptable.

Initiatives for subject retention will be instituted for this trial. These may include retention activities, materials and items, if locally acceptable. The retention items will be relevant for the subjects’ participation in the trial and/or their obesity and will not exceed local fair market value.

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

18.5 Premature termination of the trial and/or trial site

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

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

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

19 Protocol compliance

Deviations from the protocol should be avoided.

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

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

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

20 Audits and inspections

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

21 Critical documents

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

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochures[37,38]
- Signed and dated Agreement on Protocol
- Signed and dated agreement on protocol amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

For US trial sites:

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

For sites outside the US:

- All investigators outside 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 must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator must ensure adequate supervision of the conduct of the trial at the trial site.

The investigator will follow instructions from Novo Nordisk when processing data.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator’s trial master file. The documents including the subject identification code list should be kept in a secure locked facility, so no unauthorized persons can get access to the data.

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

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

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

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

23 Reports and publications

The information obtained during the conduct of this trial is considered confidential, and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

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

One (or more) investigator(s) will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator(s)) on behalf of all participating investigators. The signatory investigator(s) will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[40].

23.1 Communication of results

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

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[23].

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

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

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

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

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

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[40] (sometimes referred to as the Vancouver Criteria).

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

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

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

23.2 Investigator access to data and review of results

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

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

24 Retention of clinical trial documentation and human biospecimens

24.1 Retention of clinical trial documentation

Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for as long as the product is on the market plus 20 years.

The files from the trial site/institution must be retained for 25 years after the completion of the trial, or longer if required by local regulations or Novo Nordisk. In any case, trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biospecimens

Antibody samples may be stored at the laboratory responsible for analysis for up to 15 years after end of trial in case further analysis or characterisation related to antibody response is requested by the regulatory authorities. The samples will not be used for other purposes.

None of the data will be identified by name. Antibody samples will be identified only by a subject number, a visit number and a trial identification number.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

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

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

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

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

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

Regulatory Authorities:

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

26 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with:

Australia: Complies with Medicines Australia Form of Indemnity for clinical trials version 160104B dated 16 January 2004

Belgium: Law concerning experiments on the human person of 07 May 2004 –Article 29: §1: Even if without fault, the sponsor is liable for the damage which the subject and/or his rightful claimants sustain and which shows either a direct or an indirect connection with the trial.

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Appendix A

Monitoring of calcitonin

[redacted]

1 Background

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

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 (MEN 2) 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 (except for screening failures) will be submitted to an independent Calcitonin Monitoring Committee (CMC) of thyroid experts, together with relevant supplementary data, i.e. subject's demographics, 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 examinations 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 cannot be randomised and the subject must be referred to a thyroid specialist.

These values were found in 0.15% of a population with thyroid nodular disease published by Costante 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 0.14% of the population with thyroid nodular disease published by Costante 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. Subjects with positive pentagastrin stimulation tests will be considered to undergo surgery. In the US and other countries 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 Costante et al[1], the predictive value of calcitonin levels ≥ 20 and < 50 ng/L for 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

The value will not be submitted to the CMC. Confounding factors should be evaluated. If drugs potentially affecting calcitonin can be discontinued safely, calcitonin can be repeated after a washout period. 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.

Costante et al[1] had 216 (3.7%) patients in this category. One patient out of the 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]

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Appendix B

Impact of Weight on Quality of Life Lite for Clinical Trials

Questionnaire

[redacted]

For each of the following statements, please select the response that best applies to you currently.

		Never	**Rarely**	**Sometimes**	**Usually**	**Always**
1	I have trouble bending over, for example to pick things up from the floor or tie my shoes.	☐	☐	☐	☐	☐
2	I get tired or winded walking up one flight of stairs.	☐	☐	☐	☐	☐
3	I have difficulty standing for 10 to 15 minutes.	☐	☐	☐	☐	☐
4	I feel uncomfortable in small seats in public places, such as in airplanes, theatres, and sports arenas.	☐	☐	☐	☐	☐
5	I experience pain, such as pain in my knees, hips, or back.	☐	☐	☐	☐	☐
6	I feel self-conscious eating in restaurants or buying groceries.	☐	☐	☐	☐	☐
7	I feel less confident because of my weight.	☐	☐	☐	☐	☐
8	I feel that others are judging me on the basis of my weight.	☐	☐	☐	☐	☐
9	Others view me as less important or less worthy of respect because of my weight.	☐	☐	☐	☐	☐

		Never	**Rarely**	**Sometimes**	**Usually**	**Always**
10	I get frustrated shopping for clothes.	☐	☐	☐	☐	☐
11	I get frustrated choosing what to wear.	☐	☐	☐	☐	☐
12	I feel bad or upset when I see myself in pictures.	☐	☐	☐	☐	☐
13	I feel down or depressed about my weight.	☐	☐	☐	☐	☐
14	I am less interested in sexual activity than I would like to be.	☐	☐	☐	☐	☐
15	I avoid social gatherings because of my weight.	☐	☐	☐	☐	☐
16	I am less productive than I would like to be (at work, home, and/or school) because of my weight.	☐	☐	☐	☐	☐
17	I lack the energy to do the things I would like to do.	☐	☐	☐	☐	☐

		Not at all true	**A little true**	**Moderately true**	**Mostly true**	**Completely true**
18	I am not as physically active as I would like to be.	☐	☐	☐	☐	☐
19	I am unable to walk as far or as quickly as I would like.	☐	☐	☐	☐	☐
20	I am worried about my health.	☐	☐	☐	☐	☐
21	My self-esteem is not what it could be because of my weight.	☐	☐	☐	☐	☐
22	I am self-conscious about my weight.	☐	☐	☐	☐	☐
23	I feel frustrated or upset with myself about my weight.	☐	☐	☐	☐	☐

Appendix C

Patient Global Impression of Change (PGI-C)

[redacted]

Patient Global Impression of Change (PGI-C) Questions

How would you rate your physical functioning (ability to do physical activities, mobility and flexibility, energy, and physical comfort) at your current weight as compared to the beginning of the study?

☐ Much better
☐ Moderately better
☐ A little better
☐ No difference
☐ A little worse
☐ Moderately worse
☐ Much worse

How would you rate how you feel (emotions, self-confidence) at your current weight as compared to the beginning of the study?

☐ Much better
☐ Moderately better
☐ A little better
☐ No difference
☐ A little worse
☐ Moderately worse
☐ Much worse

Overall, how would you rate the quality of your life at your current weight as compared to the beginning of the study?

☐ Much better
☐ Moderately better
☐ A little better
☐ No difference
☐ A little worse
☐ Moderately worse
☐ Much worse

Appendix D

Nausea questionnaire

[redacted]

Trial ID: NN9536-4153	Subj. No: __ __ __ __	~~CONFIDENTIAL~~	mm/yyyy) _ _ __ __	Visit:

Nausea questionnaire

The following questions are intended to capture the subject's experience of **any single event of nausea** over the **past 24 hours** whilst participating in the NN9536-4153 trial. If more than one event of nausea were experienced within the previous 24 hours please fill out one questionnaire for each event

The questionnaire contains two parts: Six questions for you to ask the subject followed by one numeric rating scale (NRS) assessment that must be completed by the subject.

For each of the following questions, please mark an X in the box that best describes the subject's answer. Mark only one box for each question.

1. Has the subject experienced nausea at any time during the last 24 hours?

YES ☐ **NO** ☐, if YES please answer questions 2 to 6

2. To the best of the subject's recollection, at what approximate time did the event of nausea occur?

_ _:_ _ *(24 hour clock)*

3. How long did the subject's event of nausea last?

Less than 30 min	Between 30 min and 2 hours	Between 2 and 4 hours	Between 4 and 8 hours	More than 8 hours
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. How much time passed from the latest injection of trial product to the onset of nausea?

0 to3 hours	3 to 6 hours	6 to 12 hours	12 to 18 hours	>18 hours
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. How much time passed from the last food intake to the onset of nausea?

0 to1 hours	1 to 2 hours	2 to 3 hours	3 to 6 hours	>6 hours
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. Was the event of nausea accompanied by vomiting?

YES ☐ **NO** ☐

Trial ID: NN9536-4153	Subj. No: __ __ __ __	~~CONFIDENTIAL~~	mm/yyyy) _ __ __ __	Visit:

FOR THE SUBJECT TO FILL IN

A. Please make a single "X" through the number below that best shows how severe the nausea became when it was worst

Please do not place your "X" between two boxes

0	1	2	3	4	5	6	7	8	9	10

No nausea **Nausea as bad as it could be**

Thank You!

Appendix E

Medical event of special interest (MESI) and adverse events with additional data collection

[redacted]

Medical event of special interest

Event	Definition	Rationale	Event adjudication
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) Accidental administration of a lower or higher dose than intended, however the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen, as judged by the investigator, although they did not necessarily occur	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).	No

Adverse events with additional data collection

Event	Definition	Additional data collection	Event adjudication
Fatal events	All-cause mortality: 1. Cardiovascular death, 2. Non-cardiovascular death, 3. Undetermined cause of death[1]	No specific event form for fatal events. A fatal event must be reported as a SAE as described in the protocol.	Yes
Acute coronary syndrome: • Myocardial Infarction • Hospitalisation for unstable angina	All types of myocardial infarction (MI) must be reported: • Spontaneous MI (including re-infarction 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.	If an event of acute coronary syndrome is observed during the trial, this must be recorded as an AE and on a specific acute coronary syndrome form in the eCRF. The following information must be reported if available: • Duration of symptoms • Changes in ECG • Collection of cardiac biomarkers • Cardiac imaging • Cardiac stress testing • Angiography • Use of thrombolytic drugs	Yes

Event	Definition	Additional data collection	Event adjudication
Coronary Revascularisation Procedure	A coronary revascularization procedure is a percutaneous coronary intervention (PCI) or an open surgical procedure designed to improve myocardial blood flow.	If an event of coronary revascularisation is observed during the trial, this must be recorded as an AE and on a specific coronary revascularisation form in the eCRF. The following information should be obtained: • Type of revascularisation performed • Indication for the procedure	Yes
Cerebrovascular event (stroke or transient ischemic attack)	Transient ischemic attack (TIA) is defined as a transient (<24 hours) episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction.[1] Stroke (Ischemic, haemorrhagic, undetermined) is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction.[1]	If a cerebrovascular event is observed during the trial, this must be recorded as an AE and on a specific cerebrovascular event form in the eCRF. The following information must be reported if available: • Type of event (e.g. TIA, stroke) • Contributing condition • Neurologic signs and symptoms • History of neurologic disease • Imaging supporting the condition • Treatment given for the condition	Yes
Heart failure requiring hospitalisation	Clinical manifestations of new episode or worsening of existing heart failure requiring hospitalisation.	If an event of heart failure requiring hospitalisation is observed during the trial, this must be recorded as an AE and in addition on a specific heart failure event form in the eCRF. The following information must be reported if available: • Signs and symptoms of heart failure • NYHA Class • Supportive imaging • Supportive laboratory measurements • Initiation or intensification of treatment for this condition	Yes
Pancreatitis	Two of following diagnostic criteria fulfilling the diagnosis of acute pancreatitis: 1. severe acute abdominal pain 2. amylase and/or lipase activity levels >3x upper normal range (UNR) 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	If an event of pancreatitis is observed during the trial, this must be recorded as an AE and on a specific pancreatitis event form in the eCRF. The following information must be reported if available: • Signs and symptoms of pancreatitis • Specific laboratory test supporting a diagnosis of pancreatitis: o Amylase o Lipase o Alanine aminotransaminase (ALT) and aspartate aminotransferase (AST) o Bilirubin o Alkaline phosphatase (ALP)	Yes

Event	Definition	Additional data collection	Event adjudication

	findings	• Imaging performed and consistency with pancreatic disease
		• Treatment for and complications of the event
		• Relevant risk factors for pancreatic disease including
		  o History of gallstones
		  o History of pancreatitis
		  o Family history of pancreatitis
		  o Trauma	

Acute gallbladder disease	All types of acute gallbladder or acute biliary disorders	If an event of acute gallstone disease or clinical suspicion of this is observed during the trial, this must be recorded as an AE and on a specific acute gallstone disease event form in the eCRF. The following information should be reported if available:
		• Signs and symptoms of acute gallstone disease
		• Specific laboratory test supporting a diagnosis of gallstone:
		  o White blood cell count (WBC)
		  o C-reactive protein (CRP)
		  o Direct, indirect and total bilirubin
		  o ALT and AST
		  o Alkaline phosphatase (ALP)
		  o Amylase
		  o Lipase
		• Imaging performed and consistency with gallstone disease
		• Treatment given for the condition
		• Relevant risk factors for acute gallstone disease including
		  o History of gallstones
		  o Family history of gallstones
		  o Relevant surgery
			No

Neoplasm (excluding thyroid neoplasms)	All types of neoplasms must be reported including: • Malign neoplasm • Pre-malignant neoplasm/carcinoma in-situ • Benign neoplasm • Neoplasm of uncertain or unknown behaviour For operational reasons, thyroid neoplasms will be reported as thyroid disease (see below).	All events of neoplasms (excluding thyroid neoplasms) must be recorded as an AE and on a specific neoplasm event form in the eCRF. The following information should be obtained if available as part of standard of care: • Type of neoplasm • Symptoms leading to identification of event • Diagnostic imaging • Pathological examination results • Treatment for the event • Participation in screening programs	Yes

Event	Definition	Additional data collection	Event adjudication
		• Risk factors associated to the event	
Thyroid disease (including thyroid neoplasms	All disorders of thyroid gland must be reported. For operational reasons, thyroid neoplasms will be reported as thyroid disease. Only events that require thyroidectomy should be sent for adjudication	If an event of thyroid disease, including any thyroid neoplasms, observed during the trial, this must be recorded as an AE and on a specific thyroid disease event form in the eCRF. The following information must be reported if available: • History of thyroid disease • Signs and symptoms leading to investigations of thyroid disease • Specific laboratory tests describing thyroid function including : o TSH o Total and free T3 and T4 and Free Thyroid Index o Calcitonin o Thyroid peroxidase antibodies o Thyroglobulin and thyroglobulin antibody o Thyroid Stimulating Hormone receptor antibody • Diagnostic imaging performed and any prior imaging supporting the disease history • Pathologic examinations • Treatment given for the condition • Risk factors identified • Family history of thyroid disease	Yes (only events that require thyroi-dectomy)

1. Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials (DRAFT). Karen A. Hicks, H. M. James Hung, Kenneth W. Mahaffey, Roxana Mehran, Steven E. Nissen; Norman L. Strockbridge, Shari L. Targum, Robert Temple; on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative. August 20, 2014. *Or any updates hereof*

Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Protocol Amendment

no 1
to Protocol, final version 1.0
dated 17 April 2015

Trial ID: NN9536-4153

Investigation of safety and efficacy of once-daily semaglutide

A 52-week, randomised, double-blind, placebo-controlled, nine-armed, parallel group, multi-centre, multinational trial with liraglutide 3.0 mg as active comparator

Trial phase: 2

Applicable to Belgium

Amendment originator:

[redacted]

[redacted]

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1 Introduction including rationale for the protocol amendment

The rationale for this protocol amendment is to define adequate contraceptive measures for Belgium in Exclusion criterion No. 29 as required by the Belgian Health Authorities.

In this protocol amendment:

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

2 Changes

6.3 Exclusion criteria

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

FOR BELGIUM AND GERMANY: Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or *true* sexual abstinence *(i.e. refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)* or vasectomised partner.

FOR UNITED KINGDOM ONLY: Adequate contraceptive measures are defined as established use of oral, injected or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository), female sterilisation, male sterilisation (where partner is sole partner of subject), or true abstinence (when in line with preferred and usual lifestyle).

Protocol Amendment

no 2
to Protocol, final version 1.0
dated 17 April 2015

Trial ID: NN9536-4153

Investigation of safety and efficacy of once-daily semaglutide in obese subjects without diabetes mellitus

A 52-week, randomised, double-blind, placebo-controlled, nine-armed, parallel group, multi-centre, multinational trial with liraglutide 3.0 mg as active comparator

Trial phase: 2

Applicable to all countries

Amendment originator:

[redacted]

[redacted]

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1 Introduction including rationale for the protocol amendment

This global amendment contains one additional assessment for the trial and 4 clarifications:

Change	**Rationale for change**
Clarification of adequate contraceptive measures in Canada for exclusion criterion 29	Health Canada has requested that adequate contraceptive measures are defined for Canada
Clarification of data collection of History of gallbladder disease	Collection of history information for pancreatitis on the specific eCRF form is not relevant because subjects with a history of pancreatitis are excluded from the trial
Addition of standardised assessment of Injection site reactions	The FDA has requested that this assessment is added to the protocol
Clarification of thyroid disease events that must be sent for event adjudication (table 12.1)	Protocol was ambiguous with regards to which thyroid disease events should be sent for event adjudication
Clarification of figure 12.1	Figure 12.1 did not contain timelines for event adjudication

In this protocol amendment:

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

2 Changes

Section 6.3 Exclusion criteria

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

FOR CANADA ONLY: *Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices), or true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) or vasectomised partner.*

Section 8.2.2.2 History of gallbladder disease

Information related to gallbladder disease (i.e.~~, pancreatitis, gallstone~~ *gallbladder* disease and *cholecystectomy* ~~cholecystitis~~) must be recorded.

Section 8.5.10 Adverse events requiring special forms in the eCRF

Injection site reaction

If an event of injection site reaction is observed, the following additional information must be obtained if available:

- *Type of reaction – local or generalised*
- *Symptoms associated with the event*
- *Treatment given for the event*
- *Association with the trial product(s)*
- *Relevant risk factors associated with the event*

Section 12.1 Definitions

Table 12.1 is updated as seen below.

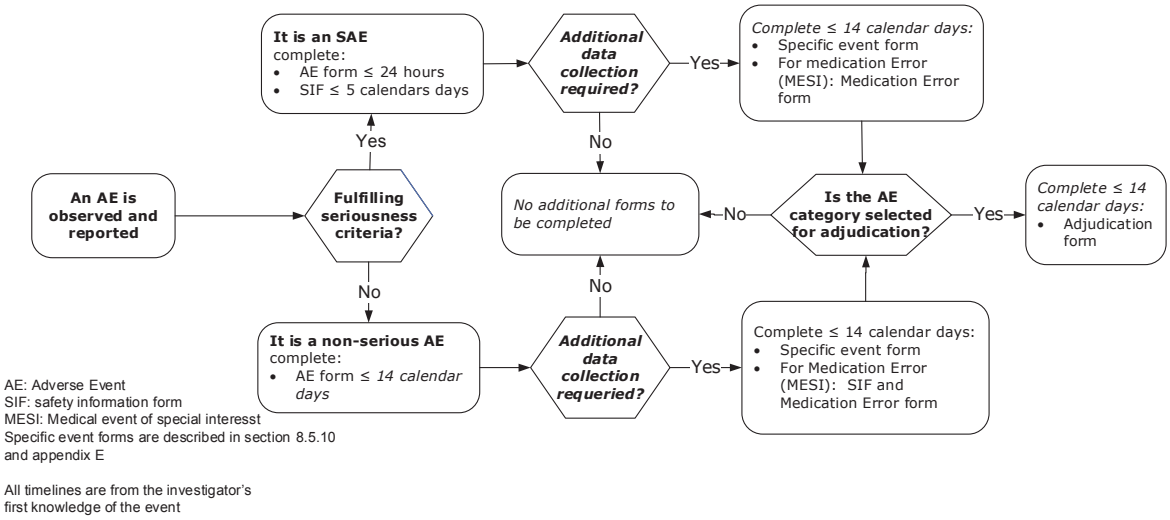
Table 12−1 Adverse events with additional data collection

Event	Event adjudication	Specific event form
Fatal events	Yes	No
Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)	Yes	Yes
Coronary revascularisation procedure	Yes	Yes
Cerebrovascular event (stroke or transient ischemic attack)	Yes	Yes
Heart failure requiring hospitalisation	Yes	Yes

Pancreatitis	Yes	Yes
Acute gallbladder disease	No	Yes
Neoplasm (excluding thyroid neoplasms)	Yes	Yes
Thyroid disease (including thyroid neoplasms)	Yes, (only events that require thyroidectomy *and/or thyroid neoplasms*)	Yes
Injection site reaction	*No*	*Yes*

Section 12.2 Reporting of adverse events

Figure 12.1 will be replaced by the below figure which contains timelines for event adjudication:



Appendix E

The following changes are made to the table in Appendix E:

Adverse events with additional data collection			
Event	**Definition**	**Additional data collection**	**Event adjudi-cation**
Thyroid disease (including thyroid neoplasms	All disorders of thyroid gland must be reported. For operational reasons, thyroid neoplasms will be reported as thyroid disease. Only events that require thyroidectomy should be sent for adjudication	If an event of thyroid disease, including any thyroid neoplasms, observed during the trial, this must be recorded as an AE and on a specific thyroid disease event form in the eCRF. The following information must be reported if available: • History of thyroid disease • Signs and symptoms leading to investigations of thyroid disease • Specific laboratory tests describing thyroid function including : o TSH o Total and free T3 and T4 and Free Thyroid Index o Calcitonin o Thyroid peroxidase antibodies o Thyroglobulin and thyroglobulin antibody o Thyroid Stimulating Hormone receptor antibody • Diagnostic imaging performed and any prior imaging supporting the disease history • Pathologic examinations • Treatment given for the condition • Risk factors identified • Family history of thyroid disease	Yes (only events that require thyroi-dectomy *and/or thyroid neoplasms*)
Injection site reaction	*All events of injection site reactions must be reported.*	*All events of injection site reactions must be reported as an AE and on a specific injection site reaction event form in the eCRF. The following information must be obtained:* • *Type of reaction – local or generalised* • *Symptoms associated with the event* • *Treatment given for the event* • *Association with the trial product(s)* • *Risk factors associated with the event*	*No*

Protocol Amendment

no 3
to Protocol, final version 2.0
dated 13 August 2015

Trial ID:NN9536-4153

Investigation of safety and efficacy of once-daily semaglutide in obese subjects without diabetes mellitus

A 52-week, randomised, double-blind, placebo-controlled, nine-armed, parallel group, multi-centre, multinational trial with liraglutide 3.0 mg as active comparator

Trial phase: 2

Applicable to all countries

Amendment originator:

[redacted]

Table of Contents

1 Introduction including rationale for the protocol amendment

This amendment will serve to address comments raised by the US Food and Drug Administration (FDA) during the Investigational New Drug (IND) review and to clarify some trial procedures.

In this protocol amendment:

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

The protocol has been amended including the following major changes.

1.1 Trial title and trial design

The trial title and trial design has been changed from a "nine-armed" to a "sixteen-armed" trial since operationally there are 16 arms in the trial design.

1.2 Statistical considerations

In addition to the pooling of placebo data, a pairwise comparison between each semaglutide dosing regimen and the corresponding placebo dosing regimen will be conducted. The imputation model is changed to be consistent with the analysis model across all endpoints. Different numbers of imputations will be used to establish stable results. According to recent developments, estimands are defined and sensitivity analyses are updated.

The following has been updated:

- Keep primary statistical analysis including pooled placebo arms and add supportive statistical analysis of primary endpoint including eight separate placebo arms
- Descriptive statistics/plots for both pooled and eight separate placebo arms

In order to evaluate the intention-to-treat (ITT) estimand, the following has been updated:

- Definition of effectiveness (and efficacy) estimand
- Keep primary imputation approach, update the imputation model and add a note of the number of imputations
- Replace sensitivity analyses with more appropriate approaches including the suggestions from FDA (McEvoy 2015)

1.3 Safety endpoints

It has been clarified that safety endpoints including AE and hypoglycaemic episodes will be evaluated using the on-treatment observation period and the in-trial observation period. Definitions of "in-trial" and "on-treatment" observation periods are added in the statistical section.

1.4 Definition of hypoglycaemia episodes

It has been clarified that hypoglycaemic episodes will be tabulated according to full ADA classifications of hypoglycaemic episodes.

1.5 Thyroidectomy

Thyroid neoplasms are already adjudicated centrally for this trial and the number of thyroid neoplasm cases is expected to be very low. Therefore all trial procedures related to collection and central reading of thyroid pathology slides are removed.

1.6 Retention of clinical trial documentation

Retention of site files has been changed to 15 years from 25 years to comply with updated Novo Nordisk Standard Operating Procedure.

1.7 Other change

Missing table note 8 in the flow chart is added to “Semaglutide plasma concentration”.

2 Changes

2.1 Section 1 Summary

Trial design

This is a 52-week, randomised, double-blind, placebo-controlled, ~~nine-armed~~ *sixteen-armed*, parallel group, multi-centre, multinational trial comparing once-daily subcutaneous administration of semaglutide in five different doses (ranging from 0.05 mg/day to 0.4 mg/day) with placebo in obese subjects without diabetes mellitus. Liraglutide 3.0 mg/day is included as an active comparator. The trial is double-blinded between active and placebo treatment. The total trial duration for the individual subject will be approximately 60 weeks.

Subjects will be randomised in a balanced manner (6:1 active:placebo) for each of the 8 active treatment arms. ~~The placebo arms are considered as one, giving a total of 9 arms.~~

2.2 Section 2 Flow chart

Table note 8 is added.

OTHER ASSESSEMENTS																						
Semaglutide plasma concentration[8, 9] (8.6.1)				X	X	X		X		X				X			X			X	X	

[8)] Subjects must be instructed to withhold their trial product dose in the morning until blood sampling has been performed at the visit. This is not applicable for subjects that have discontinued trial product. Samples taken at the follow-up visit (visit 21) must be taken fasting (as a minimum by only having consumed water for at least 2 hours).

2.3 Section 4.2.2 Secondary endpoints

Supportive secondary safety endpoints

- Number of ~~treatment-emergent~~ AEs during the trial
- Number of ~~treatment-emergent severe or blood glucose confirmed symptomatic~~ hypoglycaemic episodes during the trial
- Number of new and ongoing ~~treatment-emergent~~ nausea, vomiting, diarrhoea and constipation events by week
- Nausea:
  - Individual scores of nausea questionnaire
  - Severity by numeric rating scale (NRS) score

The safety endpoints above will be evaluated using the on-treatment observation period and the in-trial observation period based on the safety analysis set (see definition of observation periods in section 17.4.2)

2.4 Section 5.1 Type of trial

This is a 52-week, randomised, double-blind, placebo-controlled, ~~nine-armed~~ *sixteen-armed*, parallel group, multi-centre, multinational trial comparing once-daily subcutaneous administration of semaglutide in five different doses (ranging from 0.05 mg/day to 0.4 mg/day) with placebo in obese subjects without diabetes mellitus. Once-daily administration of two doses of semaglutide (0.3 mg/day and 0.4 mg/day) will be tested in a fast escalation regimen to investigate the effect of a different regimen on efficacy, safety and tolerability. Additionally, liraglutide 3.0 mg/day is included as an active comparator. The total trial duration for the individual subjects will be approximately 60 weeks. The trial includes a 1-week screening period, followed by a 52-week treatment period and a follow-up visit after 59 weeks.

2.5 Section 5.2 Rationale for trial design

The present trial is a 52-week, randomised, double-blind, placebo-controlled, ~~nine-armed~~ *sixteen-armed*, parallel group, multi-centre, multinational trial. To avoid bias in the assessment of the different semaglutide doses and the liraglutide dose, the trial will be double-blinded within treatment arm to placebo. The treatment arms will not be blinded towards each other because of different dose escalations, different pens, and different target doses.

2.6 Section 8.3 Lab assessments

Samples, including samples for ~~genetic testing and~~ specific safety assessments, will be destroyed after further analysis on an on-going basis or at the latest at the completion of the clinical trial report (CTR).

2.7 Section 8.7.2 Thyroidectomy

~~Subjects scheduled for thyroidectomy will be asked to inform the investigator prior to the operation.~~

~~**Thyroidectomy pathology slides**~~

~~In case a subject undergoes a thyroidectomy (partial or total) for any reason during the trial or after the trial secondary to an event reported during the trial, pathology slides of the thyroid tissue will be centrally reviewed in addition to the routine examination at the site level. A set of pathology slides, routinely made after thyroidectomies by the pathology laboratory of the hospital where the operation was performed, must be sent for a second reading with evaluation by a pathologist with expertise in thyroid and C-cell pathology, who will be blinded to both trial treatment and site diagnosis. Once the samples are re-examined they will be sent back to the site laboratory. Both the site pathology report and the central pathology report will be reviewed by an external independent event adjudication committee (EAC), see section 12.7.2. However, reports for thyroidectomies performed after the trial secondary to an event reported during the trial will not be reviewed by the EAC nor will the reports be part of the clinical trial database.~~

~~Thyroid tissue sample collection in case of thyroidectomy~~

~~Subjects to undergo thyroidectomy will in addition be asked to consent to have a small sample of the removed thyroid tissue collected for testing of RET Y1062 phosphorylation in the thyroid C-cells. This is only applicable if C-cell pathology is confirmed (i.e., hyperplastic or neoplastic thyroid C-cells) confirmed by the EAC, and only if allowed by local law. The tissue sample will be destroyed after examination.~~

~~FOR ISRAEL ONLY:~~ ~~The RET Y1062 phosphorylation and genetic testing will not be performed for subjects in Israel.~~

~~Genetic testing in case of a confirmed C-cell pathology~~

~~Subjects scheduled for thyroidectomy will be asked to consent to be tested (blood sample) to identify germline RET gene mutations associated with multiple endocrine neoplasia syndrome type 2 (MEN2). This RET gene mutation detection will be conducted in subjects with C-cell pathology (i.e., hyperplastic or neoplastic thyroid C-cells) confirmed by the EAC. Genetic testing will only be performed if allowed by local law and if the subject chooses to consent to it.~~

2.8 Section 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 and unblinding of the trial.

Definition of Estimands

Effectiveness estimand

The primary estimand is an effectiveness estimand (de facto) quantifying the average treatment effect of once-daily semaglutide relative to placebo and liraglutide 3.0 mg after 52 weeks, as add-on to nutritional and physical activity counselling, in all randomised subjects regardless of adherence to treatment.

Efficacy estimand

In addition, an efficacy estimand (de jure) is quantifying the average treatment effect of once-daily semaglutide relative to placebo and liraglutide 3.0 mg after 52 weeks, as add-on to nutritional and physical activity counselling, if all randomised subjects had adhered to the assigned treatment regimen for the entire planned duration of the trial.

Results from the statistical analysis will generally be presented by treatment differences with two-sided 95% confidence intervals.

The full analysis set (FAS) will be used in the analysis of efficacy endpoints. For safety endpoints the safety analysis set will be used.

The 8 different placebo arms will be pooled into one placebo treatment arm in the main analyses. This pooling assumes that there is no substantial effect of different placebo volumes or different dose escalation on the efficacy and safety endpoints. The validity of this assumption will be checked for the primary endpoint by plotting mean data for the 8 placebo arms separately, and by evaluating summaries of ~~treatment-emergent~~ adverse events for each placebo arm. ~~Should the placebo arms demonstrate substantial differences, appropriate sensitivity analysis will be included. The description of planned analysis given here assumes that all 8 placebo arms will be pooled into one placebo arm.~~

For the statistical analysis of the primary endpoint, comparisons between each semaglutide dose/escalation arm, the liraglutide arm and their corresponding placebo arms will be performed in addition to comparisons with the pooled placebo arm. ~~In general, the statistical analysis will be made by one statistical model estimation on the full dataset including all treatment arms.~~ Statistical inference and data presentations will be separated into two parts. Part A concerns identifying the optimal dose and includes inference for the liraglutide arm, the semaglutide arms with dose escalation every fourth week*, the corresponding placebo arms* and the pool of the placebo arms. Part B concerns identifying the optimal dose escalation regime and includes inference for the semaglutide arms with dose escalation every second week, the corresponding semaglutide arms (with regards to dose) with dose escalation every fourth week*, the corresponding placebo arms* and the pool of the placebo arms.

Descriptive statistics for all efficacy and safety endpoints are always presented for each of the randomised treatment arms and the pool of the placebo arms. Unless otherwise specified, the following sections describe the planned analyses using one pooled placebo arm.

The baseline value will be defined as the last measured and available value from visit 1 and 2. ~~In the case of missing data no general imputation will be performed for the analyses, unless otherwise specified.~~
Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

2.8.1 Section 17.1 Sample size calculation

For the primary endpoint change in body weight after 52 weeks of treatment, a difference (semaglutide minus placebo) of 9.5% is expected for completers *(12%* in the optimal dose group *for semaglutide vs. 2.5% in placebo)*. For the withdrawn subjects, who are anticipated to constitute up to 40% of the total trial population, the treatment difference (semaglutide minus placebo) is assumed to be 0% giving an overall expected treatment difference of *5.7*~~*8.2*~~*% (8.2% in semaglutide vs. 2.5% in placebo).* The standard deviation will also be increased using the MI approach. The standard deviation in the final data is assumed to be up to 8.*4*~~*2*~~% *(8.4% in semaglutide vs. 7.0% in*

placebo). A standard deviation of *up to* 8.*4*~~2~~% together with an expected difference of *5.7*~~8.2~~% results in a power of more than 99%*, which is not corrected for multiple comparisons between different semaglutide arms and placebo*.

2.8.2 Section 17.3 Primary endpoint

The primary endpoint, relative change from baseline in body weight (%) at 52 weeks, will be investigated using the following main analysis to compare between the randomised treatment arms using a multiple imputation (MI) analysis. The main analysis of the primary endpoint will also be referred to as the primary analysis as opposed to the sensitivity analysis of the primary endpoint. Week 52 data from subjects discontinued from trial product that return for visit 22x will be included. In this pattern mixture model approach withdrawn subjects without visit 22x from all treatment arms are assumed to respond as if treated with placebo for the entire trial. Multiple copies (100 copies) of the full dataset will be generated by imputing missing values (~~change from baseline in body weight (%)~~ *body weight (kg)* at 52 weeks) based on estimated parameters for the placebo group. This will be done as follows:

- In the first step, 100 copies of the dataset will be generated
- In the second step, an ~~enriched~~ analysis of covariance *(ANCOVA)* model with ~~treatment~~ region and sex as factors and baseline body weight~~, waist circumference, age and HbA_{1c}~~ as covariates is fitted to *body weight (kg)* ~~the change from baseline in body weight (%)~~ at 52 weeks *using only placebo subjects with non-missing body weight measurements at baseline and week 52* ~~for the completers only~~
- In the third step, for each of the 100 copies of the dataset the estimated parameters, and their variances, from this model are used to impute missing values at 52 weeks for subjects in all treatment arms, based on their region, sex~~,~~ *and* body weight~~, waist circumference, age and HbA_{1c}~~ at baseline ~~with treatment equal to placebo~~ from the ~~enriched~~ model in step two
- For each of the 100 complete data sets, the change from baseline in body weight (%) at 52 weeks is analysed using an *ANCOVA* ~~analysis of variance~~ model with treatment *(nine classes including one for pooled placebo)*, region, and sex as factors, and baseline body weight as a covariate
- The estimates and standard deviations for the 100 data sets are pooled into one estimate and associated standard deviation using Rubin's formula:

$$m_{MI} = \frac{1}{100}\sum_{i=1}^{100} m_i,\ SD_{MI} = \sqrt{\frac{1}{100}\sum_{i=1}^{100} SD_i^2 + \left(1+\frac{1}{100}\right)\left(\frac{1}{100-1}\right)\sum_{i=1}^{100}(m_i - m_{MI})^2},$$

where m_i and SD_i are the estimated means and standard deviations for each of the 100 copies of the dataset, and m_{MI}, SD_{MI} are the pooled MI estimates.

- From m_{MI} and SD_{MI}, the 95% confidence interval for the treatment differences and the associated p-value are calculated

If 100 copies are not sufficient to establish stable results, a higher number will be used. The multiple imputations will be generated using Novo Nordisk trial number 95364153 as seed number.

Pairwise treatment differences between semaglutide doses and placebo, liraglutide and placebo, different semaglutide doses, and between semaglutide doses and liraglutide at week 52 will be estimated from the model and 95% confidence intervals will be calculated.

In part A, the comparisons of semaglutide doses vs. placebo will have the family wise type I error protected in the strong sense. This will be achieved by using Dunnett's method in which simultaneous confidence intervals will be calculated. A significance level of 5% will be applied. Further, the focus of this part of the trial is to examine the dose response relationship. In part B, no multiplicity adjustment will be performed.

The dose of semaglutide providing a weight loss corresponding to liraglutide 3.0 mg will be estimated by fitting a linear approximation to the log dose vs. estimated means for the semaglutide doses and compare this to the estimated mean for liraglutide 3.0 mg. This analysis will be based on the estimated means and the covariance matrix for the means obtained from the MI analysis. Fieller's method will be used to calculate 95% confidence limits for the estimated dose of semaglutide corresponding to liraglutide 3.0 mg. If a linear approximation does not describe the log(dose)-response relationship well, a different approximation (e.g. a sigmoidal curve) may be investigated.

The MI method does not assume missing at random. It assumes that withdrawn subjects and subjects with missing endpoint at week 52 in the placebo arm have a response similar to the completers in the placebo arm given similar baseline characteristics. In the active treatment arms, the assumption is that withdrawn subjects and subjects with missing endpoint at week 52 behave as if they have been in the placebo arm during entire trial regardless of the time of discontinuation. In this way the assumptions are differential and conservative for estimating the treatment effect. ~~The estimate in the primary analysis can be said to be an intention to treat (ITT) estimand or an effectiveness estimand in all randomised subjects of the add-on effect of semaglutide to nutritional and physical activity counselling.~~

Based on previous trials in weight management the withdrawal rate from randomised treatment is expected to be up to 40%. Semaglutide treatment has in previous (T2DM) trials been effective with regard to weight loss, and this should reduce the number of withdrawals due to ineffective therapy. Based on previous experience, a higher rate of withdrawal of consent is expected in the placebo group compared to active treatment. This difference may be due to lack of efficacy with placebo treatment. A higher withdrawal rate due to gastrointestinal adverse events is expected in the high dose semaglutide treatment arms and the liraglutide 3.0 mg arm compared to placebo. Apart from this, missing data due to adverse events (AEs) is expected to be similar across groups. This

emphasises the validity of the primary analysis as a conservative analysis of the treatment effect of semaglutide.

The main analysis of the primary endpoint using the pool of the placebo arms will be repeated using the 8 different placebo arms. This supportive analysis includes comparisons between each semaglutide dose/escalation arm, the liraglutide arm and their corresponding placebo arms. As in the primary analysis, week 52 data from subjects discontinued from trial product that return for visit 22x will be included, and withdrawn subjects without visit 22x from all treatment arms are assumed to respond as if treated with placebo. In contrast to the primary analysis, a single imputation (SI) approach instead of MI will be used to handle missing body weight measurements at week 52, where subjects in each active treatment arm are imputed with the average of the corresponding placebo arm.

Pairwise treatment differences between each semaglutide dose/escalation arm, the liraglutide arm and their corresponding placebo arms at week 52 will be estimated from the model and the 95% confidence interval and associated p-value will be calculated.

For the supportive analysis, a dose-response analysis similar as for the primary analysis will be performed.

The sensitivity of the results with regard to different assumptions for missing data from withdrawn subjects will be investigated by plotting weight loss data for withdrawn subjects and compare this with plots of weight loss data for subjects completing 52 weeks of treatment. Further, for subjects that discontinue treatment but provide data at the week 52 visit (22x) plots will compare weight loss at last visit on treatment with weight loss at visit 22x. In addition, several sensitivity analyses will be performed where different assumptions are made with regard to withdrawn subjects.

The following sensitivity analyses will be performed *to address the effectiveness estimand*:

- *An ANCOVA model based on a multiple imputation approach as described by McEvoy[40], where missing body weight measurements at week 52 for discontinuing subjects are imputed by sampling from values obtained from retrieved subjects in each randomisation arm and according to the timing (monthly) of last available observation on randomised treatment (LAO-OT). Missing body weight measurements at week 52 for subjects on treatment are imputed by sampling from subjects completing treatment in the relevant randomisation arm. Thus, the imputation model for each randomised treatment arm and timing of LAO-OT is a linear regression of body weight (kg) at week 52 on the factors and covariates used in the primary MI approach with no interactions and including LAO-OT of body weight as covariate. If timing by month is too restricted, quarters, half-years, or excluding timing will be used.*

The first sensitivity analysis assumes that withdrawn subjects, who return for visit 22x, are representative for subjects, who withdrew from the same randomised treatment but are not retrieved at week 52. Similarly, it is assumed that subjects, who complete the randomised treatment, are representative for subjects, who were randomised to the same treatment arm and have a missing week 52 body weight measurement due to other reasons than withdrawal from randomised treatment.

- *A weighted ANCOVA model where returning treatment discontinuing subjects are up-weighted relative to their proportion of all withdrawn subjects to account for the subjects not returning for assessments at week 52[40]. Similar subjects with measurements at week 52 on treatment are up-weighted relative to their proportion of all subjects who completed treatment with trial product. The up-weighing is done by randomisation arm and the timing of LAO-OT. Subjects who are missing the body weight measurement at week 52 are assigned a weight of 0.*

The second sensitivity analysis is based on the same assumptions as the first sensitivity analysis. In contrast, this weighted analysis can be carried out in situations where it is not possible to realise multiple imputation according to McEvoy[40] due to e.g. too few available body weight measurements from retrieved subjects or the small size of the eight separate placebo arms.

- *An ANCOVA model is based on a single imputation approach as done by Sacks[41]. Missing body weight measurements at week 52 for withdrawn subjects are imputed using a weight regain rate of 0.3 kg/month after last available observation (LAO). Change from baseline is truncated whenever the extrapolation would lead to a positive weight gain relative to baseline. When a subject's body weight at discontinuation represented a gain in weight relative to baseline, no additional gain will be imputed, but the unfavourable gain is carried forward to week 52. Missing body weight measurements at week 52 for subjects on treatment will be imputed using LAO. The weight regain imputation will be done for all randomised arms. Additionally, a version where only the active arms use the regain rate while the placebo arms use LAO (corresponding to a weight regain rate of 0 kg/month) will be performed.*

The third sensitivity analysis assumes that subjects, who withdraw from randomised active or placebo treatment, lose any treatment effect linearly after discontinuation. In the additional version subjects discontinuing placebo treatment are assumed to experience no change in treatment effect since LAO.

- *An ANCOVA model is based on a tipping point approach. In a similar manner as above for a range of weight regain rates (starting from 0.1 kg/month and in intervals of 0.1 kg/month) for subjects in the active treatment arms, who discontinued treatment with trial product but*

were not retrieved at week 52, will be used to define a tipping point in which superiority of semaglutide disappears. In this analysis, subjects on placebo will be imputed by LAO.

The fourth sensitivity analysis assumes that subjects, who withdraw from randomised active treatment, lose any treatment effect linearly after discontinuation and that subjects, who withdraw from randomised placebo treatment, experience no change in treatment effect since LAO.

Dose-response analysis will be repeated based on estimates derived from the first three sensitivity analyses.

~~*1.* An analysis of covariance (ANCOVA) model comparing the change from baseline in body weight (%) at 52 weeks between treatments. Only on-treatment data will be included. Missing data at week 52 will be imputed from on-treatment data using the last observation carried forward (LOCF) method. The ANCOVA model will include treatment, region, and sex as factors, and baseline body weight as a covariate. This analysis corresponds to the primary analysis approach used in the liraglutide weight management development programme.~~

~~*2.* An analysis of covariance (ANCOVA) model comparing the change from baseline in body weight (%) at 52 weeks between treatments. All available data will be included. Missing data at week 52 will be imputed using the subject's baseline observed weight carried forward (BOCF). The ANCOVA model will include treatment, region, and sex as factors, and baseline body weight as a covariate. This is a conservative analysis which will underestimate the differences between semaglutide/liraglutide and placebo.~~

The following model will be performed to address the efficacy estimand:

~~3.~~ A mixed model for repeated measurements (MMRM) comparing the change from baseline in body weight (%) at 52 weeks between treatments. All post randomisation measurements at planned visits up to week 52 and obtained before withdrawal from treatment will be included in the model as dependent variables. Treatment, region, and sex will be included as fixed factors, and the baseline body weight will be included as a covariate. All factors and the covariate will be nested under the factor visit. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. Subjects without post randomisation measurements of weight will be excluded from the analysis.

The MMRM model assumes that withdrawn subjects, had they completed the trial, would not have behaved differently than completing subjects from the same treatment arm with the same baseline characteristic and change in body weight at time of withdrawal.

~~4. The primary analysis model (the MI) will be applied to data from subjects attending the end-of-treatment visit in fasting state. Any non-fasting measurements will be treated as missing measurements.~~

5. An analysis of covariance (ANCOVA) model comparing the change from baseline in body weight (%) at 52 weeks between treatments including only subjects with data for week 52 on treatment (a completer analysis). The ANCOVA model will include treatment, region, and sex as factors, and baseline body weight as a covariate.

6. The primary analysis model (MI) will be applied where data from all withdrawn subjects are imputed (i.e. data from visit 22x is disregarded).

Further sensitivity analysis may be added at time of reporting as deemed relevant.

The ANCOVA model with LOCF assumes that post treatment discontinuation, the body weight is on average stable in both treatment arms. This assumption can be evaluated over the 7 weeks follow-up period in withdrawn subjects and in completing subjects. If the assumption holds, the treatment effect (effectiveness estimand) in each arm and the treatment difference can be estimated from this analysis unbiased. If the withdrawal and the development in both arms are similar, the treatment difference can be estimated from this analysis unbiased. If the development in body weight after treatment discontinuations differs between active and placebo, this analysis might provide an optimistic or over-conservative estimate, depending on the actual circumstances. The analysis is included to be able to compare the results with legacy obesity programs, where this analysis was the main analysis of the primary endpoints.

The ANCOVA model with BOCF assumes that post treatment discontinuation subjects returns to a body weight in the proximity of their baseline body weight regardless of the timing of discontinuation. This analysis is expected to provide a conservative estimate (effectiveness estimand) of the treatment effect (in each arm). The impact of this assumption on the treatment difference depends on withdrawal pattern over time and development of body weight post treatment discontinuation and reason for withdrawal. The analysis is typically expected to provide a conservative estimate of the treatment difference (effectiveness estimand).

The MMRM model assumes that withdrawn subjects, had they completed the trial, would not have behaved differently than completing subjects from the same treatment arm with the same baseline characteristic and change in body weight at time of withdrawal. This analysis estimates the treatment effect and difference had all subjects stayed on the randomised treatment (efficacy estimand).

The MI model on fasting values examines the influence of not being fasting at the end-of-treatment visit. This analysis is expected to give similar treatment differences as the main analyses and estimate the same estimand.

The ANCOVA analysis in completers is expected to give more positive results than the primary analysis. However, this analysis has its own clinical interpretation and will serve as a benchmark

~~and provide an estimate of the efficacy estimand in the population that tolerate the trial product and endure the diet and exercise counselling program.~~

~~The MI model disregarding visit 22x data examine the influence of data from withdrawn subjects returning at week 52 on the main analysis. It is difficult to postulate expectation on the results from this sensitivity analysis. The analysis estimates the same estimand as the primary analysis.~~

2.8.3 Section 17.4.1 Efficacy endpoints

Endpoints addressing glucose metabolism

Change from baseline to 52 weeks in:

- HbA1c
- FBG
- ~~Shift in g~~*G*lycaemic category (normoglycaemia, pre-diabetes, T2DM)

2.8.4 Section 17.4.2 Safety endpoints

All adverse events, hypoglycaemic episodes as well as nausea, vomiting, diarrhoea and constipation events will be classified and analysed as 'in-trial' and 'on-treatment'.

In-trial is defined as the observation period from randomisation to last contact with trial site. On-treatment is defined as the observation period from first trial product administration to last trial product administration with a 7 weeks ascertainment window.

The endpoint "Number of ~~treatment-emergent~~ adverse events during the trial" will be extensively described using descriptive statistics and listings.

All adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). ~~An adverse event will be defined as treatment emergent if the onset of the adverse event is on or after the first day of trial product administration, and no later than whatever comes first of a) last drug date plus seven weeks or b) follow-up visit, or c) last study visit.~~

~~Treatment-emergent a~~*A*dverse events will be summarised by system organ class, preferred term, seriousness, severity and relation to trial product.

Endpoint addressing hypoglycaemic episodes:

The endpoint "Number of ~~treatment-emergent severe or blood glucose-confirmed symptomatic~~ hypoglycaemic *episodes* ~~events~~" will be tabulated according to the *ADA* definition below. ~~The remainder of the low blood glucose events (asymptomatic hypoglycaemic events) will be tabulated as well.~~

~~Given that the trial population does not have T2DM at inclusion, the risk of developing hypoglycaemia is considered low and hence no blood glucose monitoring will be instituted. However, in case of severe hypoglycaemia where third party assistance is needed or in case of a low blood glucose value detected by scheduled blood sampling accompanied by relevant symptoms, the hypoglycaemic episode will qualify for the endpoint analysis.~~

ADA Classification of hypoglycaemic *episodes* ~~*events*~~

~~Treatment-emergent: hypoglycaemic episodes will be defined as treatment-emergent if the onset of the episode occurs *within the on-treatment observation period* on or after the first day of trial product administration, and no later than whatever comes first of a) last drug date plus seven weeks or b) follow-up visit, or c) last study visit~~.

The hypoglycaemic episodes will be categorised based on the ADA classification[33] of hypoglycaemia:

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- 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).
- *Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia 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).*

Given that the trial population does not have T2DM at inclusion, the risk of developing hypoglycaemia is considered low and hence no blood glucose monitoring will be instituted. However, in case of severe hypoglycaemia where third party assistance is needed or in case of a low blood glucose value detected by scheduled blood sampling accompanied by relevant symptoms, the hypoglycaemic episode will qualify for the endpoint analysis.

Treatment-emergent: hypoglycaemic episodes will be defined as treatment-emergent if the onset of the episode occurs within the on-treatment observation period. ~~on or after the first day of trial~~

~~product administration, and no later than whatever comes first of a) last drug date plus seven weeks or b) follow-up visit, or c) last study visit~~

Safety endpoints continued

The endpoint "Number of new and ongoing ~~treatment-emergent~~ nausea, vomiting, diarrhoea and constipation events by week" will be summarised by week.

2.9 Section 18.2 Informed consent

~~In case a subject undergoes a thyroidectomy a separate informed consent will be obtained for collection of thyroid tissue sample and genetic testing (see section 8.7.2).~~

2.10 Section 24.1 Retention of clinical trial documentation

The files from the trial site/institution must be retained for *15* ~~25~~ years after the completion of the trial, or longer if required by local regulations or Novo Nordisk. In any case, trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.