Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03856047
Sponsor trial ID:	NN9838-4433
Official title of study:	Investigation of safety and efficacy of NNC0174-0833 for weight management – a dose finding trial
Document date:	18 September 2020

16.1.1 Protocol and protocol amendments

List of contents

Protocol

Protocol title: Investigation of safety and efficacy of NNC0174-0833 for weight management – a dose finding trial

Substance number: NNC0174-0833

Universal Trial Number: U1111-1214-0429

EUdraCT Number: 2018-001945-14

Redacted protocol
Includes redaction of personal identifiable information only.

Trial phase: 2

In the following, Novo Nordisk A/S and its affiliates will be stated as "Novo Nordisk".

Table of Contents

1 Synopsis

Rationale:

The prevalence of obesity has been increasing during the last 30 years[1] and globally, more than 600 million people have obesity[2]. Obesity is associated with an increased risk of developing a variety of comorbidities, reduced quality of life including physical function[3-5] and increased mortality[6, 7].

Pharmacotherapy may serve as a valuable adjunct to lifestyle intervention for individuals with obesity in order to achieve and sustain a clinically relevant weight loss, to improve comorbid conditions and to facilitate a healthier lifestyle. Few weight management medications are currently available and there is a need for more safe and effective therapeutic options for the treatment of obesity, especially treatments that also target weight maintenance and the treatment and prevention of comorbidities[8-14].

NNC0174-0833 is a long-acting amylin analogue designed for weight management treatment.

The present trial is designed to determine the dose of NNC0174-0833, which is optimal for weight management. Different doses of NNC0174-0833 will be compared against placebo and liraglutide 3.0 mg. Liraglutide 3.0 mg is included to enable comparisons of NNC0174-0833 with a weight management product (Saxenda®) that is approved in several countries.

Objectives and endpoints:

Primary objective
To compare the dose-response of increasing doses of NNC0174-0833 once weekly (OW) versus placebo and versus liraglutide 3.0 mg once daily (OD) on body weight, in subjects with overweight or obesity, when added as an adjunct to a reduced-calorie diet and increased physical activity.

Secondary objectives
To compare the effect of NNC0174-0833 OW versus placebo and versus liraglutide 3.0 mg OD, when added as an adjunct to a reduced-calorie diet and increased physical activity, on:

- Change in waist circumference
- Change in glycaemic parameters
- Safety and tolerability

Primary estimand
The estimand will quantify the average treatment effect of NNC0174-0833 relative to placebo and liraglutide 3.0 mg after 26 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects had they remained on their randomised treatment for the entire planned duration of the trial and not started any other weight loss intervention ('efficacy'/'hypothetical' estimand).

Primary endpoint
Change from randomisation at week 0 to week 26 in body weight (%).

Key supportive secondary endpoints
- Subjects who after 26 weeks achieve (yes/no):
  - Body weight reduction ≥ 5% from randomisation
- Change from randomisation at week 0 to week 26 in:
  - Glycated haemoglobin (HbA_{1c}) (%-point, mmol/mol)
- Number of treatment emergent adverse events (TEAEs) from randomisation at week 0 to week 32 ('end of trial')

Overall design:

This is a 26-week, randomised, double blind placebo-controlled, twelve-armed, parallel group, multi-centre, multi-national dose finding trial comparing five doses (0.3, 0.6, 1.2, 2.4 and 4.5 mg OW) of NNC0174-0833 with placebo and liraglutide 3.0 mg OD when added as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity.

Key inclusion criteria
- ≥ 18 years at the time of signing the informed consent
- Female subject of non-childbearing potential[1]
  or
  Male subject who is surgically sterilised (vasectomy) or who is willing to use adequate contraceptive methods (as required by local regulation or practice) throughout the trial (until 'end of trial')
- Body mass index (BMI) ≥ 30.0 kg/m^2 or BMI ≥ 27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension or dyslipidaemia (to be assessed at the investigator's discretion)

Key exclusion criteria
- HbA_{1c} ≥ 48 mmol/mol (6.5%) as measured by the central laboratory at screening
- A self-reported change in body weight > 5 kg (11 lbs) within 90 days prior to screening irrespective of medical records

[1] (see Appendix 5 for the definition of a woman of childbearing potential (WOCBP))

Number of subjects:

Approximately 933 subjects will be screened to achieve a planned 700 subjects randomly assigned to trial product.

Treatment groups and duration:

Eligible subjects will, at visit 2, be randomised to one of the five NNC0174-0833 treatment arms (0.3, 0.6, 1.2, 2.4 and 4.5 mg), to the liraglutide 3.0 mg treatment arm or to one of the volume matched placebo arms. Subjects will be randomised 6:1 between the active treatment arms and the placebo arms.

The trial includes a screening visit to assess subject's eligibility. At visit 2 (randomisation) eligible subjects will enter an up to 6-week dose escalation period, depending on which arm the subject is randomised to, followed by a maintenance period until end of treatment (week 26). To assess subject safety after the trial product has been washed out a follow-up visit ('end of trial') is scheduled 6 weeks after end of treatment. The total duration for each subject will be approximately 33 weeks.

The following trial products are supplied by Novo Nordisk A/S:

- NNC0174-0833 A, 10 mg/ml, solution for injection, NovoPen® 4
- Placebo NNC0174-0833 A, solution for injection, NovoPen® 4
- Liraglutide 6 mg/ml, solution for injection, 3 ml PDS290 pen-injector
- Liraglutide placebo, solution for injection, 3 ml PDS290 pen-injector

2 Flowchart

	Screening	Randomisation	Dose escalation/ maintenance			Maintenance					End of treatment	End of trial
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	14	18	22	26	32
Visit Window (Days)	-7	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
Attend visit fasting		X				X			X		X	
Informed consent and demography[a] (Appendix 3)	X											
Barriers and motivation interview (9)	X											
Inclusion, exclusion and randomisation criteria (6)	X	X										
Medical history/concomitant illness (9.4)	X											
Weight history (9)		X										
Concomitant medication (7.7)	X	X	X	X	X	X	X	X	X	X	X	X
Tobacco use[b] (9.4)	X											
Height (9.1.1)	X											
Body weight (9.1.1)	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference (9.1.1)		X		X		X		X		X	X	
Laboratory assessments (Appendix 2)	X	X[c]		X[c]		X[c]		X[c]	X		X[c]	X[c,d]
Urine pregnancy test (9.4.4, Appendix 2)[e]	X	X		X		X	X	X	X	X	X	X
Physical examination (9.4.1)	X										X	
Vital signs (9.4.2)	X	X	X	X	X	X	X	X	X	X	X	X
ECG (9.4.3)	X										X	
Ambulatory blood pressure monitoring (9.4.8)	X										X	
Clinical outcome assessments (9.1.3, 9.4.7)		X		X		X		X	X	X	X	
Criteria for discontinuation of trial product (8.1)			X	X	X	X	X	X	X	X		
Breast/colon neoplasms follow-up (9.4)											X	X

	Scree-ning	Rando-misation	Dose escalation/ maintenance			Maintenance					End of treatment	End of trial
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	14	18	22	26	32
Visit Window (Days)	-7	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
Attend visit fasting		X				X			X		X	
REMINDERS												
Adverse event incl. technical complaints (9.2, Appendix 4, Appendix 6)	X	X	X	X	X	X	X	X	X	X	X	X
Hand out and instruct in diet and physical activity diary (7.1.2)		X	X	X	X	X	X	X	X	X		
Diet and physical activity counselling (7.1.2)		X		X		X	X	X	X	X	X	
Hand out instructions for ambulatory blood pressure monitoring device (9.4.8)	X										X	
Collect ambulatory blood pressure monitoring device (9.4.8)		X										X
Hand out directions for use (7.1.1)		X										
Training in trial product, pen-handling (7.1.1)		X	X				X		X			
Hand out and instruct in dosing diary (7.1, 9)		X	X	X	X	X	X	X	X	X		
Collect, review and transcribe dosing diary (7.1, 9)			X	X	X	X	X	X	X	X	X	
Hand out urine collection cup (9.4.4)	X		X		X			X		X		
Collect urine collection cup (9.4.4)		X		X		X			X		X	
Hand out ID card	X											
IWRS subject status session	X	X									X	
Dispensing of trial product		X	X				X		X			
Drug accountability (7.5)		X	X				X		X		X	

[a] Demography consists of date of birth, sex, ethnicity, and race (according to local regulation).

[b] Smoking is defined as smoking at least one cigarette or equivalent daily.

[c] Blood sample for measurement of NNC0174-0833 plasma concentration and antibodies against NNC0174-0833 must be drawn before dosing of trial product. Long venous stasis time should be avoided when sampling for measurement of NNC0174-0833 plasma concentration.

[d] Subjects who have tested positive for antibodies against NNC0174-0833 at visit 12 will be requested to have a follow-up analysis performed 6 months after visit 12 and if the analysis is positive an additional follow-up analysis will be performed 12 months after visit 12.

[e] Only for postmenopausal female subjects who have stopped menstruating within the last 5 years and for female subjects with bilateral tubal ligation.

3 Introduction

3.1 Trial rationale

The prevalence of obesity has been increasing during the last 30 years[1] and globally, more than 600 million people have obesity[2]. Obesity is associated with an increased risk of developing type 2 diabetes (T2D)[15, 16], dyslipidaemia, hypertension[17], cardiovascular disease, obstructive sleep apnoea[18], non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH)[19], urinary incontinence[20], several types of cancers[21], and increased mortality[6, 7]. In addition to these pathophysiologic changes, individuals with obesity experience reduced health-related quality of life including physical function[3-5]. In recognition of the seriousness of obesity, several professional associations and organisations worldwide[9, 22-25] now classify obesity as a disease.

The risk of obesity-related complications and comorbidities increases with increasing body mass index (BMI). A weight loss of 5–10% has been shown to have significant health benefits in individuals with obesity in terms of decreasing the risk of progressing to T2D[26], improving hypertension[27], dyslipidaemia[28] and NAFLD/NASH[29]. In addition, improvements in patient-reported health-related quality of life including physical function have been demonstrated with weight loss[30]. Therefore, achieving and maintaining weight loss in individuals with obesity is crucial. Current standard of care consists of lifestyle counselling including reduced-calorie diets and increased physical activity. However, with this first line treatment for obesity only one in five individuals successfully achieve a significant long-term weight loss[31].

Pharmacotherapy may therefore serve as a valuable adjunct to lifestyle intervention for individuals with obesity in order to achieve and sustain a clinically relevant weight loss, to improve comorbid conditions and to facilitate a healthier lifestyle. Few weight management medications are currently available and there is a need for more effective and safe therapeutic options for the treatment of obesity, especially treatments that also target weight maintenance, and the treatment and prevention of comorbidities[8-14].

To assess whether patient response to NNC0174-0833 therapy can be predicted, various biomarker assessments as well deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) sequencing will be included in the trial.

The present trial is designed to determine the dose of NNC0174-0833, which is optimal for weight management. Different doses of NNC0174-0833 will be compared against placebo and liraglutide 3.0 mg. Liraglutide 3.0 mg is included to enable comparisons of NNC0174-0833 with a weight management product (Saxenda®) that is approved in several countries.

3.2 Background

3.2.1 NNC0174-0833

NNC0174-0833 is currently under development by Novo Nordisk for weight management (project NN9838).

Endogenous amylin is a 37-amino acid neuroendocrine peptide hormone that is co-secreted with insulin by pancreatic beta-cells in response to meals. It affects a number of gastrointestinal (GI) processes including delay of gastric emptying and suppression of post-prandial glucagon release[32]. In addition to this, studies indicate that amylin is also involved in the central regulation of food intake and body weight[33].

NNC0174-0833 is a long-acting amylin analogue designed for weight management treatment. Amino acid substitutions as well as acylation of native amylin were introduced in order to achieve a chemically and physically stable molecule with prolonged action and maintained biological activity.

NNC0174-0833 has agonistic effects on both the amylin receptors and the calcitonin receptor (CtR). NNC0174-0833 potently and dose-dependently reduces food intake in lean rats, dogs, and monkeys. In diet-induced obese rats, NNC0174-0833 efficiently reduces food intake and body weight in a dose-dependent manner.

NNC0174-0833 has been tested in two clinical trials: the first-in-human, single dose trial NN9838-3993 and the multiple-ascending dose trial NN9838-4021. The multiple-ascending dose trial tested daily subcutaneous (s.c.) administration of NNC0174-0833 for 8 weeks and concluded that NNC0174-0833 was considered safe and well tolerated up to 800 µg/day. Decreased appetite, nausea and vomiting were the most frequent adverse events (AEs) seen. The renin-angiotensin-aldosterone system (RAAS) seemed to be activated, apparently related to dose, but the effect was transient and declined after 2 - 4 weeks. Importantly, no increase in heart rate or blood pressure was observed. No effect on ionised or total calcium was observed and there were no symptoms of hypocalcaemia. Pharmacokinetic (PK) data indicated a half-life of approximately 180 hours, supporting once weekly (OW) dosing. Furthermore, the anticipated weight loss was confirmed by dose dependent weight loss around 6 - 8% compared to placebo after 8 weeks of treatment. No clinically relevant effects on glucose metabolism were observed in this non-diabetic population.

A comprehensive review of results from the non-clinical and clinical studies of NNC0174-0833 can be found in the current edition of the investigator's brochure (IB)[34] and any updates hereof.

3.2.2 Trial population

The trial population will consist of subjects with obesity or overweight with weight-related comorbidities. These subjects represent a clinically relevant population for pharmacotherapeutic

weight management as they are at significant risk for weight-related morbidities and mortality, and are likely to benefit from weight reduction.

Subjects with T2D are excluded from the trial. Since some antidiabetic medications influence weight, it is expected that inclusion of subjects with T2D will complicate the assessment of the effect of NNC0174-0833 on weight. Furthermore, weight loss may lead to individual and potentially NNC0174-0833 dose-related adjustment of the concomitant antidiabetic medication, because weight loss may reduce the need for antidiabetic medication. It is planned to study subjects with T2D at a later point in the clinical development program.

Reproductive toxicity studies conducted in rats and mice showed that NNC0174-0833 induced major foetal malformations at human relevant exposures. However, these findings were not seen in rabbits despite a significantly higher exposure level. Mechanistic studies are ongoing which focus on the involvement of rodent specific calcium regulation, however, the mode of action behind the embryo-foetal toxicity in rodents has thus far not been identified. Hence, at present it cannot be excluded that the rodent findings are of human relevance and therefore women of childbearing potential will be excluded from this trial.

3.3 Benefit-risk assessment

3.3.1 Benefits

Subjects will be treated with a regimen anticipated to be better than or equal to the weight management they receive at the time of entry into the trial. It is expected that all subjects (including those randomised to placebo) will benefit from participation in this trial through close contact with the trial site and counselling by a dietician or a similarly qualified healthcare professional, all of which will likely result in improved lifestyle and weight management.

Subjects randomised to treatment with NNC0174-0833 may experience a greater weight loss. Results from the 8-week long phase 1 multiple dose trial (NN9838-4021) demonstrated that treatment with NNC0174-0833, on average, resulted in a clinically relevant weight loss. Subjects randomised to liraglutide 3.0 mg can also expect a clinically relevant weight loss.

3.3.2 Identified risks for NNC0174-0833

These risks are based on data from the two completed phase 1 trials, NN9838-3993 and NN9838-4021.

Gastrointestinal side effects
The most frequently reported side effects in trials NN9838-3993 and NN9838-4021 were decreased appetite, followed by GI side effects like nausea, vomiting and diarrhoea. The frequency and severity of GI AEs were reduced when the target dose level was reached via stepwise escalations of the dose.

3.3.3 Potential risks for NNC0174-0833

These risks are based on the suspicion of an association with NNC0174-0833, however, the relationship has not been confirmed in humans.

Hypocalcaemia
NNC0174-0833 activates the CtR and nonclinical data indicate that hypocalcaemia is a potential risk. Hypocalcaemia has neither been observed in the NN9838-3993 trial nor in the NN9838-4021 trial and no changes to ionised (free) calcium or total calcium were observed in these trials.

Increased urinary volume and electrolyte excretion
Increased urinary volume and excretion of salts have been observed in animals. However, no effect on urinary volume, electrolytes or blood pressure has been observed in the two clinical trials NN9838-3993 and NN9338-4021.

Activation of the renin-angiotensin-aldosterone system
In animal studies, treatment with NNC0174-0833 was associated with increased renin activity and aldosterone. Similar findings have been observed in human studies, although only temporarily in the multiple dose study NN9838-4021 and without any stimulatory effect on blood pressure.

Decreased heart rate
Studies in dogs have shown decreases in heart rate. No signs or symptoms of decreased heart rate were observed in the two clinical trials.

Injection site reaction
Injection site reactions are always a risk when investigating the safety of injectable protein molecules. Only one injection site reaction was reported in NN9838-3993. In NN9838-4021 the number of injection site reactions did not differ between active and placebo arms.

Development of antibodies
NNC0174-0833 has a high homology to native amylin. In trial NN9838-3993, anti-NNC0174-0833 antibodies were detected in two subjects. One subject tested positive for pre-existing antibodies. The other subject was tested positive for anti-NNC0174-0833 antibodies at the follow-up visit, and this was considered treatment related. *In vitro* neutralising effect against NNC0174-0833 was negative. In the multiple dose trial NN9838-4021, 17 of 72 subjects tested positive for anti-NNC0174-0833 antibodies after initiation of treatment, with no clear dose dependency. One case of *in vitro* neutralising antibodies was detected at the follow-up visit (day 99).

Cancer (signal observed with salmon calcitonin)
NNC0174-0833 activates both the calcitonin and the amylin receptors. A meta-analysis of salmon calcitonin trials has shown a small increase in overall cancer risk[35].

Teratogenicity
Embryo-foetal development data indicate that NNC0174-0833 has teratogenic effects in rats and mice. However, teratogenic effects have not been observed in rabbits. There are no data from the use of NNC0174-0833 in pregnant women.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of NNC0174-0833 can be found in the current edition of the IB[34] and any updates hereof.

3.3.4 Identified risks for liraglutide 3.0 mg

Detailed information about the known and expected benefits and risks and reasonably expected AEs of liraglutide 3.0 mg (Saxenda®) can be found in the current edition of the IB[36] and any updates hereof.

4 Objectives and endpoints

4.1 Primary, secondary and exploratory objective(s)

4.1.1 Primary objective

To compare the dose-response of increasing doses of NNC0174-0833 OW versus placebo and versus liraglutide 3.0 mg once daily (OD) on body weight, in subjects with overweight or obesity, when added as an adjunct to a reduced-calorie diet and increased physical activity.

4.1.2 Secondary objectives

To compare the effect of NNC0174-0833 OW versus placebo and versus liraglutide 3.0 mg OD, when added as an adjunct to a reduced-calorie diet and increased physical activity, on:

- Change in waist circumference
- Change in glycaemic parameters
- Safety and tolerability

4.1.3 Exploratory objectives

To compare the effect of NNC0174-0833 OW versus placebo and versus liraglutide 3.0 mg OD, when added as an adjunct to a reduced-calorie diet and increased physical activity, on:

- Biomarkers
- Health-related quality of life

4.2 Primary and secondary estimand

4.2.1 Primary estimand

The estimand will quantify the average treatment effect of NNC0174-0833 relative to placebo and liraglutide 3.0 mg after 26 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects had they remained on their randomised treatment for the entire planned duration of the trial and not started any other weight loss intervention (‘efficacy’/‘hypothetical’ estimand).

4.2.2 Secondary estimand

The estimand will quantify the average treatment effect of NNC0174-0833 relative to placebo and liraglutide 3.0 mg after 26 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment and regardless of starting any other weight loss intervention (‘effectiveness’/‘treatment policy’ estimand).

4.3 Primary endpoint and secondary endpoint(s)

4.3.1 Primary endpoint

Change from randomisation at week 0 to week 26 in body weight (%).

4.3.2 Secondary endpoints

4.3.2.1 Supportive secondary endpoints

Efficacy endpoints

- Subjects who after 26 weeks achieve (yes/no):
  - Body weight reduction ≥ 5% from randomisation
  - Body weight reduction ≥ 10% from randomisation

- Change from randomisation at week 0 to week 26 in:
  - Body weight (kg)
  - Waist circumference (cm)
  - Fasting lipids (mg/dL)
    - Total cholesterol
    - High density lipoprotein (HDL) cholesterol
    - Low density lipoprotein (LDL) cholesterol
    - Very low density lipoprotein (VLDL) cholesterol
    - Triglycerides
  - Glycated haemoglobin (HbA_{1c}) (%-point, mmol/mol)
  - Fasting plasma glucose (FPG) (mg/dL)
  - Fasting insulin (µIU/mL)
  - Homeostatic model assessment of insulin resistance (HOMA-IR) (%-point)
  - Homeostatic model assessment of β-cell function (HOMA-β) (%-point)

Safety endpoints

- Number of treatment emergent adverse events (TEAEs) from randomisation at week 0 to week 32 ('end of trial')
- Number of treatment emergent serious adverse events (SAEs) from randomisation at week 0 to week 32 ('end of trial')
- Occurrence (yes/no) of anti-drug antibodies towards NNC0174-0833 from randomisation at week 0 to week 32 ('end of trial')

- Change from randomisation at week 0 to week 26 in:
  - Systolic blood pressure (mmHg)
  - Diastolic blood pressure (mmHg)

- Mean 24-hour systolic blood pressure (mmHg)
- Mean 24-hour diastolic blood pressure (mmHg)
- Pulse (bpm)
- High sensitivity C-Reactive Protein (hsCRP) (mg/L)
- Plasminogen Activator Inhibitor-1 (PAI-1) activity (mg/L)
- Renin activity (ng/mL/h)
- Aldosterone (ng/dL)

4.3.3 Exploratory endpoints

- Subjects who after 26 weeks achieve (yes/no):
  - Body weight reduction ≥ 15% from randomisation
  - Body weight reduction ≥ 20% from randomisation

- Change from randomisation at week 0 to week 26 in:
  - Endogenous amylin
  - Soluble leptin receptor
  - Leptin
  - Short form-36 (SF-36) v2.0 acute: 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
  - Three Factor Eating Questionnaire Revised 18-item version 2 (TFEQ-R18v2): Transformed scale scores for the three scales measured: Uncontrolled Eating, Cognitive Restraint and Emotional Eating

- Time to permanent discontinuation of randomised trial product (weeks)

5 Trial design

5.1 Overall design

This is a 26-week, randomised, double blind placebo-controlled, twelve-armed, parallel group, multi-centre, multi-national dose finding trial comparing five doses (0.3, 0.6, 1.2, 2.4 and 4.5 mg OW) of NNC0174-0833 with placebo and liraglutide 3.0 mg OD when added as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity.

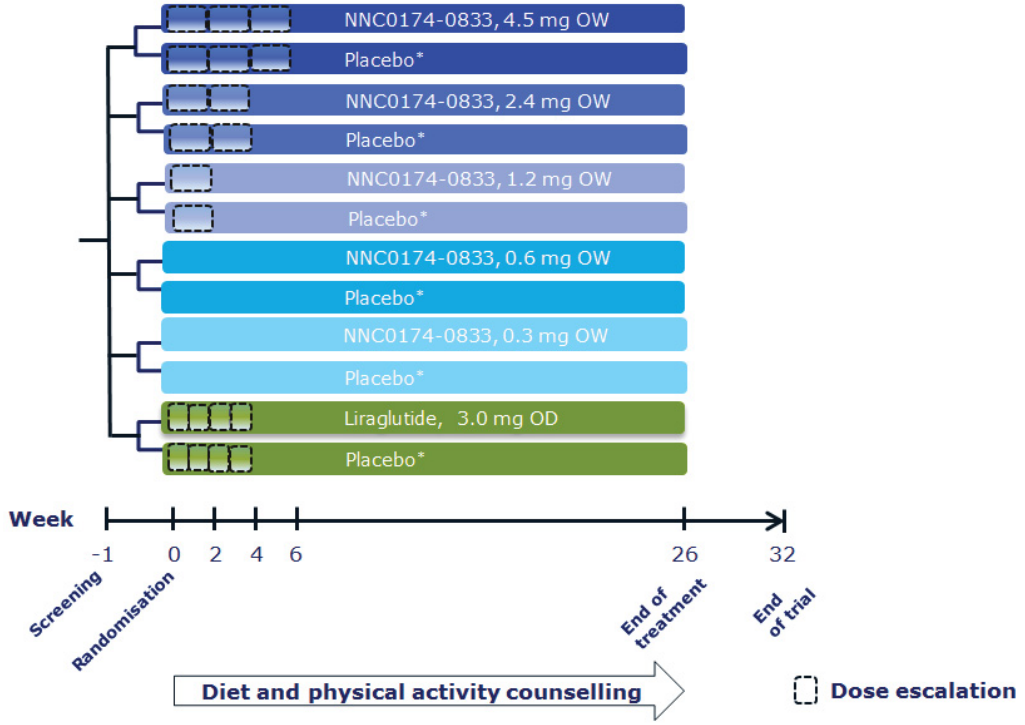
The trial includes a screening visit to assess subject's eligibility. At visit 2 (randomisation) eligible subjects will enter an up to 6-week dose escalation period, depending on which arm the subject is randomised to, followed by a maintenance period until end of treatment (week 26). To assess subject safety after the trial product has been washed out a follow-up visit ('end of trial') is scheduled 6 weeks after end of treatment. The total duration for each subject will be approximately 33 weeks.

Each NNC0174-0833 treatment arm will administer different dose volumes, but is blinded towards placebo with matching injection volumes.

Subjects will be randomised 6:1 between the active treatment arms and the placebo arms. This will result in approximately 100 subjects in each treatment arm and approximately 100 subjects in total in the placebo arms.

The five different NNC0174-0833 placebo arms and the one liraglutide placebo arm will be pooled into one placebo group in the main analyses.

The trial design is outlined in Figure 5-1.



* NNC0174-0833 placebo arms and liraglutide placebo arm will be pooled into one placebo group in the main analyses

Figure 5-1 Trial design

5.2 Subject and trial completion

Approximately 933 subjects will be screened to achieve a planned 700 subjects randomly assigned to trial products.

Trial period completion for a subject
Trial period completion is defined as when the randomised subject has completed the final scheduled visit ('end of trial' (week 32) according to the flowchart).

For subjects who have tested positive for antibodies against NNC0174-0833 at visit 12 ('end of trial') two additional analyses may be performed up to 12 months after visit 12 (Section 9.4.5). For these subjects the trial period completion is also defined as when the randomised subject has completed the final scheduled visit ('end of trial' (week 32) according to the flowchart).

Treatment period completion for a subject
Treatment period completion is defined as when the randomised subject has received the required treatment, and attended the 'end of treatment' visit (week 26) according to the flowchart.

5.3 End of trial definition

The end of the trial is defined as the date of the last visit of the last subject in the trial, not including the potential two follow-up analyses for subjects testing positive for antibodies against NNC0174-0833 at visit 12.

5.4 Scientific rationale for trial design

Parallel treatment groups and a randomised double-blinded, controlled design have been chosen in accordance with the trial objectives. To avoid bias in the assessment of the different NNC0174-0833 doses and the liraglutide dose, the trial will be double-blinded within treatment arms to placebo. The treatment arms will not be blinded towards each other because of different dose escalations, different pens, and different target volumes. All treatments are added to a standardised diet and exercise counselling.

In order to compare efficacy and safety with a widely approved medication for weight management (i.e. standard of care) a liraglutide 3.0 mg/liraglutide placebo arm has been included.

A treatment duration of 26 weeks is considered adequate to assess whether various doses of NNC0174-0833 may induce a clinically meaningful weight loss and provide sufficient insight into the NNC0174-0833 safety and tolerability profile.

Dose escalation every other week (for the 1.2 mg, 2.4 mg and 4.5 mg NNC0174-0833 treatment arms) is chosen because it is expected to attenuate the GI side effects.

5.5 Justification for dose

Based on the phase 1 multiple-ascending dose trial it was concluded that NNC0174-0833 is safe and well tolerated up to 800 µg OD following proper dose escalation for 3 weeks. Dose escalation by weekly increments reduced the frequency and severity of GI AEs. On this basis it is expected that transition into OW dosing with escalations every other week will provide a good balance between minimising GI AEs and efficacy.

Population PK modelling demonstrated that an OW dose of 4.5 mg NNC0174-0833 provides a steady state maximum concentration of NNC0174-0833 (C_{max}) similar to the mean plasma concentration observed with the highest tested dose of 800 µg OD in the multiple-ascending dose trial (NN9838-4021). Therefore, 4.5 mg OW was selected as the top dose to be explored in phase 2. Due to its higher peak-to-trough fluctuation, an OW dose of 4.5 mg NNC0174-0833 will provide 20% lower average exposure at steady state compared to OD dose of 800 µg. The lowest dose of 0.3 mg OW is anticipated to represent the 'minimal effective dose'. A trial design with 5

maintenance doses ranging from 0.3 mg to 4.5 mg including approximately two-fold increments in doses is expected to give adequate exploration of the dose-response curve for NNC0174-0833 on weight loss.

Refer to Section 7.1 for more details on treatment doses.

6 Trial population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion criteria

Subjects are eligible to be included in the trial only if all of the following criteria apply:

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. ≥ 18 years at the time of signing the informed consent
3. Female subject of non-childbearing potential[1]
   or
   Male subject who is surgically sterilised (vasectomy) or who is willing to use adequate contraceptive methods (as required by local regulation or practice) throughout the trial (until 'end of trial')
4. BMI ≥ 30.0 kg/m^2 or BMI ≥ 27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension or dyslipidaemia (to be assessed at the investigator's discretion).

For country specific requirements see Appendix 8.

6.2 Exclusion criteria

Subjects are excluded from the trial if any of the following criteria apply:

Glycaemia-related

1. HbA_{1c} ≥ 48 mmol/mol (6.5%) as measured by the central laboratory at screening
2. History of type 1 or type 2 diabetes mellitus
3. Treatment with glucose-lowering agent(s) within 90 days prior to screening

Obesity-related

4. A self-reported change in body weight > 5 kg (11 lbs) within 90 days prior to screening irrespective of medical records
5. Treatment with any medication indicated for weight management within 90 days prior to screening

[1] See Appendix 5 for the definition of a woman of childbearing potential (WOCBP)

6. Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed > 1 year prior to screening, (2) lap banding, if the band has been removed > 1 year prior to screening, (3) intragastric balloon, if the balloon has been removed > 1 year prior to screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed > 1 year prior to screening
7. Uncontrolled thyroid disease, defined as thyroid stimulating hormone (TSH) > 4.78 mIU/L or < 0.55 mIU/L as measured by the central laboratory at screening

Mental health

8. History of major depressive disorder within 2 years prior to screening
9. History of other severe psychiatric disorders (e.g. schizophrenia or bipolar disorder)
10. A lifetime history of a suicidal attempt

General safety

11. Male subject whose partner is pregnant or breastfeeding
12. Renal impairment measured as estimated glomerular filtration rate (eGFR) value of < 60 ml/min/1.73m^2 as defined by Kidney Disease Improving Global Outcomes (KDIGO) 2012[37] by the central laboratory at screening
13. Impaired liver function, defined as alanine aminotransferase (ALT) ≥ 2.5 times or bilirubin > 1.5 times upper normal limit (UNL), as measured by the central laboratory at screening
14. Inadequately treated blood pressure defined as systolic ≥180 mmHg or diastolic ≥110 mmHg at screening
15. History of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed.
16. Presence or history of cardiovascular disease including stable and unstable angina pectoris, myocardial infarction, transient ischaemic attack, stroke, cardiac decompensation, clinically significant arrhythmias or clinically significant conduction disorders
17. Subject presently classified as being in New York Heart Association (NYHA) Class IV heart failure
18. Surgery scheduled during the duration of the trial, except for minor surgical procedures, in the opinion of the investigator
19. Known or suspected abuse of alcohol or recreational drugs
20. Known or suspected hypersensitivity to trial product(s) or related products
21. Previous participation in this trial. Participation is defined as signed informed consent.
22. Participation in another clinical trial within 90 days prior to screening
23. Personal or first degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
24. Presence of acute pancreatitis within 180 days prior to screening
25. History or presence of chronic pancreatitis
26. Other subject(s) from the same household participating in any trial testing NNC0174-0833

27. Any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the subject's safety or compliance with the protocol

The criteria will be assessed at the investigator's discretion unless otherwise stated.

6.3 Lifestyle restrictions

To ensure alignment in regards to performance of assessments across subjects and trial sites, the below restrictions apply.

6.3.1 Meals and dietary restrictions

- Subjects must attend the relevant visits fasting according to the flowchart.
- Fasting is defined as at least 8 hours overnight before the visit, 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 samples have been obtained.
- 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 assessments done.
- Assessments requiring subject to fast include blood sampling of lipids, FPG, fasting serum insulin, leptin, soluble leptin receptor, and endogenous amylin.

6.3.2 Caffeine and tobacco

Subject should avoid caffeine and smoking for at least 30 minutes prior to measuring the blood pressure at clinic visits.

6.3.3 Physical activity

Subject should avoid physical activity for at least 30 minutes prior to measuring the blood pressure.

6.4 Screen/randomisation failures

Screen/randomisation failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to in/exclusion criteria or randomisation criteria. A minimal set of information is required to ensure transparent reporting to meet requirements from regulatory authorities. Minimal information includes date of visit, date of informed consent, demography, violated incl/excl/rand criteria, screen/randomisation failure date and reason and any SAE. A screen failure session must be made in the interactive web response system (IWRS).

Individuals who do not meet the criteria for participation in this trial may not be rescreened. Re-sampling is not allowed if the subject has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

6.5 Randomisation criteria

To be randomised, all randomisation criteria must be answered 'yes'.

1. A Patient Health Questionnaire-9 (PHQ-9)[38] score of < 15 at randomisation
2. No suicidal behaviour within 30 days prior to randomisation
3. No suicidal ideation corresponding to type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) within 30 days prior to randomisation

7 Treatments

7.1 Treatments administered

- All trial products listed in Table 7-1 are considered investigational medicinal products (IMPs) and are supplied by Novo Nordisk A/S.
- Liraglutide 3.0 mg/liraglutide placebo must only be used, if it appears clear and colourless.
- NNC0174-0833/NNC0174-0833 placebo must only be used, if it appears clear and almost colourless.

Table 7-1 Trial products provided by Novo Nordisk A/S

Trial product name	NNC0174-0833 A 10 mg/ml	Placebo NNC0174-0833 A	Liraglutide 6.0 mg/ml	Liraglutide placebo
Dosage form	Solution for injection	Solution for injection	Solution for injection	Solution for injection
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous
Dosing instructions	Once-weekly	Once-weekly	Once-daily	Once-daily
Packaging	3 mL cartridge under-filled with 1 mL extractable volume inserted into a NovoPen® 4	3 mL cartridge under-filled with 1 mL extractable volume inserted into a NovoPen® 4	3 mL PDS290 pen-injector	3 mL PDS290 pen-injector

- Subjects randomised to NNC0174-0833/NNC0174-0833 placebo will be instructed to inject OW on the same day of the week (to the extent possible) throughout the trial.
- Subjects randomised to liraglutide 3.0 mg/liraglutide placebo will be instructed to inject OD throughout the trial.
- Trial products can be taken at any time of day, irrespective of timing of meals.
- Trial product injections should be administered in the thigh, abdomen or upper arm.
- Dose escalation of NNC0174-0833/NNC0174-0833 placebo and liraglutide 3.0 mg/liraglutide placebo should take place during the first 6 weeks after randomisation according to Table 7-2 and Table 7-3.
- Dosing information must be collected in designated paper dosing diary and entries must be entered in the case report form (CRF).

Table 7-2 Dose escalation, target dose, injection volume and pen units for NNC0174-833 arms and corresponding placebo arms

Target dose	Unit	Randomisation	Week 2	Week 4	Week 6 until end of treatment
0.3 mg	Dose (mg) Volume (µL) Pen unit (U)	0.3 30 3	0.3 30 3	0.3 30 3	0.3 30 3
0.6 mg	Dose (mg) Volume (µL) Pen unit (U)	0.6 60 6	0.6 60 6	0.6 60 6	0.6 60 6
1.2 mg	Dose (mg) Volume (µL) Pen unit (U)	0.6 60 6	1.2 120 12	1.2 120 12	1.2 120 12
2.4 mg	Dose (mg) Volume (µL) Pen unit (U)	0.6 60 6	1.2 120 12	2.4 240 24	2.4 240 24
4.5 mg	Dose (mg) Volume (µL) Pen unit (U)	0.6 60 6	1.2 120 12	2.4 240 24	4.5 450 45

Table 7-3 Dose escalation, target dose and injection volume for liraglutide 3.0 mg arm and corresponding placebo arm

Target dose	Unit	Randomisation	Week 1	Week 2	Week 3	Week 4 until end of treatment
3.0 mg	Dose (mg) Volume (µL)	0.6 100	1.2 200	1.8 300	2.4 400	3.0 500

- In case of intolerable GI AEs as judged by the investigator, dose escalation can be postponed by one week per escalation step. As such the maximum time to reach the highest target dose of NNC0174-0833 (4.5 mg) and liraglutide 3.0 mg (3.0 mg) will be 9 weeks and 8 weeks, respectively.
- If a subject does not tolerate the randomised target dose, the subject may stay at a lower dose level. This should only be allowed if the subject would otherwise discontinue trial product completely and if considered safe to continue on trial product, as per investigator's discretion.
- It is recommended that the investigator consults Novo Nordisk in case of persistent deviations from the planned escalation regimen.
- Auxiliary supplies will be provided by Novo Nordisk in accordance with the trial materials manual (TMM), see Table 7-4.

Table 7-4: Auxiliary supplies provided by Novo Nordisk A/S

Auxiliary supply	Details
Needles	Needles for NovoPen® 4 and for the 3 mL PDS290 pen-injector Types of needle will be specified in the TMM Only needles provided by Novo Nordisk must be used for administration of trial product Maximum needle length of 6 mm should be used
Direction for use (DFU)	DFU for NovoPen® 4 DFU for 3 mL PDS290 pen-injector DFUs are not included in the dispensing unit and must be handed out separately

7.1.1 Medical devices

Non-investigational medical devices:

- NovoPen® 4
- PDS290 pen-injector

NovoPen® 4 is a durable device which is not under investigation in this trial. The use of NovoPen® 4 for s.c. administration of NNC0174-0833/NNC0174-0833 placebo for the treatment of subjects with obesity is supported by a risk assessment addressing the safety of the use of NovoPen® 4 in this trial. Information about NovoPen® 4 can be found in the current edition of the IB[34] and any updates hereof.

The PDS290 pen-injector is a prefilled pen-injector used as a delivery system for liraglutide 3.0 mg/liraglutide placebo. The PDS290 pen-injector is not under investigation in this trial. The PDS290 pen-injector has been documented for use in patients with obesity and to be in compliance with relevant standards and regulations. Information about the PDS290 pen-injector can be found in the current edition of the IB[36] and any updates hereof.

Training in NovoPen® 4 and PDS290 pen-injector
The subjects must be trained according to the DFU in how to handle the NovoPen® 4 and the PDS290 pen-injector, when handed out the first time. Training must be repeated during the trial at regular intervals in order to ensure correct use of the NovoPen® 4 and for PDS290 pen-injector.

The investigator must document that the DFU is given to the subject orally and in writing at the first dispensing visit.

7.1.2 Diet and physical activity counselling

All subjects will receive counselling with regards to diet (a goal of 500 kcal deficit per day relative to the estimated total daily energy expenditure (TEE) calculated once at randomisation) and physical activity (a goal of 150 min of physical activity per week). Counselling should be done by a dietician or a similar qualified healthcare professional at visits outlined in the flowchart.

Subjects will be instructed to record their food intake and physical activity daily (via paper diary, app or similar tool) in order to assist and evaluate their lifestyle intervention.

The subjects can use a tool of their own choice (paper/app/other tool) for recording, ensuring it can be reviewed for content and number of entries during diet and physical activity counselling.

Calculation of estimated TEE
The TEE is calculated by multiplying the estimated basal metabolic rate (BMR) (Table 7-5) with a physical activity level value of 1.3[39].

$$TEE = BMR \times 1.3$$

Table 7-5 Equation for estimated BMR

Sex	Age	BMR (kcal/day)
Male	18-30 years 31-60 years > 60 years	15.057 × weight at randomisation in kg + 692.2 11.472 × weight at randomisation in kg + 873.1 11.711 × weight at randomisation in kg + 587.7
Female	18-30 years 31-60 years > 60 years	14.818 × weight at randomisation in kg + 486.6 8.126 × weight at randomisation in kg + 845.6 9.082 × weight at randomisation in kg + 658.5

If a BMI ≤ 22.5 kg/m^2 is reached the recommended energy intake should be recalculated with no kcal deficit (maintenance diet) for the remainder of the trial. If deemed necessary the investigator could consult Novo Nordisk to discuss when maintenance diet can be initiated.

7.2 Dose modification

Not applicable for this trial.

7.3 Method of treatment assignment

All subjects will be centrally randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed at the trial visits summarised in the flowchart.

7.4 Blinding

The active trial product and matching placebo are visually identical for the following trial products:

- NNC0174-0833/NNC0174-0833 placebo
- Liraglutide 3.0 mg/liraglutide placebo

The IWRS is used for blind-breaking instructions. The blind may be broken in a medical emergency

if knowing the actual treatment would influence the treatment of the subject. Novo Nordisk will be notified immediately after breaking the blind. The date when and reason why the blind was broken must be recorded in the source documentation.

Whenever the blind is broken, the person breaking the blind must print the 'code break confirmation' notification generated by the IWRS and sign and date the document.

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

If the blind has been broken by investigator, the subject must discontinue treatment with trial product and a treatment status session to register discontinuation of treatment must be completed in the IWRS.

7.5 Preparation/Handling/Storage/Accountability

Only subjects enrolled in the trial may receive trial product and only authorised site staff may supply or administer trial product.

- Trial product storage, in-use conditions and in-use time will be available on the label and in the TMM.
- Each trial site will be supplied with sufficient trial products for the trial on an ongoing basis controlled by the IWRS. Trial product will be distributed to the trial sites according to screening and randomisation.
- The investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the TMM.
- 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 is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- For subjects randomised to liraglutide 3.0 mg/liraglutide placebo, drug accountability should be performed on a pen level for the PDS290 pen-injector.

- For subjects randomised to NNC0174-0833/NNC0174-0833 placebo, drug accountability should be performed on a cartridge level for the cartridges supplied for the NovoPen® 4. No accountability is performed for the NovoPen® 4.
- Drug accountability must be documented in the IWRS.
- The subject must return all used, partly used and unused trial product including empty packaging materials during the trial as instructed by the investigator.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- Destruction of trial products must be documented in the IWRS.
- All returned, expired or damaged trial products (for technical complaint samples see Appendix 6) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the trial site.

7.6 Treatment 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 a single dose of NNC0174-0833/NNC0174-0833 placebo is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 2 days (48 hours). If the next scheduled dose is less than 48 hours away, the missed dose should be skipped and the subject should await the next scheduled dose. The scheduled dosing day of the week should be kept the same, to the extent possible.
- If two or more consecutive doses of NNC0174-0833/NNC0174-0833 placebo are missed, continuation of NNC0174-0833/NNC0174-0833 placebo should be encouraged if considered safe as per the investigator's discretion and if the subject does not meet any of the discontinuation criteria (Section 8.1). The trial product should be administered as early as the situation allows unless there is less than 48 hours to the next scheduled dose. The missed doses should not affect the scheduled dosing day of the week. The start dose for re-initiation of NNC0174-0833/NNC0174-0833 placebo is at the investigator's discretion.
- If one or two doses of liraglutide 3.0 mg/liraglutide placebo are missed no changes should be made to the following administrations.
- If more than 3 consecutive doses of liraglutide 3.0 mg/liraglutide placebo are missed, continuation of liraglutide 3.0 mg/liraglutide placebo should be encouraged if considered safe as per the investigator's discretion and if the subject does not meet any of the discontinuation criteria (Section 8.1). The start dose for re-initiation of liraglutide 3.0 mg/liraglutide placebo is at the investigator's discretion.

- In case of questions related to re-initiation or re-escalation of trial product, the investigator should consult Novo Nordisk.
- Dosing information must be collected in designated paper dosing diary and entries must be entered in the CRF (Section 9).

7.7 Concomitant medication

Any medication (including over-the-counter or prescription medicines), other than the trial product, that the subject is receiving at the time of visit 2 or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Start and stop dates

During the trial subjects should not initiate any weight management treatment (e.g. medication) which is not part of the trial procedures. If such treatment is initiated, the subject should be instructed to stop the weight management treatment.

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE/SAE, then this must be reported according to Section 9.2.

7.8 Treatment after the end of the trial

When discontinuing trial products, either at the scheduled 'end of treatment' visit or if trial product is discontinued, the subject should be treated at the discretion of the investigator.

8 Discontinuation/Withdrawal criteria

8.1 Discontinuation of trial product

The subject may be discontinued from trial product at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

The subject must be discontinued from trial product, if one or more of the following applies:

1. Safety concern as judged by the investigator
2. Pregnancy
3. Simultaneous participation in another clinical trial of an approved or non-approved IMP.

The subjects randomised to liraglutide 3.0 mg/liraglutide placebo must also be discontinued from trial product, if any of the following applies:

4. Calcitonin ≥ 100 ng/L
5. Suspicion of pancreatitis

If acute pancreatitis is suspected appropriate management should be initiated, including local measurement of amylase and lipase (see Appendix 4 for reporting).

Subjects meeting discontinuation of trial product criteria no. 1 and 2 are allowed to resume trial product, if the criteria are no longer met (Section 8.1.1).

Subjects meeting discontinuation of trial product criterion no. 5 are allowed to resume trial product if the Atlanta criteria[40] are not fulfilled and thus the suspicion of acute pancreatitis is not confirmed. Trial product may be resumed for subjects with a gallstone-induced pancreatitis in case of cholecystectomy.

The primary reason for discontinuation of trial product must be specified in the medical record at the time of treatment discontinuation and in the 'end of treatment' form in the CRF, and final drug accountability must be performed. A treatment status session to register discontinuation of treatment must be made in the IWRS.

Efforts must be made to have the subjects, who discontinue trial product, attend and complete all scheduled visit procedures. Only subjects who withdraw consent will be considered as withdrawn from the trial. Subjects must be educated about the continued scientific importance of their data, even if they discontinue trial product.

If the subject does not wish to attend the scheduled clinic visits efforts should be made to have the visits converted to phone contacts. However, all efforts should be made to attend at least visit 11

'end of treatment' (26 weeks post-randomisation), containing the final data collection of the primary endpoint, and visit 12 'end of trial' (32 weeks post-randomisation).

The 'end of trial' visit is scheduled approximately 6 weeks after the 'end of treatment' visit (week 26), to ensure the safety of the subject.

If the subject refuses to attend the 'end of treatment' visit and/or the 'end of trial' visit, information about the attempts to follow up with the subject must be documented in the subject's medical record.

8.1.1 Temporary discontinuation of trial product

If a subject has discontinued trial product, the subject should follow the guide for missed doses (Section 7.6) if treatment should be resumed.

If a 'treatment status' session previously has been made in IWRS to indicate discontinuation of trial product, a new 'treatment status' session must be made to resume trial product.

8.2 Withdrawal from the trial

A subject may withdraw consent at any time at his/her own request. Only subjects who withdraw consent will be considered as withdrawn from the trial.

If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessments performed according to the 'end of treatment' visit. See the flowchart for data to be collected.

Final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment status session to register discontinuation of treatment must be made in the IWRS.

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the medical record.

If the subject withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

Although a subject is not obliged to give his/her reason(s) for withdrawing, 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 withdrawal must be specified in the 'end of trial' form in the CRF.

8.2.1 Replacement of subjects

Subjects who discontinue trial product or withdraw from trial will not be replaced.

8.3 Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site at the 'end of treatment' visit.

The following actions must be taken if a subject fails to return to the trial site for a required visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule or at least attend visit 11 and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). If attempts have failed, family members or other contacts consented by the subject can be contacted for alternative contact details. These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable at the 'end of treatment' visit, he/she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

9 Trial assessments and procedures

- Trial procedures and their timing are summarised in the flowchart and in Appendix 2.
- Informed consent must be obtained before any trial related activity, see Appendix 3.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- Assessments should be carried out according to the clinic's standard of practice unless otherwise specified in the current section. Efforts should be made to limit bias between assessments. The suggested order of the assessments:
    - Blood sampling (at fasting visits)
    - Electrocardiogram (ECG) and vital signs
    - Other assessments
- Source data of clinical assessments performed and recorded in the CRF must be available and will usually be the subject's medical records. Additional recordings to be considered source data include, but are not limited to laboratory reports, ECGs and diaries.
- Subjects must be instructed how to collect dosing information in a designated paper dosing diary and entries must be entered in the CRF.
- Only the subject can make entries and corrections in the diaries, unless the section is specified for site staff.
- Subjects must receive instructions in how to capture their diet and physical activity. The entries from the diet and physical activity diary will not be entered into the CRF.
- Only the subject can make entries and corrections in the diaries, unless the section is specified for site staff.
- The barriers and motivation interview identifies barriers to and motivation for lifestyle change and compliance with the protocol. The interview must be conducted at screening to assist in identifying subjects who are unable or unwilling to comply with protocol procedures as per the exclusion criteria. In addition, the interview will ensure that any minor barriers are addressed during lifestyle counselling.
- The results of the barriers and motivation interview will not be entered into the CRF. It will be at the investigator's discretion to evaluate the motivation of the subject and related eligibility.
- Weight history must be recorded in the subject's medical record and the CRF. Weight history should include the following questions: what was subject's weight a year ago?, what has been the subject's maximum weight?, how old was the subject at that time when he/she gained maximum weight?, in the subject's own opinion, was the subject obese when 5 years old, 11

years old, 18 years old?, what is the least the subject has ever weighed as an adult?, how many times has the subject intentionally lost ≥ 11 lb/5 kg?, did any of the subject's first degree relatives ever have overweight or obesity?

- Review of completed diaries, clinical outcome assessments (COAs), ECG, laboratory reports etc. must be documented either on the documents or in the subject's medical record. If clarification of entries or discrepancies in the diary or COA 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.
- Repeat laboratory samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Refer to Appendix 2 for further details on laboratory samples.

9.1 Efficacy assessments

9.1.1 Body measurements

- Body weight should be measured without shoes, on an empty bladder and only wearing light clothing. It should be measured on a digital scale and recorded in kilograms or pounds (both to one decimal precision) using the same scale throughout the trial. The scale must be calibrated according to local requirements.
- Height is measured without shoes in inches (one decimal precision) or to the nearest centimeter (cm). BMI will be calculated automatically in the CRF.
- Waist circumference is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest. Measures must be obtained in standing position with a non-stretchable measuring tape and to the nearest cm or inch. The tape should touch the skin but not compress soft tissue. The subject should be asked to breathe normally. The same measuring tape should be used throughout the trial.

9.1.2 Clinical efficacy laboratory assessments

All protocol required efficacy laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the flowchart in Section 2 and the laboratory flowchart.

9.1.3 Efficacy clinical outcome assessments

Efficacy COAs will be obtained at visit 2, 6 and 11.

The COAs will be available on a tablet in a linguistically validated version. Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. Each questionnaire takes approximately 10 minutes to complete. The questionnaires should preferably be completed after fasting related activities (i.e. blood sampling) have been concluded.

The following efficacy COAs will be used:

- SF-36 v2.0 acute[41] measures the subject's overall health related quality of life. It is a 36-item generic measure of health status that yields two summary scores for physical health and mental health, and eight domain scores.

- TFEQ-R18v2[42] measures dietary restraint. There are three different factors: (1) Cognitive Restraint, comprised of three items, (2) Uncontrolled Eating, comprised of nine items, and (3) Emotional Eating, comprised of six items. TFEQ-R18v2 comprises a total of 18 items, which are aggregated to three separate scale scores. Higher scores indicate more uncontrolled eating, cognitive restraint and emotional eating.

9.2 Adverse events

The definitions of AEs and SAEs can be found in Appendix 4.

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE.

9.2.1 Time period and frequency for collecting AE and SAE information

All AEs will be collected from the first trial related activity after obtaining informed consent and until the 'end of trial' visit, at the time points specified in the flowchart.

All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours, as indicated in Appendix 4. The investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former trial subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related to the investigational trial product or trial participation, the investigator must promptly notify Novo Nordisk.

The method of recording, evaluating and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

Timelines for reporting of AEs are listed in Figure 9-1.

Some AEs require additional data collection via a specific event form. This includes medication errors observed during the trial. The relevant specific events are listed in Table 9-1 and the reporting timelines in Figure 9-1.

Table 9-1 AEs requiring additional data collection (via specific event form)

Event type
Medication error
Acute gallbladder disease
Acute coronary syndrome
Cerebrovascular events
Heart failure
Coronary artery revascularisation
Neoplasm
Hypocalcaemia

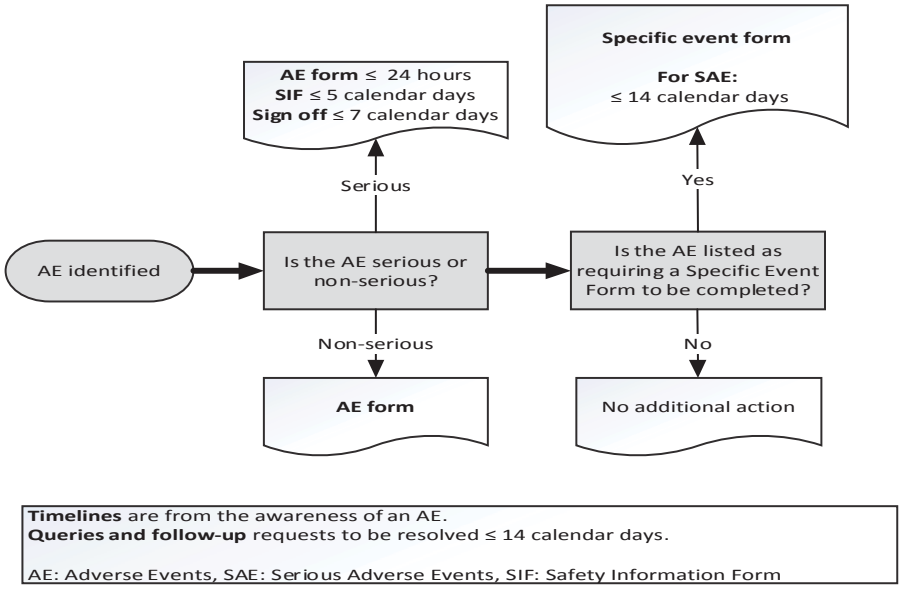


Figure 9-1 Decision tree for determining the event type and the respective forms to complete with associated timelines

9.2.2 Method of detecting AEs and SAEs

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about events.

9.2.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, or if the event is otherwise explained (e.g. chronic condition) or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial product under clinical investigation are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Independent Ethics Committee (IEC) and Institutional Review Board (IRB), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Novo Nordisk policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs), from Novo Nordisk will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to AE/SAEs description in Section 9.2.1.

9.2.6 Disease related events and/or disease related outcomes not qualifying as an AE or SAE

Not applicable for this trial.

9.2.7 Pregnancies and associated adverse events

Details of pregnancies in female subjects and female partners of male subjects (paternal) will be collected after the first trial related activity after obtaining informed consent and until the ‘end of trial’ visit.

If a pregnancy is reported in female subjects, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Figure 9-2 and Appendix 5.

If a pregnancy is reported in female partners of male subjects, the pregnancy should be documented in the medical record of the male subject and in case of abnormal outcome, the investigator should inform Novo Nordisk within 14 calendar days of learning of the abnormal outcome and should follow the procedures outlined in Figure 9-3 and Appendix 5

Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.

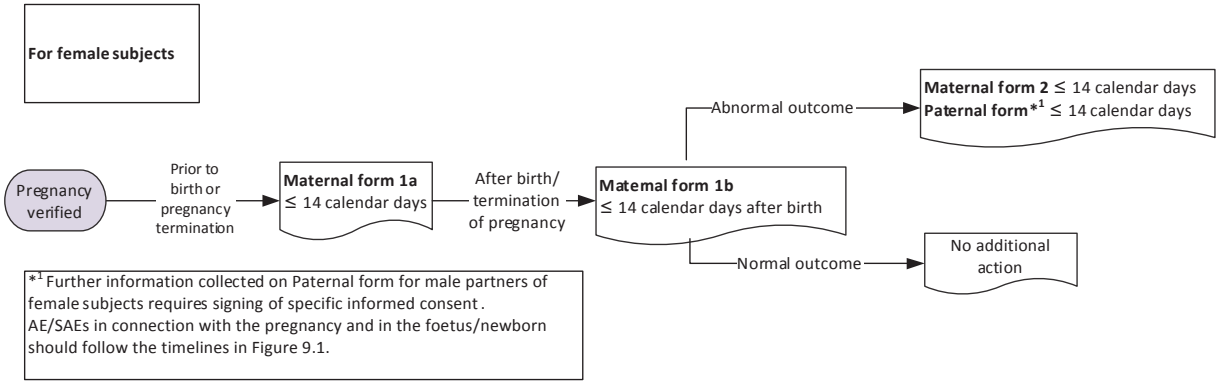


Figure 9-2 Decision tree for determining the forms to complete with associated timelines for pregnancy

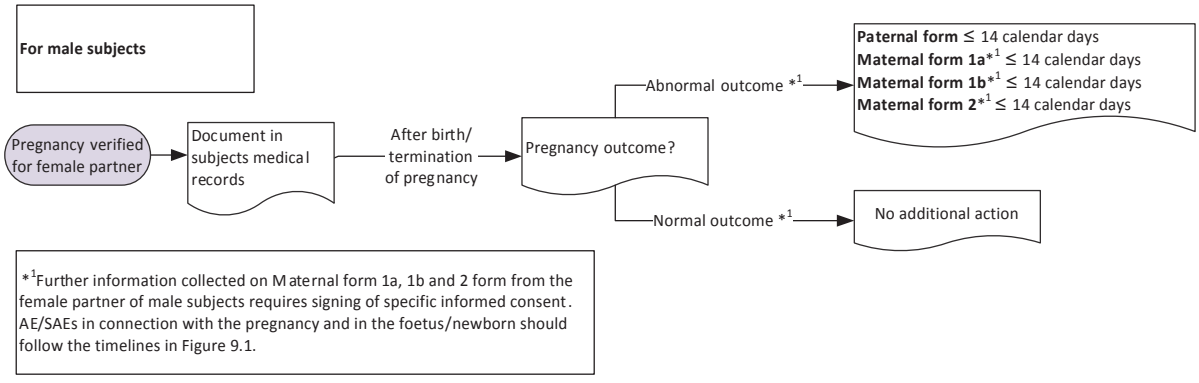


Figure 9-3 Decision tree for determining the forms to complete with associated timelines for pregnancy

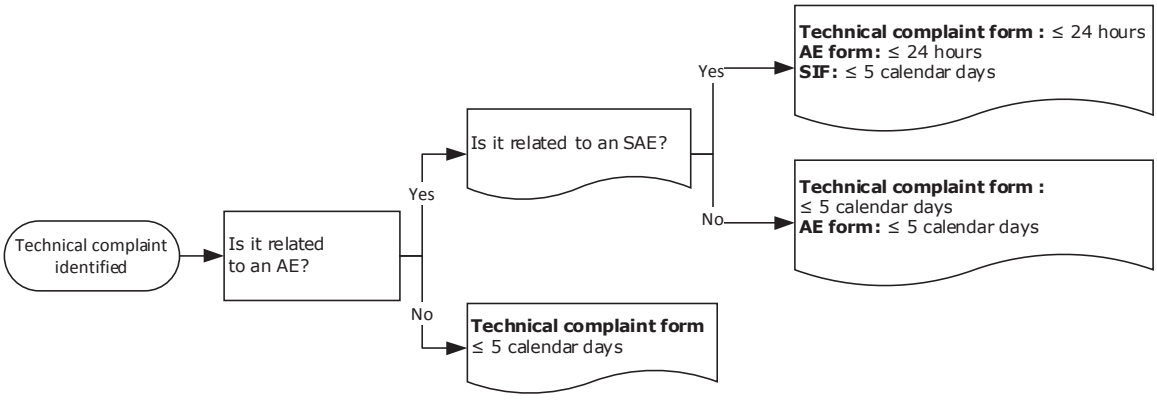
9.2.8 Medical device incidents (including malfunctions)

Section is not applicable for this trial. Refer to technical complaints in Section 9.2.9.

9.2.9 Technical complaints

The investigator must assess whether a technical complaint is related to an AE. The definitions and reporting process for technical complaints can be found in Appendix 6.

Timelines for reporting technical complaints are listed in Figure 9-4.



AE: Adverse Event, SAE: Serious Adverse Event, SIF: Safety Information Form

Figure 9-4 Decision tree for determining the forms to complete with associated timelines for technical complaints

9.3 Treatment of overdose

An overdose is defined at the investigator's discretion and must be reported as a medication error. Remember that symptoms can develop over time. Refer to Section 9.2.1 for further details.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE and laboratory abnormalities until clinically safe, taking into account the long half-life of NNC0174-0833. Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the subject.

Repeated doses of NNC0174-0833 up to 1300 µg/weekly without dose escalation and 800 µg/day with appropriate dose escalation have been found safe and well tolerated. Dosing a similar dose without escalation may lead to GI side effects like nausea and vomiting.

Likewise, based on clinical trials and marketed use of liraglutide 3.0 mg, overdoses up to 24 times the recommended dose have been reported (72 mg/day vs 3 mg/day). One case of a 6-fold overdose (18 mg/day) given for 7 months has been reported. Generally, the patients reported severe nausea,

vomiting and diarrhoea, but recovered without complications. None of the reports included severe hypoglycaemia.

For more information on potential clinical effects of an overdose, also consult the current edition of the liraglutide 3.0 mg or NNC0174-0833 IB[34, 36] and any updates hereof and/or contact Novo Nordisk.

9.4 Safety assessments

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the first visit) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

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

As part of the medical history information related to history of gallbladder disease, breast neoplasms, colon neoplasms, skin cancer and psychiatric disorders will be recorded. Follow-up questions will be asked at the 'end of treatment' and 'end of trial' visits, related to the breast neoplasm (for female subjects) and colon neoplasm.

In case of an abnormal and clinically significant finding, the investigator must record the finding on the 'Medical History/Concomitant Illness' form in the CRF if it is present at screening. Any new finding fulfilling the AE definition (Appendix 4) during the trial and any clinically significant worsening from screening (visit 1) must be reported as an AE (Section 9.2.1).

Tobacco use will be recorded at screening. Smoking is defined as smoking at least one cigarette or equivalent daily.

9.4.1 Physical examinations

- A physical examination will include assessments of the general appearance, thyroid gland, abdomen, as well as the cardiovascular, respiratory, central and peripheral nervous systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2 Vital signs

- Pulse rate, as well as diastolic and systolic blood pressure will be assessed.
- Blood pressure and pulse measurements should be preceded by at least five minutes of rest for the subject in a quiet setting without distractions (e.g. television, cell phones).
- Blood pressure at screening will consist of 3 diastolic and systolic blood pressure measurements with intervals of at least 1 minute. All three readings must be entered in the CRF and the average of the 3 blood pressure readings will be calculated in the CRF. At the subsequent visits, the blood pressure should only be measured once.

- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

9.4.3 Electrocardiograms

- 12-lead ECG will be obtained as outlined in the flowchart using a local ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals.

9.4.4 Clinical safety laboratory assessments

All protocol required safety laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the flowchart in Section 2 and the laboratory flowchart.

- Urine pregnancy tests, supplied by central laboratory, must be performed for postmenopausal female subjects who have stopped menstruating within the last 5 years and for female subjects with bilateral tubal ligation. Urine pregnancy test must be repeated at any time during the trial if pregnancy is suspected.
- Urinalysis: Proteinuria should be assessed using urine collection to measure urine protein-to-creatinine ratio. The urine specimen should be collected on first morning sample on the day of visit 2, 4, 6, 9 and 11.

9.4.5 Immunogenicity assessments

Assessment of antibodies against NNC0174-0833 in serum will be performed by a laboratory assigned by Novo Nordisk for subjects randomised to NNC0174-0833/NNC0174-0833 placebo.

Blood samples to be analysed for serum antibodies against NNC0174-0833 will be drawn as outlined in Appendix 2 and the laboratory flowchart. All samples must be drawn prior to trial product administration if trial product administration is planned on the sampling day.

The *in vivo* neutralising effect of anti-NNC0174-0833 antibodies will be evaluated by correlation to PK, weight loss and other relevant parameters, if relevant.

In addition, samples confirmed positive for NNC0174-0833 antibodies at visit 12 will be further characterised for *in vitro* neutralising effect using a neutralising antibody assay. Detailed description of the assay methods will be included in an analytical report. Antibody assays will be validated according to international guidelines and recommendations.

As native amylin is extremely prone to fibrillation it may not be feasible to analyse for cross reactivity to endogenous amylin or the potential neutralising effect on endogenous amylin.

Follow-up analyses
Subjects who have tested positive for antibodies against NNC0174-0833 (high titre antibodies and/or *in vitro* neutralising antibody response) at visit 12 ('end of trial' visit) will be requested to

have a follow-up analysis performed 6 months after visit 12. If the follow-up analysis is positive for antibodies against NNC0174-0833, the subject will be requested to have an additional follow-up analysis performed 12 months after visit 12.

The result from additional follow-up analyse(s) will be reported in separate analytical report. Thus, the results will not be part of the clinical trial report (CTR).

9.4.6 Hypersensitivity

In case of suspicion of a severe systemic hypersensitivity reaction to the trial product, the subject must be discontinued from trial product but should remain in the trial.

The following information in Section 9.4.6 is only relevant for subjects randomised to NNC0174-0833/NNC0174-0833 placebo.

In the event of a severe systemic hypersensitivity reaction possibly or probably related to trial product, a blood sample should be taken as soon as possible and no later than 1-2 weeks after the reaction. A second sample should be taken 3-4 weeks after the reaction.

The following assessments will be performed:
- Anti-NNC0174-0833 IgE antibodies
- Anti-NNC0174-0833 binding antibodies
- Tryptase

If deemed relevant by Novo Nordisk other relevant exploratory tests may be performed, e.g. basophil activation, complement tests, prick tests and/or intra-dermal tests.

The analyses will be performed by a laboratory assigned by Novo Nordisk.

9.4.7 Safety clinical outcome assessments

Safety COAs will be obtained at visit 2, 4, 6, 8, 9, 10 and 11.

The following COAs will be used:

- PHQ-9[38] is a 9-item depression module of the patient health questionnaire, which is a self-administered diagnostic tool used for assessment of mental disorders.
    - The questionnaire will be available in a linguistically validated translated version.

- C-SSRS[43] is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation.
    - The questionnaire (C-SSRS Baseline and C-SSRS Since Last Visit) will be available in a linguistically validated translated version.
    - The questionnaire will be administered as an interview by the investigator or a qualified delegate, who prior to administering the questionnaire, must complete sufficient training.

At the randomisation visit PHQ-9 and C-SSRS should be obtained, prior to randomising the subject, and scores evaluated according to the randomisation criteria. If the subject does not fulfil the randomisation criteria, SF-36 and the TFEQ-R18v2 are not required.

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 or
- 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 due to safety concern as judged by the investigator.

9.4.8 Ambulatory blood pressure monitoring

At, the end of visit 1 all subjects will have an ambulatory blood pressure monitoring (ABPM) device attached, by site personal, and blood pressure monitoring must be performed for a full 24 hours. At visit 11, only subjects randomised to NNC0174-0833/NNC0174-0833 placebo, will have an ABPM device attached and blood pressure monitoring performed for 24 hours.

During the 24 hour periods the subject is allowed to leave the clinic.

The subject must be trained by the investigator or delegated site staff to remove the ABPM device after 24 hours of blood pressure monitoring and bring the ABPM device to the clinic at the next visit. The investigator or delegated site staff must assess if all blood pressure data have been collected. In case of invalid data the subject must have ABPM performed for another 24 hour period starting at the current visit. If needed the subject should be re-trained in removing the ABPM device.

An ABPM device instruction should be handed out to the subject according to the flowchart.

9.5 Pharmacokinetics

The plasma concentration measurements of NNC0174-0833 will be performed by a laboratory assigned by Novo Nordisk.

Blood samples will be used to evaluate PK of NNC0174-0833 and may also be used to evaluate safety or efficacy aspects that address concerns arising during the trial.

Blood samples for measuring plasma concentration of NNC0174-0833 will be drawn and collected in P800 tubes, for NNC0174-0833/NNC0174-0833 placebo subjects at visits outlined in Appendix 2 and in the laboratory flowchart. Subject must be instructed to withhold their trial product dose in the morning of the clinic visit until blood sampling has been performed.

Long venous stasis time should be avoided when sampling, as venous stasis activates fibrinolytic processes, which may induce proteolytic degradation of NNC0174-0833.

Blood sampling and handling must be performed as detailed in the laboratory flowchart.

The NNC0174-0833 plasma concentration will be measured for all samples from subjects dosed with NNC0174-0833 and selected NNC0174-0833 placebo samples. The remaining NNC0174-0833 placebo samples will only be analysed if the concentration of the selected samples are not below the lower level of quantification.

9.6 Pharmacodynamics

Not applicable for this trial.

9.7 Genetics

Blood samples for genetic analyses will be collected at visit 2, 6 and 11 (Appendix 2 and the laboratory flowchart) from subjects who have consented to participate in the genetic analysis component of the trial. A blood sample for DNA sequencing will be taken at visit 2 and blood samples for RNA sequencing will be taken at visit 2, 6 and 11. Participation in the genetic analysis is optional. Subjects who do not wish to participate in the genetic analysis may still participate in the trial.

The RNA and DNA samples will be sequenced using RNAseq and DNA-sequencing methods. The sequence data will be used for analysis of correlations between weight loss efficacy and expression profiles (RNAseq) or SNP analysis (DNA-sequencing) to provide a better mechanistic understanding of the effects of NNC0174-0833, including whether weight loss can be predicted from baseline characteristics.

Details on processes for collection, shipment and destruction of these samples can be found in the laboratory manual and the laboratory flowchart.

These data will first be analysed after the trial has come to an end, and results will, therefore, not be part of the CTR.

9.8 Biomarkers

Collection of blood samples for biomarker analysis is part of this trial and will be collected from all subjects in this trial as specified in Appendix 2 and in the laboratory flowchart.

9.9 Biosamples for future analysis

Collection of blood samples for future analysis is a component of this trial. Participation in this component is optional and subjects who do not wish to participate may still participate in the trial. Blood samples will be collected for future biomarker analyses at visit 2, 6 and 11 and for future genetic analyses at visit 2 and 11 (Appendix 2 and the laboratory flowchart). All blood samples will be stored for future use.

The samples are collected for the purpose of allowing future biomarker and genetic analyses when new knowledge or improved measurement techniques may have become available.

Biomarker analyses may include biomarkers currently known or discovered in the future. Genetic analyses may include analysis of candidate genes or genetic markers throughout the genome.

Potential biomarker and genetic analyses will be performed with the purpose of understanding and predicting response to NNC0174-0833 as well as understanding obesity or other related diseases. The subject will not be informed about potential results as the analyses are intended for finding trends in the population and not in the individual subject.

The analyses will be performed after the trial has come to an end, and results will, therefore, not be part of the CTR.

10 Statistical considerations

Taxonomy of week 26 assessments
For each subject a given assessment at week 26 may be available or missing and the subject may be on randomised treatment or not. Table 10-1 describes the taxonomy for this. Note, that this is done per assessment and per subject; subjects may be a different type for different assessments (a subject may have 'available on randomised treatment (AT)' for body weight but 'missing on randomised treatment (MT)' for waist circumference).

Table 10-1 Taxonomy for subjects based on week 26 assessments

Assessment at week 26	Subjects on randomised treatment at week 26	Type description	Type Abbreviation
Available	Yes	**Available on randomised treatment**: Subjects who complete the trial on randomised treatment with an assessment at week 26. This includes those that stop and restart trial product.	AT
	No	**Available but discontinued** Subjects who discontinue randomised treatment prematurely but return to have an assessment at week 26. These are also called retrieved subjects.	AD
Missing	Yes	**Missing on randomised treatment**: Subjects who complete the trial on randomised treatment without an assessment at week 26. This includes those that stop and restart trial product.	MT
	No	**Missing and discontinued**: Subjects who discontinue randomised treatment prematurely and do not return to have an assessment at week 26. These are also called non-retrieved subjects.	MD

Treatment non-adherence
'Treatment non-adherence' is defined as the occurrence of either one of the following events:

- Missing two consecutive doses with NNC0174-0833/NNC0174-0833 placebo or seven consecutive doses with liraglutide 3.0 mg/liraglutide placebo

- Lowering the dose for:
  - two consecutive doses with NNC0174-0833/NNC0174-0833 placebo after reaching the target dose
  - one of the weekly collected doses with liraglutide 3.0 mg/liraglutide placebo after reaching the target dose
- Initiating any other weight management drugs
- Undergoing bariatric surgery or use of weight loss device (e.g. intragastric baloons)
- Not reaching target dose according to the escalation regimen. For the respective treatment arms this will be evaluated at the following weeks:

Active treatment / placebo	NNC0174-0833 0.3 mg	NNC0174-0833 0.6 mg	NNC0174-0833 1.2 mg	NNC0174-0833 2.4 mg	NNC0174-0833 4.5 mg	Liraglutide 3.0 mg
Evaluation week	0	0	3	6	9	8

10.1 Sample size determination

The sample size is based on the objective of finding the optimal dose of NNC0174-0833 and is based on the primary endpoint. To characterise the shape of the curve for the dose-response relationship it is considered adequate to test 5 doses of NNC0174-0833 and the sample size for each dose is determined in order to achieve a good precision on this relationship. Furthermore, sample size estimation is based on addressing assumptions corresponding to the analyses of both the primary and secondary estimands.

In the imputation approach used for the sample size calculations addressing the primary estimand missing values (MT and MD) and assessments from retrieved subjects (AD) are assumed to be similar to treatment completers (AT) within the same treatment group. In the imputation approach used for the sample size calculations addressing the secondary estimand, missing values (MT and MD) are assumed to be similar to placebo subjects regardless of treatment arm.

The five different injection volumes in each of the NNC0174-0833 placebo arms and the one liraglutide placebo arm will be pooled into one placebo group 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. This is consistent with findings from previous obesity trials (NN8022-1922 and NN9536-4153).

The assumptions for the sample size calculations are:

- The significance level is 5%

- 100 subjects are included in each of the NNC0174-0833 arms, 100 subjects in the liraglutide 3.0 mg OD arm and 100 subjects in total in the pool of NNC0174-0833 placebo and liraglutide placebo arms

- Assumptions corresponding to the primary estimand:
  - Standard deviation of 5.2% for relative change in weight loss at week 26 (based on data from trial NN9536-4153)
  - Treatment effect versus the pooled placebo group of at least 8% for the optimal dose among completers (based on data from trial NN9536-4153)
  - Treatment effect versus liraglutide 3.0 mg of at least 3% among completers (based on data from trial NN9536-4153 and NN8022-1839)

- Assumptions corresponding to the secondary estimand:
  - Standard deviation of 5.6% for relative change in weight loss at week 26 (based on data from trial NN9536-4153)
  - 13% of subjects discontinue randomised treatment permanently and 60% of these are retrieved (AD) at week 26 (Based on data from trial NN9536-4153)
  - All subjects in the pooled placebo group are assumed to have the same effect as subjects who complete the trial on placebo (AT)
  - Retrieved subjects (AD) in any of the active arms are assumed to have an effect corresponding to half the treatment difference (compared to the pooled placebo group) of subjects who complete the trial in that arm (AT)
  - Non-retrieved subjects (MD) in any of the active arms are assumed to have an effect corresponding to the pooled placebo group
  - Treatment effect versus the pooled placebo group of at least 7.3% for the optimal dose after adjustment for treatment discontinuation and missing data

- The treatment differences are analysed by two-sided t-tests which is a simplification of the main analyses including explanatory variables

The probabilities and power calculations beneath are based on assumptions for the secondary estimand (primary estimand for the treatment effect versus liraglutide 3.0 mg). However, both the primary and secondary estimands will be covered, since the probabilities and power for the primary estimand are higher compared to the secondary estimand.

To characterise the dose-response relationship well, the precision of the mean difference between any NNC0174-0833 dose and the pooled placebo group is evaluated by calculating the probability of the half-width of the confidence interval (CI) to be equal to or below a given value. Table 10-2 gives this probability for different number of subjects and values for the CI half-width.

Table 10-2 Probability of desired CI half-width

N per active arm / N for pooled placebo group	CI half-width (%)	Probability
100	1.7	96%
80	1.7	32%
100	1.6	69%
80	1.6	7%

A sample size of 100 subjects in each active treatment arm compared with a pooled placebo group of 100 subjects allows the 95% CI for the treatment difference between any active arm and placebo to be contained within +/-1.7% of the estimate with 96% probability. This is considered to be a sufficient precision to characterize the dose-response relationship. In total this requires a sample size of 700 subjects.

For the primary endpoint, change from randomisation at week 0 to week 26 in body weight (%), a sample size of 100 subjects in each active treatment arm results in a power of more than 99% for a significant difference between the optimal dose of NNC0174-0833 and the pooled placebo group.

For the primary endpoint a sample size of 100 subjects in each active treatment arm results in a power of 98% for detecting a significant difference between the optimal dose of NNC0174-0833 and liraglutide 3.0 mg for the primary estimand.

10.2 Definition of analysis sets

Two analysis sets are defined:

The *full analysis set* (FAS) includes all randomised subjects according to the intention-to-treat principle.

The *safety analysis set* (SAS) includes all randomised subjects exposed to at least one dose of randomised treatment.

Any observation excluded from the analysis will be documented before database lock with the reason for exclusion provided.

10.2.1 Observation periods

Three observation periods are defined for each subject:

- In-trial: The *in-trial period* is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. Follow-up time for positive antibodies is not included in the in-trial period.

- On-treatment: A time-point is considered as 'on-treatment' if any dose of trial product has been administered within the prior 6 weeks. The on-treatment period is defined as all times which are considered on-treatment. The on-treatment period will therefore be from the date of first trial product administration to date of last trial product administration excluding potential off-treatment time intervals triggered by at least 6 consecutive missed doses for NNC0174-0833 or 6 consecutive weeks of missed dosing with liraglutide.

- Treatment-adherent: A time-point is considered as 'treatment-adherent' if trial product has been administered within the prior 2 weeks with NNC0174-0833 or 1 week with liraglutide and only before the first event of 'treatment non-adherence'. The derived date of the missed or lowered dose causing treatment non-adherence (second consecutive with NNC0174-0833 or seventh consecutive with liraglutide) will be used as the latest date for including assessments in this observation period. For subjects who initiate any other weight loss intervention before this date, the date of starting other weight management drugs or undergoing bariatric surgery will be used as latest date for using assessments in this observation period. Thus, the assessment closest in time and before the date of starting any weight loss intervention will be used as last assessment on randomised treatment. For subjects not reaching target dose according to the escalation regimen no post-baseline assessments will be included.

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

10.3 Statistical analyses

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.

Efficacy endpoints will be analysed using the FAS; safety endpoints will be analysed using the SAS.

Handling of missing baseline data
The last available and eligible observation at or before randomisation is used as the baseline value. If no assessments are available, the mean value at randomisation across all subjects is used as the baseline value.

10.3.1 Primary endpoint

Definition of primary endpoint: % weight change

Change from randomisation at week 0 to week 26 in body weight (%) is defined as:

$$\% \text{ weight change} = \frac{(\text{body weight at week 26} - \text{body weight at baseline})}{\text{body weight at baseline}} \times 100\%$$

10.3.1.1 Analyses addressing the primary estimand

The primary estimand for % weight change addresses the efficacy of NNC0174-0833 and will be estimated based on the FAS using post-baseline measurements up to and including week 26 from the treatment-adherent observation period.

The primary analysis for the primary estimand for % weight change is an analysis of covariance (ANCOVA) with randomised treatment as factor and baseline body weight (kg) as a covariate.

Handling of missing week 26 values for the primary estimand
Observations outside the treatment-adherent observation period such as week 26 assessments for retrieved drop-outs (AD) will be handled as if they were missing and will be imputed using multiple imputation assuming that missing data is missing at random (MAR). Missing data will be imputed using observed data within the same randomised treatment group. This approach makes the assumption that subjects with missing data and subjects with dose non-adherence or weight loss intervention have the same effect as subjects adhering to randomised treatment without initiating any other weight loss intervention.

In case the definition of treatment non-adherence is too restrictive excluding observations due to dose lowering will not be implemented. Next, a higher number of allowed missed dose will be considered.

The multiple imputation is done in three steps:

1. **Imputation:**
    a. Intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each of the treatment groups separately and 1000 copies of the dataset will be generated
    b. A sequential regression approach for imputing monotone missing values at planned visits will be implemented starting with the first visit after baseline and sequentially continuing to the last planned visit at week 26. A model used to impute missing values at each planned visit will be fitted for each of the treatment groups (each NNC0174-0833 dose, liraglutide 3.0 mg or pooled placebo) using observed data. The model will include gender (male/female) and region as factors and baseline and post-baseline body weight (kg) values observed prior to the visit in question as covariates.

2. **Analysis:** An ANCOVA with treatment as categorical effects and baseline body weight (kg) as a covariate will be used to analyse body weight % change at week 26 for each of the 1000 complete data sets generated as part of the imputation of missing values.

3. **Pooling:** Rubin's rule will be used to combine the analysis results in order to draw inference.

The proportion of missing weight change data at week 26 is estimated to be 5% (based on data from trial NN9536-4153) and is expected to be similar in all treatment arms.

Of relevance for the estimation of the primary estimand, the combined proportion of missing data and subjects with treatment non-adherence is estimated to be 13%. This is based on data on proportion of subjects discontinuing treatment from trial NN9536-4153 and a very low expected proportion of subjects undergoing bariatric surgery or starting other weight management drugs. NNC0174-0833 treatment is expected to be effective with regard to weight loss, and this should reduce the number of missed doses due to ineffective therapy. A higher rate of missed doses due to GI AEs is expected in the high NNC0174-0833 dose treatment arms and the liraglutide 3.0 mg arm compared to placebo. Apart from this, the rate of missed doses due to AEs is expected to be similar across groups. Based on previous experience, a higher rate of treatment discontinuation due to other reasons is expected in the placebo group compared to active treatment. This difference may be due to lack of efficacy with placebo treatment.

The estimated treatment difference between individual NNC0174-0833 doses and pooled placebo group will be reported together with the associated two-sided 95% CI and corresponding two-sided p-value. The pooled placebo group will include all subjects on NNC0174-0833 placebo as well as liraglutide placebo.

Confirmation of superiority for each NNC0174-0833 dose vs. placebo will be evaluated using a hierarchical testing procedure starting with the treatment difference between the highest NNC0174-0833 dose and placebo and ending with the lowest dose. In the case of a non-significant treatment difference the testing procedure will stop. This will protect the family-wise type 1 error in the strong sense on a 5% level of significance.

The superiority test for NNC0174-0833 vs. placebo will be carried out as follows. Let $\mu_{\text{NNC0174-0833 ,x}}$ and μ_{placebo} denote the true mean of % weight change for dose level x of NNC0174-0833 and the pooled placebo group, respectively. The null and alternative hypotheses tested are

$$H_0: \mu_{\text{NNC0174}-0833\ ,x} \geq \mu_{placebo} \text{ vs. } H_A: \mu_{\text{NNC0174}-0833\ ,x} < \mu_{placebo}$$

The null hypothesis will be rejected if the upper limit of the estimated two-sided 95% CI for the treatment difference is below 0.

Dose-response modelling
In order to evaluate the effect of NNC0174-0833 dose vs. placebo on % weight change and to characterise the dose-response relationship the mean % weight change will be estimated using dose as a continuous variable.

The dose-response candidate models in Table 10-3 will be fit.

Table 10-3 Dose-response candidate models

Model	Functional form f(d,θ)
E_{max}	$E_0 + E_{max}\frac{d}{ED_{50} + d}$
Sigmoidal E_{max}	$E_0 + E_{max}\frac{d^{\lambda}}{ED_{50}{}^{\lambda} + d^{\lambda}}$
Linear	$E_0 + \beta d$
Linear log-dose	$E_0 + \beta \log(d + 1)$
Quadratic	$E_0 + \beta_1 d + \beta_2 d^2$

The candidate models will be fit to the estimated % weight change means at week 26 for the employed NNC0174-0833 doses and placebo from the primary analysis model described above. Thus all subjects in the FAS will be included and the same assumptions regarding missing values and the impact of explanatory variables will be applied. When fitting the models estimated % weight change means will be weighted by their inverse estimated variances.

The model used to evaluate dose-response will be selected among the candidate models based on the best fit to data. The best fit will be evaluated based on convergence, model complexity, Akaike information criterion (AIC) value and visual evaluation.

Dose-response curves will be estimated and plotted using the fitted dose-response model both for placebo-adjusted and non placebo-adjusted estimates.

Analysis addressing the effect of NNC0174-0833 vs. liraglutide 3.0 mg
This analysis will evaluate the treatment difference between NNC0174-0833 and liraglutide 3.0 mg using the same analysis as the primary analysis for the primary estimand described above. However, the treatment differences between NNC0174-0833 doses and liraglutide will be estimated and no confirmatory testing will be carried out.

Sensitivity analyses
Post-baseline measurements excluded for subjects with treatment non-adherence: This sensitivity analysis will evaluate the robustness to the assumption that post-baseline data for subjects with treatment non-adherence is informative for the weight change had the subjects adhered. The same

analysis model and multiple imputation approach as for the primary analysis will be carried out, but for subjects with dose treatment non-adherence all post-baseline measurements will be handled as missing and imputed using multiple imputation.

10.3.1.2 Analyses addressing the secondary estimand

The following statistical analyses and imputation methods are designed to address the secondary estimand, i.e. to assess the effectiveness of NNC0174-0833.

The analysis model for % weight change is an ANCOVA with randomised treatment as factor and baseline body weight (kg) as a covariate.

Handling of missing week 26 values for the secondary estimand
All available data at week 26 (AT and AD) are used. Missing values (MT and MD) at week 26 will be imputed and the endpoints will be derived from the imputed values. First, a description of the primary imputation approach to address the secondary estimand for the primary endpoints is given followed by a description of the sensitivity analyses used to assess the robustness of the primary analysis results. The sensitivity analyses investigate how assumptions on body weight development after discontinuation of randomised treatment impact the estimated treatment contrasts between active doses and placebo.

Primary imputation approach for the secondary estimand (RS-MI)
The primary analysis of the secondary estimand is a retrieved subjects based multiple imputation approach (RS-MI) which is simplified but similar to the one described by McEvoy[44]. Missing body weight measurement at week 26 for non-retrieved subjects (MD) are imputed using assessments from retrieved subjects (AD). Missing body weight measurements at week 26 for subjects on randomised treatment (MT) are imputed using available measurements at week 26 from subjects on randomised treatment (AT). The multiple imputation approach is done in three steps:

1. **Imputation**: An imputation model is defined using retrieved subjects (AD) from the FAS. The model will be a linear regression of body weight (kg) at week 26 with treatment as factor and baseline body weight (kg), last available treatment-adherent observation of body weight (kg) and number of days in the treatment-adherent observation period as covariates. No interactions will be included. If any subjects are MT, an imputation model for missing body weight measurements at week 26 for MT subjects will also be defined using AT subjects in a similar way. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 26 body weight values. This will be done 1000 times, resulting in 1000 complete data sets.

2. **Analysis**: Analysis of each of the 1000 complete data sets using the ANCOVA with treatment as factor and baseline body weight as covariate, resulting in 1000 estimates for each treatment comparison.

3. **Pooling**: The 1000 estimation results are integrated into a final result using Rubin's formula.

Treatment comparisons for NNC0174-0833 doses vs. placebo will be carried out as described for the primary analysis addressing the primary estimand. However, no confirmatory testing will be carried out.

Dose-response modelling
The selected model shape for the primary estimand will also be estimated based on mean estimates and their variances for % weight change from the ANCOVA model using the primary imputation approach for the secondary estimand.

Analysis addressing the effect of NNC0174-0833 vs. liraglutide 3.0 mg
This analysis will evaluate the treatment difference between NNC0174-0833 and liraglutide 3.0 mg using the same analysis as the primary analysis for the secondary estimand described above. However, the treatment differences between NNC0174-0833 doses and liraglutide will be estimated.

Sensitivity analyses
Multiple imputation approach using retrieved subjects (J2R-MI): A jump to reference multiple imputation approach will be applied. Missing values of body weight at week 26 (MT and MD) for all treatment groups are imputed by using available assessments at week 26 in the placebo group (AT and AD). This approach makes the assumption that subjects with missing data (MT and MD) lose any effect of randomised treatment beyond what can be expected from placebo treatment as adjunct to diet and physical activity. The multiple imputation approach is done in three steps. The imputation step is described below and step two and three are similar to the primary analysis for the secondary estimand.

An imputation model is defined using all placebo subjects from FAS with a week 26 measurement (AT and AD). The model will be a linear regression of body weight (kg) at week 26 on gender (male/female) and region as factors and baseline body weight (kg) as covariate. No interactions will be included. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 26 body weight values for each randomised treatment arm. This will be done 1000 times and results in 1000 complete data sets.

Treatment comparisons for NNC0174-0833 doses vs. placebo and liraglutide will be carried out as described for the analyses addressing the primary estimand.

Tipping-point multiple imputation analysis (TP-MI): First, missing data are imputed according to the primary RS-MI analysis. Second, for the active treatment arm a penalty will be added to the imputed values at week 26. The approach is to gradually increase this penalty until all conclusions from the primary analysis are reversed. For each superiority hypothesis testing an NNC0174-0833

dose vs. placebo the specific value of the penalty that reverses the conclusion will be used to evaluate the robustness of the assumption that subjects with missing data have the same effect as placebo.

10.3.2 Secondary endpoints

10.3.2.1 Supportive secondary endpoints

Supportive secondary endpoints are listed in Section 4. All supportive secondary endpoints will be analysed to address the primary estimand.

Efficacy endpoints

Continuous efficacy endpoints

- Change from randomisation at week 0 to week 26 in:
  - Body weight (kg)
  - Waist circumference (cm)
  - Fasting lipids (mg/dL)
    - Total cholesterol
    - HDL cholesterol
    - LDL cholesterol
    - VLDL cholesterol
    - Triglycerides

These continuous supportive secondary efficacy endpoints will be analysed using the same analysis model as the primary analysis for the primary endpoint addressing the primary estimand described in Section 10.3.1.1. The outcome variable % weight change and the covariate baseline body weight will be replaced by the corresponding outcome and baseline assessments of the endpoint to be analysed. Treatment differences will be estimated comparing each NNC0174-0833 dose with placebo and liraglutide.

For fasting lipids a multiplicative model will be used, i.e. the ratio between post randomisation measurements and baseline will be analysed as the outcome variable instead of differences, and both the outcome variable and the baseline assessment will be log-transformed prior to analysis.

- Change from randomisation at week 0 to week 26 in:
  - HbA_{1c} (%-point, mmol/mol)
  - FPG (mg/dL)
  - Fasting insulin (µIU/mL)
  - HOMA-IR (%-point)
  - HOMA-β (%-point)

These endpoints will be summarised by descriptive statistics using the FAS.

Binary efficacy endpoints

- Subjects who after 26 weeks achieve (yes/no):
  - Body weight reduction ≥ 5% from randomisation
  - Body weight reduction ≥ 10% from randomisation

The analysis model for the 5% and 10% body weight reduction endpoints is a logistic regression using randomised treatment as a factor and baseline body weight (kg) as covariate.

The analysis will be based on FAS using the treatment-adherent observation period and observations outside this observation period will be handled as missing. Missing values of body weight at week 26 are imputed under the same assumption of MAR as for the primary analysis for the primary endpoint addressing the primary estimand using multiple imputation. The imputed data sets for continuous weight change % as described in Section 10.3.1.1 will be used to derive the binary weight reduction endpoints. The logistic regression model will be used to estimate log odds ratios comparing each NNC0174-0833 dose with placebo and liraglutide for each complete data set and Rubin's rule will be used to draw inference. The results after applying Rubin's rule will be back-transformed and described by the odds ratio.

Composite strategy
The following composite variables are defined by subjects who after 26 weeks achieve (yes/no):

- Body weight reduction ≥ 5% from randomisation and no treatment non-adherence
- Body weight reduction ≥ 10% from randomisation and no treatment non-adherence

The analysis approach is the same as the logistic regression model including multiple imputation described above addressing the primary estimand except that for subjects with treatment non-adherence no imputation of missing data will be used. Instead they will be considered not achieving the composite body weight variable.

Dose-response modelling for body weight reduction endpoints
The dose-response analysis of 5% and 10% body weight reduction endpoints will be carried out on the mean estimates of treatment log odds for each NNC0174-0833 dose and placebo obtained via the logistic regression with treatment as factor addressing the primary estimand described above. Candidate shapes listed in Table 10-4 will be fit and evaluated based on the best fit. Normal distribution of the mean estimates for the specific model will be assumed. Mean estimates will be weighted by the inverse of the estimated variances of the mean log odds.

Table 10-4 Binary dose-response candidate models

Model	Link function for probability p	Functional form f(d,θ)
Logistic	$\log[p/(1-p)]$	$E_0 + \beta_1 d$
E_{max}	log[p/(1-p)]	$E_0 + E_{max}\frac{d}{ED_{50}+d}$
Sigmoidal Emax	log[p/(1-p)]	$E_0 + E_{max}\frac{d^{\lambda}}{ED_{50}{}^{\lambda}+d^{\lambda}}$

Sensitivity analyses for supportive secondary endpoints
For supportive secondary endpoints no sensitivity analysis will be carried out.

Safety endpoints

Adverse events and anti-drug antibodies

- Number of TEAEs from randomisation at week 0 to week 32 ('end of trial')
- Number of SAEs from randomisation at week 0 to week 32 ('end of trial')
- Occurrence (yes/no) of anti-drug antibodies towards NNC0174-0833 from randomisation at week 0 to week 32 ('end of trial')

Adverse events will be defined as 'treatment-emergent' (TEAE), if the onset of the event occurs in the on-treatment period, see definition in Section 10.2.1. TEAEs and treatment emergent SAEs will be summarised by descriptive statistics, such as frequencies and rates, using the SAS. No formal statistical inference will be carried out based on the number of TEAEs and SAEs.

Occurrence of anti-drug antibodies towards NNC0174-0833 will be summarised by descriptive statistics using the SAS.

Dose-response modelling for GI AEs
Analyses of the dose-response for the probability of subjects meeting two different response criteria:

- Treatment discontinuation due to a GI adverse event (yes/no)
- Having a GI adverse event (yes/no)

Dose-response modelling will be done on the SAS with binary response status (yes/no) for each subject during the on-treatment observation period as the outcome variable and dose as a continuous covariate. Candidate shapes listed in Table 10-4 will be fit and evaluated based on the best fit.

Continuous safety endpoints

- Change from randomisation at week 0 to week 26 in:
    - Systolic blood pressure (mmHg)

- Diastolic blood pressure (mmHg)
- Mean 24-hour systolic blood pressure (mmHg)
- Mean 24-hour diastolic blood pressure (mmHg)
- Pulse (bpm)
- hsCRP (mg/L)
- PAI-1 activity (mg/L)
- Renin activity (ng/mL/h)
- Aldosterone (ng/dL)

These continuous safety endpoints will be summarised by descriptive statistics using the SAS.

10.3.3 Exploratory endpoints

- Subjects who after 26 weeks achieve (yes/no):
  - Body weight reduction ≥ 15% from randomisation
  - Body weight reduction ≥ 20% from randomisation

These endpoints will be analysed using the same logistic regression approach as described for body weight reduction ≥ 5% and ≥ 10% in Section 10.3.2.1.

- Change from randomisation at week 0 to week 26 in:
  - Endogenous amylin
  - Soluble leptin receptor
  - Leptin
  - SF-36 v2.0 acute:
    - Physical component summary score
    - Mental component summary scores
    - Scores on the individual sub-domains:
      - Physical functioning
      - Role functioning
      - Bodily pain
      - General health
      - Vitality
      - Social functioning
      - Role emotional
      - Mental health
  - TFEQ-R18v2: Transformed scale scores for the three scales measured: Uncontrolled Eating, Cognitive Restraint and Emotional Eating.

- Time to permanent discontinuation of randomised trial product (weeks)

Date of permanent discontinuation of randomised trial product is evaluated by the investigator in the 'end of treatment' form and used to derive the time to permanent discontinuation.

Physical functioning score will be analysed using the same analysis model as the primary analysis for the primary endpoint addressing the primary estimand described in Section 10.3.1.1. The outcome variable % weight change and the covariate baseline body weight will be replaced by the corresponding outcome and baseline assessments of the physical functioning score. Treatment differences will be estimated comparing each NNC0174-0833 dose with placebo and liraglutide.

The remaining endpoints will be summarised by descriptive statistics.

10.3.4 Explorative statistical analysis for pharmacogenetics and biomarkers

No statistical analyses are planned for the genetic data described in Section 9.7. Planned analyses for biomarkers are handled in Section 10.3.1, 10.3.2 and 10.3.4.

10.3.5 Other analyses

All collected data that were not defined as endpoints will be summarised by descriptive statistics.

10.4 Pharmacokinetic and/or pharmacodynamic modelling

Population PK and exposure-response analyses will be used as supportive evidence for the evaluation of efficacy and safety and further to support the dose selection of NNC0174-0833 for future clinical development in subjects with obesity. First, plasma NNC0174-0833 concentrations will be analysed using a population PK model, quantifying covariate (such as baseline body weight, age, gender, race, ethnicity, and injection site) effects on NNC0174-0833 exposure. Second, model based estimates of steady-state average concentrations will be derived for each subject, in order to facilitate subsequent exposure-response analyses. Relevant efficacy and safety endpoints will be related to steady-state average concentrations and subjected to model based analysis.

A modelling analysis plan will be prepared before database lock, outlining details of the analyses. The modelling will be performed by Quantitative Clinical Pharmacology at Novo Nordisk and will be reported separately from the CTR.

11 Appendices

Appendix 1 Abbreviations and Trademarks

AD	available but discontinued
AE	adverse event
AIC	akaike information criterion
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ABPM	ambulatory blood pressure monitoring
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AT	available on randomised treatment
BMI	body mass index
BMR	basal metabolic rate
CFR	Code of Federal Regulations
CI	confidence interval
CLAE	clinical laboratory adverse event
Cmax	maximum concentration of compound
COA	clinical outcome assessment
CRF	case report form
C-SSRS	columbia-suicide severity rating scale
CtR	calcitonin receptor
CTFG	Clinical Trial Facilitation Group
CTR	clinical trial report
DFU	direction for use
DNA	deoxyribonucleic acid
DUN	dispensing unit number
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDAAA	Food and Drug Administration Amendments Act

FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
GI	gastrointestinal
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA_{1c}	glycated haemoglobin
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HOMA-IR	homeostatic model assessment of insulin resistance
HOMA-β	homeostatic model assessment of β-cell function
HRT	hormone replacement therapy
hsCRP	high sensitivity c-reactive protein
IB	investigator's brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalised ratio
IRB	Institutional Review Board
IWRS	interactive web response system
J2R-MI	multiple imputation approach using retrieved subjects
KDIGO	Kidney Disease Improving Global Outcomes
LDL	low density lipoprotein
LH	luteinizing hormone
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MD	missing and discontinued
MPH	mental health professional
MT	missing on randomised treatment
NAFLD/NASH	non-alcoholic fatty liver disease/non-alcoholic steatohepatitis

NYHA	New York Heart Association
OD	once daily
OW	once weekly
PAI-1	plasminogen activator inhibitor-1
PCD	primary completion date
PD	pharmacodynamics
PHQ-9	patient health questionnaire-9
PK	pharmacokinetics
PR	specific ECG interval describing atrioventricular conduction
PTH	parathyroid hormone
PYE	patient years of exposure
PYO	patient years of observation
QRS	specific ECG interval describing ventricular depolarisation
QT	specific ECG interval describing ventricular depolarisation/repolarisation
QTc	heart-rate corrected QT interval
RAAS	renin-angiotensin-aldosterone system
RNA	ribonucleic acid
RS-MI	retrieved subjects based multiple imputation approach
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous
SF-36	short form-36
SIF	safety information form
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TEAE	treatment emergent adverse event
TEE	total daily energy expenditure
TFEQ-R18v2	three factor eating questionnaire revised 18-item version 2
TMM	trial materials manual
TP-MI	tipping-point multiple imputation

TSH	thyroid stimulating hormone
UNL	upper normal limit
VLDL	very low density lipoprotein
WOCBP	woman of child bearing potential

Appendix 2 Clinical laboratory tests

Table 11-1 Protocol required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism[1] (V2, V6, V9, V11)	• HbA_{1c} (also taken at V1) • FPG • Fasting serum insulin • HOMA-IR , calculated • HOMA-β, calculated
Lipids (V2, V6, V9, V11)	• Total cholesterol • HDL cholesterol • LDL cholesterol • Triglycerides • VLDL cholesterol

Table 11-2 Protocol required safety laboratory assessments

Laboratory assessments	Parameters

Haematology
(V1, V2, V4, V6, V8, V9, V11)
	• Erythrocytes
	• Haematocrit
	• Haemoglobin
	• Leucocytes
	• Thrombocytes
	• Mean corpuscular volume
	• Differential count (absolute and percent):
	  o Eosinophils
	  o Neutrophils
	  o Basophils
	  o Lymphocytes
	  o Monocytes

Biochemistry (V1, V2, V4, V6, V8, V9, V11)	• ALT[1,2] • Albumin • Alkaline phosphatase (ALP) • Aspartate aminotransferase (AST)[1,2] • Creatinine • Potassium • Sodium • Total bilirubin • Magnesium • Chloride • hsCRP • eGFR, calculated • Bicarbonate • Creatine kinase

Biochemistry (V1, V2, V4, V6, V8, V9, V11)	• Urea • Gamma glutamyltransferase (GGT) • Amylase • Lipase • Total protein • Uric acid • Phosphate • Total calcium[3] • Albumin adjusted calcium[3], calculated
Biomarkers	• Calcitonin (V2, V6, V9, V11) • Parathyroid hormone (PTH) (V2, V4, V6, V8, V9, V11) • Calcitriol (V2, V4, V6, V8, V9, V11) • TSH (V1) • Follicle-stimulating hormone (FSH)[4] (V1) • Cortisol (V2, V6, V9, V11) • PAI-1 activity (V2, V6, V9, V11) • Renin activity (V2, V6, V9, V11) • Aldosterone (V2, V6, V9, V11) • Alpha-subunit[5] (V2, V6, V11)
Antibodies (V2, V4, V6, V8, V11, V12)	• Anti-NNC0174-0833 antibodies[6]
Pregnancy testing (V1, V2, V4, V6, V7, V8, V9, V10, V11, V12)	• Urine human chorionic gonadotropin (hCG) pregnancy test[7,8]
Urinanalysis (V2, V4, V6, V9, V11)	• Protein-to-creatinine ratio
Other tests (V4, V6, V8, V11, V12)	• NNC0174-0833 plasma concentration[6]

Notes:

[1] If ALT or AST > 3x UNL, additional blood samples should be taken from the subject to analyse international normalised ratio (INR) (except at screening visit). Repeated testing of the abnormal lab assessments should be performed for the subject until abnormalities return to normal or baseline state.

[2] A laboratory 'hepatic event' form should be completed in the CRF once for each time that the liver parameters increase the below thresholds:

- ALT > 5x UNL or
- AST > 5x UNL

[3] If the investigator has a suspicion of hypocalcaemia, additional blood sample must be taken from the subject to measure the ionised calcium level at local laboratory. If hypocalcaemia is confirmed then an AE must be reported and the ionised calcium result must be entered on an additional data collection form for hypocalcaemia in the CRF.

[4] Only applicable for postmenopausal women.

[5] Alpha-subunit is a pituitary tumour marker corresponding to the common alpha-subunit peptide in luteinizing hormone (LH), FSH, hCG and TSH.

[6] Only applicable for subjects randomised to NNC0174-0833/NNC0174-0833 placebo.

[7] Only for postmenopausal female subjects who have stopped menstruating within the last 5 years and for female subjects with bilateral tubal ligation.

[8] Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.

Table 11-3 Protocol required exploratory laboratory assessments

Laboratory assessments	Parameters
Biomarkers (V2, V6, V9, V11)	• Leptin • Soluble leptin receptor • Endogenous amylin
Genetics analyses[1]	• DNA sequencing (V2) • RNA sequencing (V2, V6, V11)
Biosamples for future analysis[1]	• Biomarkers analyses (V2, V6, V11) • Genetic analyses (V2, V11)
Notes: [1] Only to be taken from subjects who have consented.	

- The tests detailed in Table 11-1, Table 11-2 and Table 11-3 will be performed by a central laboratory, with the exception of the following which will be performed at a specialised laboratory:
  - NNC0174-0833 plasma concentration
  - Anti-NNC0174-0833 antibodies
  - Leptin
  - Soluble leptin receptor
  - Endogenous amylin
  - Pregnancy testing (local urine test)
- Laboratory results that could unblind the trial (i.e. antibodies and NNC0174 -0833 plasma concentration) will not be reported to the trial sites until the trial has been unblinded. Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.
- Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local 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.
- Laboratory samples will be destroyed no later than at finalisation of the CTR except human biosamples for future analysis and samples for measurements of NNC0174-0833 plasma concentration and antibodies, which will be stored as described in Appendix 7.

- For haematology samples (differential count) where the test result is not normal, then a part of the sample may be kept for up to two years or according to local regulations.

Appendix 3 Trial governance considerations

1) Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[45] and applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guideline[46]
  - Applicable laws and regulations
- The protocol, informed consent form, IB (as applicable) and other relevant documents (e.g. advertisements), must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
  - providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
  - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
  - ensuring submission of the CTR synopsis to the IRB/IEC.

2) Financial disclosure

Investigators and subinvestigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and one year after completion of the trial.

For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

3) Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the subject and answer all questions regarding the trial.
- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[46], Declaration of Helsinki[45] and the IRB/IEC or trial site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the trial.
- A copy of the informed consent form(s) must be provided to the subject.

4) Information to subjects during trial

The site will be offered a communication package for the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the subjects. The written information will be translated and adjusted to local requirements and distributed to the subject at the discretion of the investigator.

The subject may receive a 'welcome to the trial letter' and a 'thank you for your participation letter' after completion of the trial.

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

Different initiatives for subject retention will be implemented throughout this trial. Site retention activities may include cooking classes, group meetings, fitness memberships and others. Materials and items will be supplied 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.

The initiatives for subject retention must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

5) Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.
- The subject must be informed that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

6) Committee structure

Novo Nordisk safety committee
Novo Nordisk will constitute an internal NNC0174-0833 safety committee to perform ongoing safety surveillance. The NNC0174-0833 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.

7) Publication policy

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 investigators 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 CTR for this trial.
One investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators. The signatory investigator(s) will be

appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[47].

Communication of results
Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed 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. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR is available. This includes the right not to release the results of interim analyses, because the release of such information may 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. 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.

Authorship
Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the trial concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors[47].

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned 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.

Site-specific publication(s) by investigator(s)
For a multicentre 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. Thus, Novo Nordisk may deny a

request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the trial.

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.

8) Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[48], the Food and Drug Administration Amendment Act (FDAAA)[49], European Commission Requirements[50, 51] 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.

The primary completion date (PCD) is the last assessment of the primary endpoint, and is for this trial last subject first treatment + 26 weeks corresponding to visit 11 'end of treatment' visit. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 11. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

9) Data quality assurance

Case Report Forms

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- For some data both electronic and paper CRFs are used.
- The following will be provided as paper CRFs:
    - Pregnancy forms
- The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:
    - AE forms
    - Safety information forms (SIFs)

- Technical complaint forms (also to be used to report complaints that are not subject related, e.g. discovered at trial site before allocation)

- Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.
- The investigator must ensure that data is recorded in the CRF as soon as possible after the visit, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

Monitoring

- The investigator must permit trial related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data 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).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site staff are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Monitoring will be conducted using a risk based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to trial sites.
- Monitors will review the subject's medical records and other source data, e.g. the diaries, to ensure consistency and/or identify omissions compared to the CRF.

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 CRF or via listings from the trial database.

10) Source documents

- All data entered in the CRF must be verifiable in source documentation other than the CRF.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the trial site.
- Data reported on the paper CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify subject's medical history in source documents such as subject's medical record.
- Subjects completing electronic patient reported outcomes instruments are the data originators. Data will be transmitted to a technology service provider database, thus the service provider database is the source.
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each trial site. There will only be one source document defined at any time for any data element.

11) Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the trial site. If the provided electronic 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.
- Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

12) Trial and site closure

Novo Nordisk reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or 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.

Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a trial site by Novo Nordisk or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further trial product development

13) Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the trial site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.
A qualified physician, who is an investigator or a subinvestigator for the trial, must be responsible for all trial related medical decisions.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents, including the subject identification code list must be kept in a secure locked facility so that 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 staff must have sufficient English skills according to their assigned task(s).

14) 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 may pay additional costs incurred in relation to assessments relevant for following the safety of the subject. Investigator must contact Novo Nordisk on a case by case basis for whether the costs will be covered.

Novo Nordisk accepts liability in accordance with: Belgian law concerning experiments on the human person of 07 May 2004 - Article 29: §1.

Appendix 4 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting

AE definition
• An AE is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • An AE can be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • A clinical laboratory adverse event (CLAE): a clinical abnormal laboratory finding 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. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms or the clinical sequelae of a suspected overdose of trial product regardless of intent.
Events NOT meeting the AE definition
• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product. Note: pre-existing conditions should be recorded as medical history/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.

Definition of an SAE
An SAE is an AE that fulfils at least one of the following criteria:
• **Results in death**
• **Is life-threatening** The term 'life-threatening' in the definition of 'serious' 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 were more severe.
• **Requires inpatient hospitalisation or prolongation of existing hospitalisation** o Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious. o Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Note: ▪ 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.

- **Results in persistent disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions
  - This definition is not intended to include experience of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Important medical event:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
  - The following adverse events must always be reported as SAEs using the important medical event criterion, if no other seriousness criteria are applicable:
    - suspicion of transmission of infectious agents via the trial product.
    - risk of liver injury defined as ALT or AST >3x UNL and total bilirubin >2x UNL, where no alternative aetiology exists (Hy's law).

Description of AEs requiring additional data collection (via specific event form)

AEs requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the safety of the trial product, see Table 9-1.

Event type	Description
Medication error	A medication error concerning trial products is defined as: • Administration of wrong drug. ○ Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in a confirmed administration of wrong drug. • Wrong route of administration, such as intramuscular instead of subcutaneous. • Administration of an overdose with the intention to cause harm, misuse or abuse of trial product. • Accidental administration of more than the planned dose of liraglutide and/or NNC0174-0833 or a higher dose(s) than intended during dose escalation. The administered dose(s) must deviate from the intended dose(s) to an extent where clinical consequences for the subject were likely to happen as judged by the investigator, although they did not necessarily occur.
Acute gallbladder disease	Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis)
Acute coronary syndrome	Acute Coronary Syndrome conditions include all types of acute myocardial infarction and hospitalisation for unstable angina pectoris
Cerebrovascular events	Episode of focal or global neurological dysfunction that could be caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction
Heart failure	Presentation of the patient for an urgent, unscheduled clinic/office/emergency department visit or hospital admission, with a primary diagnosis of heart failure (new episode or worsening of existing heart failure)

Coronary artery revascularisation	A coronary revascularisation procedure is a catheter-based (percutaneous coronary intervention) or a surgical procedure (coronary artery bypass grafting) designed to improve myocardial blood flow
Neoplasm	Neoplasm by histopathology or other substantial clinical evidence
Hypocalcaemia	A suspicion of hypocalcaemia or assessment of concentration of ionised calcium lower than 0.9 mmol/L (3.6 mg/dL) (must be confirmed by a single repeat test at local lab)

The selection of these events is based on the non-clinical and clinical data with NNC0174-0833 and liraglutide, knowledge from the glucagon-like peptide-1 receptor agonist (GLP-1 RA) drug class as well as regulatory requirements.

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the CRF.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
- For all non-serious AEs the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE related forms refer to 'SAE reporting via paper CRF' later in this section.
- Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the SIF. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

The investigator will assess intensity for each event reported during the trial and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: Severe is a category used for rating the intensity of an event; and both an AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the outcomes described in the definition of an SAE and not when it is rated as severe.

Assessment of causality

The investigator is obligated to assess the relationship between trial product and the occurrence of each AE/SAE.

Relationship between an AE/SAE and the relevant trial product*(s)* should be assessed as:

- 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.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to trial product administration will be considered and investigated.

The investigator should use the IB for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data**.

The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate 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 sequelae 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 a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the subject is lost to follow-up.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology.

New or updated information will be recorded in the CRF.

SAE reporting via electronic CRF

- Relevant forms (AE and SIF) must be completed in the CRF.
- For reporting and sign-off timelines, see box below.
- If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form and if the CRF is

unavailable for more than 5 calendar days then the site will use the paper SIF (see box below).
- The site will enter the SAE data into the CRF as soon as it becomes available, see Section 9.2.1.
- After the trial is completed at a given site, the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after CRF decommission, then the site can report this information on a paper AE and SIF (see box below) or to Novo Nordisk by telephone.

SAE reporting via paper CRF

- Relevant CRF forms (AE and SIF) must be forwarded to Novo Nordisk either by fax, e-mail or courier.
- Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and SIF within the designated reporting time frames (as illustrated in Figure 9-1):
  - AE form within 24 hours
  - SIF within 5 calendar days
  - Both forms must be signed within 7 calendar days

Contact details for SAE reporting can be found in the investigator trial master file.

Appendix 5 Contraceptive guidance and collection of pregnancy information

Definitions

Woman of childbearing potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP

1. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
   - Documented bilateral tubal ligation[1]

   Note: Documentation can come from the site staff's review of subject's medical records, medical examination or medical history interview.
2. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before trial enrolment.

Pregnancy testing
Only women not considered WOCBP are eligible for inclusion in this trial.

- Urine pregnancy tests must be performed for postmenopausal female subjects who have stopped menstruating within the last 5 years and for female subjects with bilateral tubal ligation.
- Urine pregnancy test must be repeated at any time during the trial if pregnancy is suspected.

[1] Female subjects with bilateral tubal ligation must ensure the use of an occlusive cap (e.g. diaphragm) with/without the use of spermicide or that their male partner uses a condom throughout the trial (until 'end of trial').

Collection of pregnancy information

Male subjects with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any female partner who becomes pregnant while male subject is participating in this trial. This applies only in case of abnormal outcome of the pregnancy and in case male subject receives trial product.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to Novo Nordisk within 14 calendar days of learning of the abnormal outcome of the partner's pregnancy. Information on the status of the mother and child will be included.
- Generally, follow-up will be 1 month following the delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for procedure.

Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to Novo Nordisk. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to Novo Nordisk as described in Appendix 4. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the trial must discontinue trial product.

Appendix 6 Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

Technical complaint definition
• 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:

- Problems with the physical or chemical appearance of trial products (e.g. discoloration, particles or contamination).
- Problems with packaging material including labelling.
- Problems related to medical devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen-injector and the needle).

Time period for detecting technical complaints
All technical complaints, which occur from the time of receipt of the product at trial site until the time of the last usage of the product, must be collected for products predefined on the technical complaint form.

Reporting of technical complaints to Novo Nordisk
Contact details (fax, e-mail and address) for Customer Complaint Center – refer to Attachment I Technical complaints must be reported on a separate technical complaint form: 1. One technical complaint form must be completed for each affected DUN 2. If DUN is not available, a technical complaint form for each batch, code or lot number must be completed

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within the timelines specified in Figure 9-4 . If the CRF 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 CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

Follow-up of technical complaints
The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples
The investigator must collect the technical complaint sample and all associated parts that were packed in the same DUN and notify the monitor within 5 calendar days of obtaining the sample at trial site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical

complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together. Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

Reporting of technical complaints for Novo Nordisk products not included in technical complaint form
Technical complaints on Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk affiliate with a reference to trial ID.

Appendix 7 Retention of human biosamples

Antibody samples and samples for measurement of NNC0174-0833 plasma concentration

- Residual antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug if required by health authorities or for safety reasons. Residual antibody samples may also be used for exploratory investigation of antibodies.
- The antibody analyses will be performed by Immunogenicity Assessment at Novo Nordisk or a laboratory assigned by Novo Nordisk.
- Residual samples for measurement of NNC0174-0833 plasma concentration may be retained to allow residual PK/pharmacodynamics (PD) analyses or exploratory investigation of metabolites, method validation purposes or further characterisation of antibody response.
- The residual PK/PD analyses/exploratory investigations will be performed by Development Bioanalysis at Novo Nordisk, or a laboratory assigned by Novo Nordisk.
- All samples will be stored at Novo Nordisk or at a Novo Nordisk designated biorepository/ laboratory after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.
- Residual samples for measurement of NNC0174-0833 plasma concentration may be stored for a shorter period of time pending the stability of the compound or metabolites to be assessed.
- Only Novo Nordisk personnel and biorepository/laboratory personnel will have access to the stored samples.
- The samples may be transferred to other countries for analysis, if not prohibited by local regulations.
- The subject's identity will remain confidential and the samples will be identified only by subject number, visit number and trial identification number. No direct identification of the subject will be stored together with the samples. The analyses will not have any medical consequences for the subjects or their relatives.
- Subjects can contact the investigator if they wish to be informed about results derived from stored samples obtained from their own body.
- Results will be documented independently and reported separately from the CTR.

Biosamples for future analysis

- The trial will involve collection of human biosamples (blood samples) to be stored for future analysis. Subjects must sign and date a separate informed consent form before blood samples are collected for storage for future analysis.
- The biosamples are collected at visit 2, 6 and 11 (Section 9.9).

- The biosamples will be stored at Novo Nordisk or at a Novo Nordisk designated biorepository after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.
- Only Novo Nordisk personnel and biorepository personnel will have access to the stored samples.
- The biosamples may be transferred to other countries for analysis, if not prohibited by local regulations.
- The subject may request the stored biosamples to be destroyed by withdrawing the designated informed consent. The results obtained from any already performed analyses of the samples will still be used.

Appendix 8 Country-specific requirements

Section 3.3.4 Identified risks for liraglutide 3.0 mg
For Japan: Detailed information about reasonably expected AEs can be found in the local package insert for Victoza®.

Section 6.1 Inclusion criterion no. 2
For Japan: age ≥ 20 years at the time of signing the informed consent

Section 6.1 Inclusion criterion no. 3
For Belgium, Denmark, Finland, Ireland, Poland, Serbia and United Kingdom: Adequate contraceptive methods as defined by the Clinical Trial Facilitation Group (CTFG)[52]: Use of condoms (with or without spermicide) or sexual abstinence (i.e. refraining from heterosexual intercourse) throughout the trial (until 'end of trial').

Section 7.5 Preparation/Handling/Storage/Accountability
For Japan: The head of the study site or the trial product storage manager assigned by the head of the study site (a pharmacist in principle) is responsible for control and accountability of the trial products.

Section 9.9 Biosamples for future analysis
For South Africa: Biosamples for future analysis will not be collected in South Africa.

Appendix 3, 1) Regulatory and ethical considerations
For Japan: A name and seal is accepted as a signature.

Appendix 3, 14) Indemnity statement
For 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.

12 References

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766-81.
2. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017;377(1):13-27.
3. Zeller MH, Hunsaker S, Mikhail C, Reiter-Purtill J, McCullough MB, Garland B, et al. Family factors that characterize adolescents with severe obesity and their role in weight loss surgery outcomes. Obesity (Silver Spring). 2016;24(12):2562-9.
4. Han TS, Tajar A, O'Neill TW, Jiang M, Bartfai G, Boonen S, et al. Impaired quality of life and sexual function in overweight and obese men: the European Male Ageing Study. Eur J Endocrinol. 2011;164(6):1003-11.
5. Soltoft F, Hammer M, Kragh N. The association of body mass index and health-related quality of life in the general population: data from the 2003 Health Survey of England. Qual Life Res. 2009;18(10):1293-9.
6. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013;309(1):71-82.
7. Prospective Studies C, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373(9669):1083-96.
8. American Society for Metabolic and Bariatric Surgery (ASMBS). Obesity is a Disease: Leading Obesity Groups Agree. 19 Jun 2103.
9. Mechanick JI, Garber AJ, Handelsman Y, Garvey WT. American Association of Clinical Endocrinologists' position statement on obesity and obesity medicine. Endocr Pract. 2012;18(5):642-8.
10. Toplak H, Woodward E, Yumuk V, Oppert JM, Halford JC, Frühbeck G. 2014 EASO Position Statement on the Use of Anti-Obesity Drugs. Obes Facts. 2015;8(3):166-74.
11. Fruhbeck G, Toplak H, Woodward E, Yumuk V, Maislos M, Oppert JM, et al. Obesity: the gateway to ill health - an EASO position statement on a rising public health, clinical and scientific challenge in Europe. Obes Facts. 2013;6(2):117-20.
12. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(2):342-62.
13. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al. European Guidelines for Obesity Management in Adults. Obes Facts. 2015;8(6):402-24.
14. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care. 1995;18(4):517-22.
15. Hofso D, Jenssen T, Hager H, Roislien J, Hjelmesaeth J. Fasting plasma glucose in the screening for type 2 diabetes in morbidly obese subjects. Obes Surg. 2010;20(3):302-7.
16. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, et al. Diabetes trends in the U.S.: 1990-1998. Diabetes Care. 2000;23(9):1278-83.

17. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2006;113(6):898-918.
18. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009;9:88.
19. Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. Gastroenterology. 2012;142(4):711-25 e6.
20. Deitel M, Stone E, Kassam HA, Wilk EJ, Sutherland DJ. Gynecologic-obstetric changes after loss of massive excess weight following bariatric surgery. J Am Coll Nutr. 1988;7(2):147-53.
21. Eheman C, Henley SJ, Ballard-Barbash R, Jacobs EJ, Schymura MJ, Noone AM, et al. Annual Report to the Nation on the status of cancer, 1975-2008, featuring cancers associated with excess weight and lack of sufficient physical activity. Cancer. 2012;118(9):2338-66.
22. Round-table discussion on obesity and weight loss. There is no miraculous cure but persistent physicians can help most people to reduce. Nord Med. 1975;90(5):145-53.
23. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical evaluation of medicinal products used in weight management (EMA/CHMP/311805/2014). 23 Jun 2016.
24. OECD. Obesity Update 2014.
25. Frühbeck G, Sbraccia P, Nisoli E, Woodward E, Yumuk V, Farpour-Lambert NJ, et al. 2015 Milan Declaration: A Call to Action on Obesity - an EASO Position Statement on the Occasion of the 2015 EXPO. Obes Facts. 2016;9(4):296-8.
26. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403.
27. Mertens IL, Van Gaal LF. Overweight, obesity, and blood pressure: the effects of modest weight reduction. Obes Res. 2000;8(3):270-8.
28. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr. 1992;56(2):320-8.
29. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology. 2015;149(2):367-78 e5; quiz e14-5.
30. Warkentin LM, Das D, Majumdar SR, Johnson JA, Padwal RS. The effect of weight loss on health-related quality of life: systematic review and meta-analysis of randomized trials. Obes Rev. 2014;15(3):169-82.
31. Wing RR, Phelan S. Long-term weight loss maintenance. Am J Clin Nutr. 2005;82(1 Suppl):222S-5S.
32. Young A, Denaro M. Roles of amylin in diabetes and in regulation of nutrient load. Nutrition. 1998;14(6):524-7.

33. Boyle CN, Lutz TA, Le Foll C. Amylin - Its role in the homeostatic and hedonic control of eating and recent developments of amylin analogs to treat obesity. Molecular metabolism. 2018;8:203-10.
34. Novo Nordisk A/S. Investigator's Brochure, NNC0174-0833, project NN9838, (edition 4). Sep 2018.
35. Wells G, Chernoff J, Gilligan JP, Krause DS. Does salmon calcitonin cause cancer? A review and meta-analysis. Osteoporos Int. 2016;27(1):13-9.
36. Novo Nordisk A/S. Investigator's Brochure, Liraglutide 3.0 mg (Saxenda®), project NN8022 (edition 11). 31 Mar 2018.
37. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3(1):1-150.
38. Kroenke K, Spitzer RL, Williams JB. The PHQ-9 - Validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-13.
39. FAO/WHO/UNU. Human energy requirements. Report of a joint FAO/WHO/UNU expert consultation. FAO: food and nutrition technical report series 1. 2004.
40. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11.
41. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
42. Cappelleri JC, Bushmakin AG, Gerber RA, Leidy NK, Sexton CC, Lowe MR, et al. Psychometric analysis of the Three-Factor Eating Questionnaire-R21: results from a large diverse sample of obese and non-obese participants. Int J Obes (Lond). 2009;33(6):611-20.
43. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164(7):1035-43.
44. McEvoy BW. Missing data in clinical trials for weight management. J Biopharm Stat. 2016;26(1):30-6.
45. World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.
46. International Conference on Harmonisation. ICH Harmonised Tripatite Guideline. Guideline for Good Clinical Practise E6(R2), Step 4. 09 Nov 2016.
47. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals; current version available at www.icmje.org.
48. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351(12):1250-1.
49. U.S. Food and Drug Administration. Food and Drug Administration Amendments Act of 2007 as amended by the Final Rule "Clinical Trials Registration and Results Information Submission". 21 September 2016.
50. The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the

laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, article 11. Official Journal of the European Communities. 01 May 2001.

51. The European Parliament and the Council of the European Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. 30 April 2004.

52. Clinical Trial Facilitation Group (CTFG), Heads of Medicines Agencies. Recommendations related to contraception and pregnancy testing in clinical trials. 15 Sep 2014.

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, version 2.0 dated 02 October 2018

Trial ID:NN9838-4433

Investigation of safety and efficacy of NNC0174-0833 for weight management – a dose finding trial

Trial phase: II
Applicable to United Kingdom

Table of Contents

1 Introduction including rationale for the protocol amendment

The protocol is amended for the following reasons:

- To include the end of trial definition for the United Kingdom
- To clarify that United Kingdom subjects meeting treatment discontinuation criterion 2 will not be allowed to resume trial product.

In this protocol amendment:

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

2 Changes

2.1 Appendix 8 Country-specific requirements

Section 5.3 End of trial definition

For United Kingdom: *The end of the trial is defined as the date of the last visit of the last subject in the trial, including the potential two follow-up analyses for subjects testing positive for antibodies against NNC0174-0833 at visit 12.*

Section 8.1 Discontinuation of trial product

For United Kingdom: *Subjects meeting treatment discontinuation criterion 2 (pregnancy) will not be allowed to resume trial product if the criterion is no longer met.*

Protocol Amendment

no 2

to Protocol, version 2.0 dated 02 October 2018

Trial ID: NN9838-4433

Investigation of safety and efficacy of NNC0174-0833 for weight management – a dose finding trial

Trial phase: 2
Applicable to Japan

Table of Contents

1 Introduction including rationale for the protocol amendment

The protocol is amended for the following reason:

- To specify the contraceptive methods for Japan.

In this protocol amendment:

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

2 Changes

2.1 Appendix 8 Country-specific requirements

Section 6.1 Inclusion criterion no.3

For Japan: *Adequate contraceptive methods for male subjects are use of condoms (with or without spermicide) or sexual abstinence (i.e. refraining from heterosexual intercourse) throughout the trial (until 'end of trial')*

~~CONFIDENTIAL~~

Completed

Memo

To: Health Authorities and Ethics Committees in Countries Affected by the COVID-19 Pandemic

From: Novo Nordisk A/S

Trial ID: NN9838-4433

Pages: X

25-JUN-2020

Notification of the impact, mitigation measures, and high-level risk assessment of the outbreak of the coronavirus (COVID-19)

This memo is submitted for notification and serves as a short overview of the impact of the COVID-19 pandemic, with the mitigation measures taken and a high-level conclusion to the risk assessment for NN9838-4433 conducted in Country.

In case any changes required/requiring a substantial amendment, this was/will be submitted separately for approval.

It is important to emphasize, that the measures described below, only have been implemented where deemed needed. The trial sites should always follow the trial protocol to the extent possible.

Novo Nordisk will make an update to this memo, whenever any significant changes to the risk-benefit balance occur, until the COVID-19 pandemic has stabilised, and normal practice has been restored in all countries.

A more comprehensive impact assessment will be included in the Clinical Trial Report for all COVID-19 impacted trials.

Novo Nordisk A/S [redacted]

Telephone: [redacted]
Direct dial:

Internet:
www.novonordisk.com

~~CONFIDENTIAL~~

Impact, mitigation measures taken and a high-level risk assessment, <u>trial level</u>

Trial ID:	NN9838-4433
Protocol title:	Investigation of safety and efficacy of NNC0174-0833 for weight management – a dose finding trial
Status:	Completed (except long-term follow-up on antibodies for a few number of subjects)
First subject first treatment:	07-MAR-2019
Last subject last treatment:	13-MAR-2020
Database lock:	06-MAY-2020 The clinical trial report is expected completed Q4 2020.
Visit schedule:	Only 'End of trial' visits (V12) were outstanding when the Covid-19 pandemic started. For subjects who were not allowed to attend the clinical trial sites or refused to attend the clinical trial sites, the site staff was recommended to convert the V12 to phone visit and collect data as applicable verbally to secure subjects' safety. In cases where site staff was concerned the clinical trial site would close, or subject would refuse to attend the last visit, V12 could be performed at the clinical trial site prior to visit window, however, at the earliest 5 weeks after V11 (End of treatment). V12 then had to be followed up by a phone visit within V12 visit window specified in the protocol, where AEs, concomitant medication and urine pregnancy test result were collected.

	To the extent possible, site staff continued to collect all trial-related information/data in the subject's medical records and continue to update the relevant data capture systems in a timely manner (e.g., EDC, IWRS).
Primary endpoint:	As primary endpoint is body weight change from baseline to V11, there is no impact on the primary endpoint. For a small group of subjects, body weight could not be performed on-site at V12 and the visit was converted to phone visit. When V12 was converted to a phone visit, the subject was instructed to measure body weight on own scale.
Trial product treatment:	No impact
Subject safety:	For very few subjects, where V12 clinic visit was converted to a phone visit, pulse and blood pressure and blood sampling for protocol-required assessments (antibody and PK) were not collected, these are considered missing. Pregnancy testing was advised to be performed at home for the subjects requiring a pregnancy test at V12 according to protocol.
Informed Consent:	No changes to the IC form have been required.
Substantial amendment:	No substantial amendment has been submitted.
Conclusion on risk assessment:	The Trial Team has evaluated that the measures recommended do not impact the overall integrity and quality of the trial and did not impose an increased risk for the participating subjects.

Below section to be completed by Local affiliate:

~~CONFIDENTIAL~~

Adjust on local level and complete according to expectation from local authorities.
The section can be deleted, if not a local requirement
Keep the text short. Only describe relevant local changes which are different than the above or not implemented locally.

Impact, mitigation measures taken and a high-level risk assessment, country level

Visit schedule:	Implemented as described above at all/some sites, 'not applicable' or describe if different than above
Primary endpoint:	'Implemented as described above' 'not applicable, or describe if different than above
Trial Product treatment:	'Implemented as described above' 'not applicable, or describe if different than above
Subject safety:	'Implemented as described above' 'not applicable, or describe if different than above
Informed Consent:	'Implemented as described above' 'not applicable, or describe if different than above
Monitoring:	When necessary, on-site monitoring has been replaced by additional off-site monitoring activities and centralised monitoring. Please add any relevant country specific information.
Alternative dispensing of trial product, from site to subject:	'Not applicable' or describe if any of the alternative dispensing methods have been implemented: The following alternative dispensing method(s) has/have been implemented where the subject cannot visit the site and the investigator has judged it safe to continue treatment: 1. Trial Products are collected at site by appointed substitute 2. Trial Products are delivered by a site staff member to the subject/substitute off site 3. Trial Products are delivered to the subject by an approved courier. 4. Shipment of trial product from sponsor (central or local depot) directly to subjects

	If information on alternative dispensing method has already been submitted to your Health Authority; then consider deleting the text and only refer to that application. Please note that option 4 requires Health Authority approval. Include information if you have option 4 approved in your country, e.g., with a reference to the application and approval.
Substantial amendment:	Comment on whether any of the above or other mitigations have been submitted as a substantial amendment
Conclusion on risk assessment:	Include a short conclusive description of the local risk assessments

Novo Nordisk will continue to keep Health Authorities and Ethics Committees notified of changes to trial conduct, in accordance with local regulations and guidance on reporting of impacted trial conduct due to the COVID-19 pandemic.

With regards

Local affiliate contact