Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04102189
Sponsor trial ID:	NN9536-4451
Official title of study:	Effect and safety of semaglutide 2.4 mg once weekly on weight management in adolescents with overweight or obesity
Document date*	03 February 2021

*Document date refers to the date on which the document was most recently updated. Note: The date in the header of Page 2 is the date of compilation of the documents and not of an update to content.

16.1.1 Protocol and protocol amendments

List of contents

Protocol

Protocol title:

Effect and safety of semaglutide 2.4 mg once weekly on weight management in adolescents with overweight or obesity

Substance: semaglutide

Universal Trial Number: U1111-1215-7560

EUdraCT Number: 2018-002431-18

Trial phase: 3a

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
Protocol version 2.0	06 January 2021	Austria, Belgium, Croatia, Ireland, Mexico, Russia, United Kingdom, United States
Original protocol version 1.0	09 April 2019	All countries

Protocol version 2.0 (06 January 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union[1] for the countries participating in the NN9536-4451 trial.

Overall rationale for preparing protocol, version 2.0:

Co-participation in other clinical trials is generally not allowed while participating in a Novo Nordisk trial. However, given the large societal impact of the COVID-19 pandemic, Novo Nordisk will allow for co-participation in trials with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions. For the current trial it has been evaluated that the safety profile of semaglutide is well established and based on current knowledge it is expected that co-participation in COVID-19 trials will not lead to unreasonable unforeseen risks for trial subjects. Discontinuation criterion 6 regarding simultaneous participation in other trials has thus been amended. A number of other changes were implemented for clarification of trial procedures; see below.

Section # and name	Description of change	Brief rationale
Table of Contents	Addition of the two attachments I and II to the Table of Contents.	Correction of omission.
Section 7.6	Further details added for how to assess drug treatment compliance.	Implementation of information previously sent out by memo to sites.
Section 8.1	Amending discontinuation criterion 6, so that subjects are allowed to continue in the trial, while also participating in a COVID-19 trial.	To allow for simultaneous participation in current trial and a COVID-19 trial.
Section 9.1.1	Waist circumference to be measured to the nearest 0.5 cm or 0.2 inch, instead of to the nearest cm or inch.	To increase precision of measurement.
Section 9.4	Correction of the definition of concomitant illness.	The previous definition of concomitant illness was faulty.
Section 9.9 and Appendix 7	Correction of the requirement for signing the separate ICF for biosamples.	The requirement for signing of the separate ICF for biosamples depends on local legislation.
Section 10	Description of the 'available on randomised treatment (AT)' category updated in Table 10.1 "Taxonomy for subjects based on week 68 assessments being available or missing"	Clarification that subjects must have a week 68 assessment to be in scope for this category.
Appendix 2	Details added of how abnormal values identified by the central lab should be handled.	Clarification in order to avoid misunderstandings of process.
Appendix 5	Detailed description of timing of pregnancy tests replaced with a cross-reference to Appendix 2 where the visits are listed.	Alignment of directions for urine pregnancy testing given in Appendix 2, Appendix 5 and section 9.4.7.

Throughout	Minor updates to wording and references	To correct errors and omissions, and to provide updated references

Table of Contents

Page

1 Synopsis

Rationale:

Obesity is currently one of the most significant public health challenges. There has been a dramatic increase in the prevalence of obesity among adults, children and adolescents in recent years with increasing trends in both developed and developing countries causing an immense burden on health care systems[2].

Similarly to obesity in adults, children with obesity can have multiple immediate serious comorbidities. In studies conducted in children and adolescents with obesity, weight loss has been associated with improvements in cardiometabolic risk factors, including measures of glycaemic control, beta-cell function, insulin sensitivity/resistance, lipid profile, systolic/diastolic blood pressure and metabolic syndrome[3-6]. Thus, obesity in childhood can have profound long-term consequences as it tracks strongly into adulthood, especially in those with severe obesity, which also increase the severity of their future health risk[7].

Lifestyle intervention in the form of diet and exercise is first line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss[8-17]. Pharmacotherapy may therefore serve as a valuable adjunct to lifestyle intervention for adolescents with obesity in order to achieve and sustain a clinically relevant weight loss, to improve or prevent comorbid conditions and to facilitate a healthier lifestyle. Currently, orlistat is the only pharmacotherapy with U.S. Food and Drug Administration approval for the management of obesity in the paediatric population and is indicated for those aged ≥12 years[18].

The NN9536–4451 trial is being conducted to assess the effect and safety of semaglutide in the paediatric population in order to potentially address the unmet need for treatment of adolescents ages 12 to <18 years with obesity.

Objectives and endpoints

Primary objective

To compare the effect of semaglutide subcutaneous once-weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity on weight management in adolescents (ages 12 to <18 years) with overweight or obesity.

Secondary objectives

To compare the effect of semaglutide subcutaneous once weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity in adolescents (ages 12 to <18 years) with overweight or obesity on:

- Cardiovascular risk factors
- Glucose metabolism

To compare the safety and tolerability of semaglutide subcutaneous once weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity in adolescents with overweight or obesity

Primary estimand

The estimand will quantify the average treatment difference of semaglutide relative to semaglutide placebo after 68 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment or initiation of rescue interventions (weight management drugs or bariatric surgery) ("effectiveness"/"treatment policy" estimand). The estimand will cover all effect-related objectives.

Primary endpoint

Change in body mass index from baseline (week 0) to week 68 (%)

Confirmatory secondary endpoint

Subjects achieving ≥5% reduction of body weight from baseline (week 0) to week 68 (yes/no)

Overall design:

This is a 68-week double-blind, randomised, parallel group, placebo-controlled, multi-national clinical trial comparing semaglutide subcutaneous 2.4 mg once weekly with semaglutide placebo in pubertal adolescents, ages 12 to <18 years, with obesity or overweight with ≥1 weight-related comorbidity.

Key inclusion criteria

- Informed consent of parent(s) or legally acceptable representative of subject and child assent, as appropriate obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
- Male or female, ages 12 to <18 years at the time of signing informed consent
- BMI ≥95th percentile* OR ≥85th percentile* with ≥1 weight related comorbidity (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or type 2 diabetes
- History of at least one self-reported unsuccessful dietary effort to lose weight

* on gender and age-specific growth charts (CDC.gov)

For subjects with type 2 diabetes at screening the following inclusion criteria apply in addition:

- HbA1c ≤10.0% (86 mmol/mol) as measured by central laboratory at screening

Key exclusion criteria

- Prepubertal subjects (Tanner stage 1)
- History of type 1 diabetes
- A self-reported (or by parent(s)/legally acceptable representative where applicable) change in body weight >5 kg (11 lbs) within 90 days before screening irrespective of medical records
- Subjects with secondary causes of obesity (i.e., hypothalamic, monogenic or endocrine causes)
- For subjects with type 2 diabetes only: Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening (V1). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination

Number of subjects:

Approximately 237 subjects will be screened to achieve 213 subjects to be included in the run-in period to reach the anticipated 192 subjects randomly assigned to trial product.

Treatment groups and duration:

The total duration for the individual subject will be approximately 89 weeks. The trial includes a screening period of approximately 2 weeks followed by 12 weeks run-in period before randomisation. Eligible subjects fulfilling all randomisation criteria will be randomised in a 2:1 manner to receive either semaglutide 2.4 mg or placebo once weekly as an adjunct to lifestyle intervention.

Randomisation will be stratified according to gender and Tanner stage (2-3 vs 4-5).

Dose escalation of semaglutide/semaglutide placebo will take place every 4 weeks during the first 16 weeks after randomisation. All subjects should aim at reaching 2.4 mg once weekly. The treatment continues with 52 weeks on maintenance dose until the 'end of treatment' visit followed by a 7 weeks follow-up period.

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

- Semaglutide B 1.0 mg/mL PDS290 and Semaglutide placebo, solution for injection, 3 mL PDS290 pre-filled pen-injector
- Semaglutide B 3.0 mg/mL PDS290 and Semaglutide placebo, solution for injection, 3 mL PDS290 pre-filled pen-injector

2 Flowchart

For subjects with type 2 diabetes (T2D) at screening or if diagnosed during the trial, refer to flowchart in Appendix 8.

	Screening	Run-in						Randomisation	Dose escalation								Maintenance												End of treatment	End of trial
Visit[a]	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	P25	V26	P27	V28	P29	V30	V31
Timing of Visit (Weeks)	-14	-12	-10	-8	-6	-4	-2	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7/0	±3	±7	±3	±7	±3	±7	±0	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	0/7
Attend visit fasting (6.5.1)		X						X												X										X	X
Informed consent, Informed assent and Demography[b] (Appendix 3)	X																														
Inclusion and exclusion criteria (6.1, 6.2)	X	X																													
Run-in criteria (6.3)			X	X	X	X	X																								
Randomisation criteria and randomisation (6.4)								X																							
Medical history/ Concomitant illness and Tobacco Use[c] (6.5.2, 9.4)	X																														
Concomitant medication (7.7)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Childbearing potential[d], Menstrual cycle[e] and Pregnancy test[f] (9.2.6, 9.4.7, 9.10.2, Appendix 5)	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pubertal Status (9.4.3)	X							X												X										X	
ECG (9.4.6)	X							X																						X	
Vital Signs (9.4.4)	X							X		X		X		X		X		X		X		X		X		X		X		X	X
Laboratory assessments (Appendix 2)	X	X						X[g]				X[h]				X[h]				X[h]		X[h]				X[h]				X[h]	X
Biosamples for future analysis[i] (9.7, 9.9)								X																						X	
Clinical Outcome Assessments (9.1.2, 9.4.1)	X							X												X										X	
Physical examination (9.4.2)	X							X												X										X	
Height (9.1.1)	X							X						X						X				X		X				X	X
Body Weight (9.1.1)	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	X

	Screening	Run-in						Randomisation	Dose escalation								Maintenance												End of treatment	End of trial
Visit[a]	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	P25	V26	P27	V28	P29	V30	V31
Timing of Visit (Weeks)	-14	-12	-10	-8	-6	-4	-2	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7/0	±3	±7	±3	±7	±3	±7	±0	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	0/7
Waist Circumference (9.1.1)	X							X												X										X	
Bone age measurement (x-ray) (9.4.5)								X																						X	
Evaluation of glycaemic status (9)								X												X										X	
Adverse event (9.2, Appendix 4, Appendix 6)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diet and physical activity counselling[j] (7.1.2, 7.1.3)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hand out and instruct in Diary (9)	X[k]									X				X				X		X				X				X			
Collect, review and transcribe diary (9.10, 9.10.1, 9.10.2)								X[k]				X				X				X		X				X				X	
Connect to IWRS (7.3)	X							X																						X	
Training in trial product, pen-handling (7.1.1)								X				X				X		X		X		X		X		X		X			
Drug handling (7.1, 7.3, 7.5)								X				X				X		X		X		X		X		X		X		X	
Trial product compliance (7.1, 7.6)									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

a) Visits marked as phone visits can be replaced by site visits or video calls to ensure flexibility for the subjects
b) Demography consists of date of birth, sex, ethnicity, and race (according to local regulation)
c) Smoking is defined as smoking at least one daily cigarette or equivalent (e.g. cigar, hookah or e-cigarette)
d) Only for females
e) Only for females that have started their menstrual period (of childbearing potential)
f) Only for females that have started their menstrual period (of childbearing potential): Urine pregnancy test should also be performed at any time during the trial if pregnancy is suspected, if a menstrual period is missed, and/or according to local regulations/law. If a female becomes of childbearing potential (has first menstrual period) during the trial a urine pregnancy test must be performed for that subject at the latest at the next site visit. For country specific requirements, see Appendix 11.
g) Blood samples should be taken prior to product dosing
h) Due to PK sampling, subjects must be instructed to withhold their trial product dose in the morning until blood sampling has been performed at the visit. This is not applicable for subjects that have discontinued trial product
i) Only for subjects where the separate informed consent for future research has been signed
j) The counselling can be done independent of the site visits within the visit window and flexibly as site visits or phone or video call
k) Only for females (for menstrual period record in run-in period)

3 Introduction

3.1 Trial rationale

Obesity is currently one of the most significant public health challenges. There has been a dramatic increase in the prevalence of obesity among adults, children and adolescents in recent years with increasing trends in both developed and developing countries causing an immense burden on health care systems. Around 2.1 billion people worldwide are currently estimated to be either overweight or obese[2].

Similarly to obesity in adults, children with obesity can have multiple immediate serious comorbidities. These include T2D, hypertension, non-alcoholic fatty liver disease, obstructive sleep apnoea (OSA), and dyslipidaemia as well as various psychosocial implications including reduced health related quality of life. Thus, obesity in childhood can have profound long-term consequences as it tracks strongly into adulthood, especially in those with severe obesity, which also increases the severity of their future health risks[7].

In studies conducted in children and adolescents with obesity, weight loss has been associated with improvements in cardiometabolic risk factors, including measures of glycaemic control, beta-cell function, insulin sensitivity/resistance, lipid profile, systolic/diastolic blood pressure and metabolic syndrome[3-6].

Lifestyle intervention in the form of diet and exercise is first line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss[8-17]. Surgical treatments may offer an effective alternative for some adolescents with severe obesity[19, 20], but surgery carries a risk in connection with the procedure and is not without complications. Furthermore, surgery requires long-term follow-up of the individual which can be cumbersome and costly[8-13, 21, 22]. Pharmacotherapy may therefore serve as a valuable adjunct to lifestyle intervention for adolescents with obesity in order to achieve and sustain a clinically relevant weight loss, to improve or prevent comorbid conditions and to facilitate a healthier lifestyle. No pharmacotherapy is currently approved for the treatment of obesity in individuals <18 years of age outside USA. Currently, orlistat is the only pharmacotherapy with U.S. Food and Drug Administration (FDA) approval for the management of obesity in the paediatric population and is indicated for those aged ≥12 years[18]. However, orlistat effects modest weight loss in adolescents and treatment compliance is low due to gastrointestinal (GI) adverse events (AEs)[18, 23, 24], and there is a need for more safe and effective therapeutic options for treatment of obesity in children and adolescents, especially treatments that also target weight maintenance, prevention and treatment of comorbidities[7-11, 25, 26].

The NN9536–4451 trial is being conducted to assess the effect and safety of semaglutide in the paediatric population in order to address the unmet need for treatment of adolescents ages 12 to <18 years with obesity. This clinical trial is also being conducted to fulfil the regulatory requirement for

paediatric trials from the U.S. Food and Drug Administration and the European Paediatric Committee (PDCO) of the European Medicines Agency (EMA).

3.2 Background

3.2.1 Semaglutide

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist (RA) currently under development by Novo Nordisk for the weight management indication (NN9536). Semaglutide has a half-life of approximately 160 hours, making it suitable for once-weekly dosing[27]. GLP-1 is a physiological regulator of appetite and GLP-1 receptors are present in several areas of the brain involved in appetite regulation[28].

Clinical[27, 29-33] and non-clinical data[34] indicate that the body weight-reducing effect of semaglutide may be mediated primarily by a reduced energy intake. No unexpected safety findings in adults have been identified and the tolerability and safety profile was overall consistent with previous findings in the adult semaglutide T2D development programme and the GLP-1 RA class in general.

In a 52-week phase 2 dose-finding trial in adults, within weight management (NN9536-4153), the estimated weight loss at week 52 was 13.8 % at the highest dose tested (0.4 mg once-daily) compared to the weight loss of 2.3% achieved by diet, exercise and placebo alone[35].

A comprehensive review of results from the non-clinical and clinical studies of semaglutide can be found in the current edition of the investigator's brochure (IB)[36] and any updates hereof.

3.2.2 Trial population

The trial population will consist of pubertal adolescents ages 12 to <18 years with obesity (BMI ≥ 95th percentile on CDC's gender and age-specific growth charts) or with overweight (BMI ≥ 85th percentile on CDC's gender and age-specific growth charts) and at least 1 weight-related comorbidity. These adolescents represent a clinically relevant population for pharmacotherapeutic weight management as they are at significant risk for weight-related comorbidities and have increased long-term mortality[37], and are likely to benefit from weight reduction. Information about weight-related comorbidities, including T2D, hypertension, dyslipidaemia or OSA, will be collected systematically at screening by the investigators as part of the medical history.

First line treatment in weight management should always be lifestyle modification through a reduced-calorie diet and increased physical activity. Thus only adolescents who have tried but failed a dietary weight loss intervention will be included in accordance with regulatory guidelines[38, 39].

3.3 Benefit-risk assessment

3.3.1 Benefits

The adolescents 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. Results from the adult phase 2 trial (NN9536-4153) demonstrated that semaglutide once-daily as an adjunct to a reduced calorie diet and increased physical activity was effective for weight loss in subjects with obesity, while displaying a satisfactory tolerability profile. Overall, a monotone dose-dependent weight loss was observed across all tested doses of semaglutide (0.05 to 0.4 mg once-daily). The weight loss was 11.55 percentage points larger for the 0.4 mg group compared with placebo. Weight loss was accompanied by a consistent improvement in the weight-related comorbidities, indicated by cardiovascular risk factors, lipid profile and glycaemic factors, as well as improvements in clinical outcome assessments (COAs). Semaglutide exposure is expected to be the same as in adults (refer to Section 5.5 for more details).

In addition, it is expected that the adolescents and their parent(s)/LAR will benefit from participation through close contact with the trial site medical staff and counselling by a dietician or a similarly qualified healthcare professional according to local standard, all of which may result in improved weight management.

3.3.2 Risks and precautions

The sections below describe identified and potential risks associated with semaglutide treatment. For classification and further details of the risks, please refer to the current version of the IB[40] or any updates hereof. The identified/potential risks are based on findings in non-clinical studies and clinical trials in adults with semaglutide as well as other GLP-1 RAs. For each of these risks, mitigating actions have been implemented to address the risks for subjects enrolled in this trial.

- Gastrointestinal adverse events
  Consistent with findings with other GLP-1 RAs, the most frequently reported AEs in clinical trials with semaglutide were gastrointestinal (GI) AEs. A low starting dose and dose escalation steps will be implemented in the trial to mitigate the risk of GI AEs.
- Cholelithiasis
  Events of cholelithiasis were the most frequently reported gallbladder events in the phase 2 weight management trial (NN9536-4153) and were in a few instances co-reported with the event adjudication committee (EAC) confirmed acute pancreatitis. As a precaution, if cholelithiasis is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.
- Hypoglycaemia (identified for T2D subjects)
  The risk of hypoglycaemic episodes is low, when semaglutide is used as monotherapy in adults. Adults treated with semaglutide in combination with a sulfonylurea or insulin may

have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide.

- Diabetic retinopathy complication (identified for T2D subjects)

  The cardiovascular outcome trial in the adult semaglutide T2D development programme showed an increased risk of events related to diabetic retinopathy complications in subjects treated with semaglutide compared to placebo, albeit the proportion of subjects with an event of diabetic retinopathy complications was low. The imbalance was driven by subjects with a history of diabetic retinopathy at randomisation and subjects who were treated with insulin. As a precaution, adolescents with T2D and a history of uncontrolled and potentially unstable diabetic retinopathy or maculopathy will be excluded from the trial, and fundus photography or slit-lamp biomicroscopy examination with pharmacologically dilated pupils will be performed according to flowchart in Appendix 8.
- Acute pancreatitis

  Acute pancreatitis has been observed with the use of GLP-1 RA drug class. As a precaution, subjects with a history of chronic or acute pancreatitis will not be enrolled in the trial. In addition, trial product should be discontinued in case of suspicion of acute pancreatitis in accordance to Section 8.1.
- Medullary thyroid cancer (MTC) (based on non-clinical data)

  Expected proliferative thyroid C-cell changes were seen in the mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. No hyperplasia was observed in monkeys after 52 weeks exposure up to 13-fold above the clinical plasma exposure at 2.4 mg/week. In clinical trials with semaglutide, there have been no clinically relevant changes in calcitonin levels. The C-cell changes in rodents are mediated by the GLP-1 receptor, which is not expressed in the normal human thyroid. Accordingly, the risk of GLP-1 receptor-mediated C-cell changes in humans is considered to be low. As a precaution, exclusion and discontinuation criteria related to medical history of multiple endocrine neoplasia type 2 (MEN2) or MTC and elevated plasma levels of calcitonin (biomarker for MTC) have been implemented in the trial.
- Pancreatic cancer

  There is currently no support from non-clinical studies, clinical trials or post-marketing data that GLP-1 RA-based therapies increase the risk of pancreatic cancer, but pancreatic cancer has been classified as a potential class risk of GLP-1 RAs by EMA. As a precaution, subjects with a history of malignant neoplasms within the past 5 years prior to screening will be excluded from the trial.
- Allergic reactions

  As is the case with all protein-based pharmaceuticals, subjects treated with semaglutide are at risk of developing immunogenic and allergic reactions. As a precaution, subjects with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this trial.
- Pregnancy and fertility (based on non-clinical data)

Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. Exclusion and discontinuation criteria related to pregnancy have been implemented in the trial.

3.3.3 Conclusion on benefit-risk profile

Necessary precautions have been implemented in the design and planned conduct of the trial in order to mitigate the risks and inconveniences of participation in the trial. The safety profile for semaglutide generated from the clinical and non-clinical development programme has not revealed any safety issues that would prohibit administration of semaglutide s.c. 2.4 mg once-weekly in the adolescent population with obesity. The results of the adult phase 2 trial (NN9536-4153) indicate that semaglutide will provide a clinically meaningful weight loss.

In conclusion, the potential risk to the subjects in this trial is considered to be low and to be outweighed by the anticipated benefits that semaglutide as well as dietitian counselling would provide subjects included in the trial.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of semaglutide may be found in the current version of the IB[40] and any updates hereof.

4 Objectives and endpoints

4.1 Primary, secondary and exploratory objective(s)

Primary objective

To compare the effect of semaglutide s.c. once-weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity on weight management in adolescents (ages 12 to <18 years) with overweight or obesity.

Secondary objectives

To compare the effect of semaglutide s.c. once weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity in adolescents (ages 12 to <18 years) with overweight or obesity on:

- Cardiovascular risk factors
- Glucose metabolism

To compare the safety and tolerability of semaglutide s.c. once weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity in adolescents with overweight or obesity.

Exploratory objectives

To compare the effect of semaglutide s.c. once weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity in adolescents (ages 12 to <18 years) with overweight or obesity on:

- Clinical Outcome Assessments (COAs)

To compare additional safety and tolerability of semaglutide s.c. once weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity in adolescents with overweight or obesity.

Estimands

Primary estimand

The estimand will quantify the average treatment difference of semaglutide relative to semaglutide placebo after 68 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment or initiation of rescue interventions (weight management drugs or bariatric surgery) ("effectiveness"/"treatment policy" estimand). The estimand will cover all effect-related objectives.

The following expansion of the primary estimand will cover the exploratory endpoint "Change in body mass index from baseline (week 0) to week 52 (%)". The estimand will quantify the average treatment effect of semaglutide relative to semaglutide placebo after 52 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment or initiation of rescue interventions.

The following expansion of the primary estimand will cover the exploratory endpoint "Change in body mass index from baseline (week 0) to week 75 (%)". The estimand will quantify the average treatment effect of semaglutide relative to semaglutide placebo after 75 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment or initiation of rescue interventions.

Secondary estimand

The estimand will quantify the average treatment difference of semaglutide relative to semaglutide placebo after 68 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 rescue intervention (weight management drugs or bariatric surgery) ("efficacy"/"hypothetical" estimand). The estimand will cover the primary objective.

4.2 Primary, secondary and exploratory endpoint(s)

4.2.1 Primary endpoint

Change in BMI from baseline (week 0) to week 68 (%)

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

Subjects achieving ≥5% reduction of body weight from baseline (week 0) to week 68 (yes/no)

4.2.2.2 Supportive secondary endpoints

Effect endpoints from baseline (week 0) to week 68:

- Change in:
  - Body weight (kg)
  - Body weight (%)
  - BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov) (%)
  - BMI (standard deviation score) (WHO.int)[41]
  - Waist circumference (cm)
  - Systolic blood pressure (mmHg)
  - Diastolic blood pressure (mmHg)
  - HbA1c (% point)
- Subjects achieving ≥5% reduction of BMI (yes/no)

Safety endpoints from baseline (week 0) to week 75:

- Number of treatment-emergent adverse events (TEAEs)
- Number of treatment-emergent serious adverse events (SAEs)

Safety endpoints from baseline (week 0) to week 68:

Change in:
- Pulse (bpm)
- Amylase (U/L)
- Lipase (U/L)
- Calcitonin (ng/L)

4.2.3 Exploratory endpoints

- Effect endpoints

Change from baseline (week 0) to week 68 in:

- BMI (kg/m^2)
- Fasting plasma glucose (mmol/L)
- Fasting insulin (mU/L)
- Lipids (mmol/L)
  - Total cholesterol
  - High density lipoprotein (HDL) cholesterol
  - Low density lipoprotein (LDL) cholesterol
  - Very low density lipoprotein (VLDL) cholesterol
  - Triglycerides

- Homeostasis model assessment (HOMA-B and HOMA-IR)
- Impact of Weight on Quality of Life Kids (IWQOL-Kids)
  - physical comfort domain score
  - body esteem domain score
  - social life domain score
  - family-relations score
  - total score

- Subjects who after 68 weeks achieve (yes/no):
  - Body weight reduction ≥ 10% from baseline

- Change in body mass index from baseline (week 0) to week 52 (%)
- Change in body mass index from baseline (week 0) to week 75 (%)

Safety

Safety endpoints for adolescents with T2D from baseline (week 0) to week 75:

- Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episodes
- Number of treatment-emergent hypoglycaemic episodes:
  - According to ADA/ISPAD classification
  - According to Novo Nordisk classification

Other Safety Assessments

Change from baseline (week 0) to week 68 (unless otherwise stated):

- Occurrence of anti-semaglutide antibodies (also to week 75)
- Bone age assessment, x-ray (years)

- Electrocardiogram (ECG)
- Laboratory parameters
- Pubertal status (Tanner staging) (stage 2-5 where 5 is full sexual maturity)
- Height standard deviation score (SDS)
- Mental health assessed by Columbia Suicidality Severity Rating Scale (C-SSRS)
- Patient Reported Health Questionnaire 9 (PHQ-9)
- For subjects with T2D: Ophthalmological evaluation

PK analysis

- Sparse PK sampling: Clearance (CL/F) including between-subject variability, area under the steady state concentration – time curve in the dosing interval (AUCτ) and average concentration (Cavg)

5 Trial design

5.1 Overall design

This is a 68-week double-blind, randomised, parallel group, placebo-controlled, multi-national clinical trial comparing semaglutide s.c. 2.4 mg once weekly with semaglutide placebo in pubertal adolescents, ages 12 to <18 years, with obesity or overweight with ≥1 weight related comorbidity.

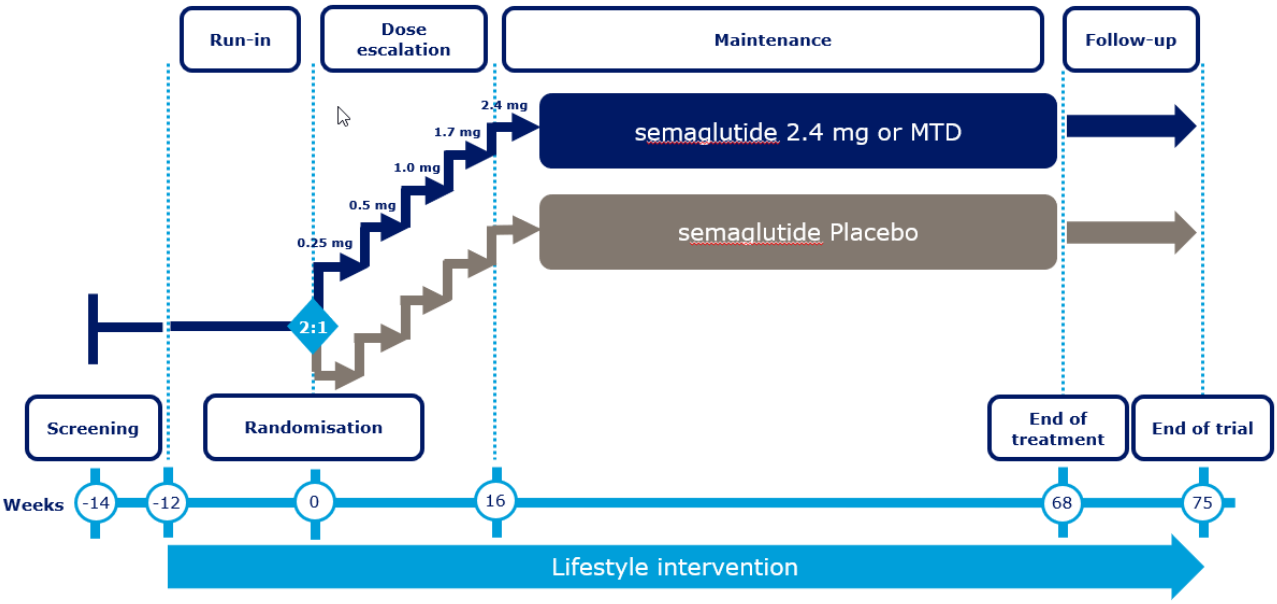
The trial includes a screening visit to assess the subject's eligibility. Subjects fulfilling the eligibility criteria commence with a 12-week non-pharmacological lifestyle intervention run-in period before randomisation. The run-in period is to ensure that lifestyle intervention which is first line treatment for children with obesity is insufficient. Lifestyle intervention consists of diet and physical activity counselling for weight loss and continues throughout the trial until 'end of trial' (week 75).

Subjects who have fulfilled the randomisation criteria (see Section 6.4) will be randomised 2:1 to receive semaglutide s.c. once weekly or semaglutide placebo s.c. once weekly for a dose escalation period of 16 weeks and a maintenance period of 52 weeks.

Site visits/phone calls will take place with an interval of maximum 4 weeks from run-in until 'end of treatment' (week 68) according to the flowchart.

The follow-up period is 7 weeks after 'end of treatment' due to the long half-life of semaglutide.

The trial design is outlined in Figure 5-1



MTD, Maximum Tolerated Dose

Figure 5-1 A schematic diagram of the trial design

5.2 Subject and trial completion

Approximately 237 subjects will be screened to achieve 213 subjects to be included in the run-in period to reach the anticipated 192 subjects randomly assigned to trial product.

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' (V31) according to the flowchart).
'Date of trial completion' is the date the subject completed the final scheduled visit.

Treatment period completion for a subject:

Treatment period completion is defined as when the randomised subject has attended the 'end of treatment' visit (V30) 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.

5.4 Scientific rationale for trial design

A randomised, double-blinded, placebo-controlled, multi-centre trial design is chosen to minimise bias in the assessment of the effect and safety of semaglutide 2.4 mg once-weekly versus semaglutide placebo, as an adjunct to a reduced-calorie diet and increased physical activity.

The treatment duration of the trial is 68 weeks comprising of 16 weeks of dose escalation and 52 weeks of maintenance dose. This duration is considered sufficient to assess weight loss, safety and tolerability in the paediatric phase 3 weight management development programme in accordance with regulatory guidelines from EMA/PDCO and FDA. The off-drug follow-up period is 7 weeks and a follow-up visit ('end of trial' (V31)) for safety assessments is included to account for the long half-life of semaglutide and allowing for anti-semaglutide antibody measurement.

The trial includes a 12-week non-pharmacological lifestyle intervention run-in period before randomisation. The run-in period is to ensure documentation of at least one failed lifestyle intervention attempt. All subjects will undergo diet and physical activity counselling for weight loss beginning at run-in (week -12) and continuing through the entire trial.

After the run-in period, subjects who fulfil the randomisation criteria will enter the active double-blind trial phase.

Subjects will be randomised 2:1 to receive semaglutide s.c. once weekly or semaglutide placebo s.c. Randomisation will be stratified by gender and Tanner stage (2-3 vs 4-5) to ensure an even distribution of males vs. females, and early vs. late pubertal development.

5.5 Justification for dose

Population pharmacokinetic (PK) analyses of semaglutide in adults with T2D show that the most important covariate for exposure is body weight[42], and the same has been shown for adults with obesity (NN9536-4153). The range of baseline body weight observed in the PK/clinical pharmacology trial with liraglutide in an adolescent population of 12 to <18 years with obesity (NN8022-3967: 79 to 164 kg) was covered by the observed range in adults with obesity (SCALE, NN8022-1839: 63 to 244 kg). Thus, semaglutide exposure is expected to be the same in adults and adolescents.

Results from the adult phase 2 dose-finding trial (NN9536-4153) showed that the semaglutide 0.4 mg once-daily dose was most effective in terms of weight loss while displaying an acceptable tolerability profile. Using population pharmacokinetic modelling, it was estimated that a once-weekly maintenance dose of 2.4 mg semaglutide will result in similar C_{max} at steady-state as that obtained by the once-daily 0.4 mg semaglutide dose in trial NN9536- 4153.

It is well known that to mitigate GI side effects with GLP-1 RA treatment, dose escalation to the target dose is required. Based on experience from the adult semaglutide T2D development programme, a similar fixed-dose escalation regimen was selected, with dose escalation every 4 weeks until the target dose of 2.4 mg is reached after 16 weeks.

A maintenance dose of 2.4 mg semaglutide once-weekly has been chosen for the phase 3 weight management development programme. The once-weekly dosing is anticipated to ease the burden of drug administration in clinical practice. Subjects will be initiated at a once-weekly dose of 0.25 mg

and follow a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), until the target dose is reached after 16 weeks. In the trial specific setting, the maintenance dose may depend on tolerability.

Please 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.

For country specific requirements on inclusion and exclusion criteria, refer to Appendix 11.

6.1 Inclusion criteria

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

1. Informed consent of parent(s) or legally acceptable representative (LAR) of subject and child assent, as appropriate 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
   a) The parent(s) or LAR of the child must sign and date the Informed Consent Form (according to local requirements)
   b) The child must sign and date the Child Assent Form or provide oral assent (according to local requirements)
2. Male or female, ages 12 to <18 years at the time of signing informed consent
3. BMI ≥95th percentile* OR ≥85th percentile* with ≥1 weight related comorbidity (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or T2D
4. History of at least one self-reported unsuccessful dietary effort to lose weight

*On gender and age-specific growth charts (CDC.gov) (Appendix 9)

For subjects with T2D at screening the following inclusion criteria apply in addition to criteria 1-4:

5. Subject treated with either diet and exercise alone or stable treatment for at least 90 days prior to screening with metformin
6. HbA1c ≤10.0% (86 mmol/mol) as measured by central laboratory at screening

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

6.2 Exclusion criteria

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

The following criteria apply to all subjects:

Obesity related

1. A self-reported (or by parent(s)/LAR where applicable) change in body weight >5 kg (11 lbs) within 90 days before screening irrespective of medical records
2. Treatment with any medication for the indication of obesity within the past 90 days before screening

3. Previous surgical treatment for obesity (excluding liposuction if performed >1 year before screening)
4. Uncontrolled thyroid disease at screening, in the opinion of the investigator
5. Subjects with secondary causes of obesity (i.e., hypothalamic, monogenic or endocrine causes)

Mental health

6. History of major depressive disorder within 2 years before screening
7. Diagnosis of other severe psychiatric disorders (e.g., schizophrenia, bipolar disorder)
8. A Patient Health Questionnaire-9 (PHQ-9) score of ≥15 at screening
9. A lifetime history of suicidal attempt
10. Suicidal behaviour within 30 days before screening
11. Suicidal ideation corresponding to type 4 or 5 based on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the past 30 days before screening
12. Subjects with confirmed diagnosis of bulimia nervosa disorder

General Safety

13. Prepubertal subjects (Tanner stage 1)
14. History or presence of pancreatitis (acute or chronic)
15. Calcitonin ≥50 ng/L
16. Personal or first degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
17. History of type 1 diabetes
18. Impaired renal function defined as serum-creatinine >upper normal range (UNR) for age in children unless renal function is proven normal by further assessments at the discretion of the investigator
19. History of malignant neoplasms within the past 5 years prior to the day of screening
20. Surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator
21. Known or suspected abuse of alcohol or recreational drugs
22. Known or suspected hypersensitivity to trial product(s) or related products
23. Previous participation in this trial. Participation is defined as signed informed consent
24. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening
25. Other subject(s) from the same household participating in any semaglutide trial
26. Known history of heart disease (including history of clinically significant arrhythmias or conduction delays on ECG) within 180 days before screening, new clinically significant arrhythmias or conduction delays on ECG identified at screening
27. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method

28. 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

Glycaemia-related for subjects without T2D

29. Treatment with glucose-lowering agent(s) within 90 days before screening (except for metformin)
30. Treatment with a GLP-1 receptor agonist within 180 days before screening

Diabetes related for subjects with T2D

31. Treatment with any medication for the indication of diabetes other than stated in the inclusion criteria within the past 90 days prior to the day of screening
32. Treatment with a GLP-1 receptor agonist within 180 days before screening
33. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening (V1). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

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

6.3 Run-in criteria

Subjects will be considered screen failures, if any of the run-in criteria apply, see Section 6.6

1. Included in the trial in violation of the inclusion and/or exclusion criteria.
2. Pregnancy
3. Intention of becoming pregnant
4. Participation in another clinical trial during the run-in period
5. Any safety concern judged at the investigators discretion

6.4 Randomisation criteria

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

1. BMI corresponding to
   a) ≥95th percentile* OR
   b) ≥85th percentile* with ≥1 weight related comorbidity (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or T2D
2. Compliance with trial procedures and visit schedule as judged by the investigator
3. A PHQ-9 score of <15 at randomisation
4. No suicidal behaviour in the period between screening and randomisation
5. No suicidal ideation corresponding to type 4 or 5 on the C-SSRS in the period between screening and randomisation

6. Absence of uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 30 days prior to randomisation (V8)**. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

*On gender and age-specific growth charts (CDC.gov) (Appendix 9)
**Diabetes related for subjects with T2D only (at screening or if diagnosed during the trial)

Subjects not fulfilling the randomisation criteria will be considered screen failures.

6.5 Lifestyle restrictions

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

6.5.1 Meals and dietary restrictions

- The subjects must attend several visits fasting according to the flowchart
- Fasting is defined as at least 8 hours 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
- At the 'end of trial' visit only 2 hours of fasting is required prior to the anti-semaglutide antibody sampling
- If the subject is not fasting as required, the subject should be called in for a new visit within the visit window to have the fasting procedures done

6.5.2 Caffeine and tobacco

- Subject should avoid caffeine and smoking at least 30 minutes prior to measuring the blood pressure

6.6 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible according to in/exclusion criteria, run-in criteria or randomisation criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (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 re-screened. 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.

7 Treatments

7.1 Treatments administered

- All trial products listed in Table 7-1 are considered investigational medicinal products (IMP)
- Trial product must only be used, if it appears clear and colourless

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

Trial product name:	Semaglutide B 1.0 mg/mL PDS290 or semaglutide placebo*	Semaglutide B 3.0 mg/mL PDS290 or semaglutide placebo
Dosage form:	Solution for injection	Solution for injection
Route of administration:	Subcutaneous	Subcutaneous
Dosing instructions:	Once weekly	Once weekly
Packaging: Delivery device	3 mL PDS290 pre-filled pen-injector	3 mL PDS290 pre-filled pen-injector

* Semaglutide B 1.0 mg/mL PDS290/semaglutide placebo will only be dispensed at the first dispensing visit (V8)

- Treatment will be initiated with 0.25 mg once-weekly dosing and will follow a dose-escalation regimen with 4-week dose escalation steps to 0.5, 1.0, 1.7 and 2.4 mg
- The first dose of trial product must be taken at site on the day of randomisation and documented in the subject's medical record
- Dose escalation of semaglutide/semaglutide placebo should take place during the first 16 weeks after randomisation. All subjects should aim at reaching the recommended target dose of 2.4 mg semaglutide once-weekly or the corresponding volume of placebo
- If a subject does not tolerate the designated target dose (2.4 mg once-weekly), 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 the investigator’s discretion. It is recommended that the subject makes at least one attempt to re-escalate to the designated target dose (2.4 mg once-weekly), as per the investigator’s discretion
- In case the subject needs to be on a lower dose level than 1.0 mg after V12, the site must advise the subject how to administer the 0.25 or 0.50 mg dose using the 3 mg/mL pen.
- It is recommended that the investigator consults Novo Nordisk in case the subject should be on a lower dose than 1.0 mg using the 3.0 mg/mL pen or in case of persistent deviation from the planned escalation regimen
- A dose reminder card will be handed out to the subjects at each site visit during the escalation period. This is to remind the subjects of the dose to be taken until next site visit and provide a conversion of the dose to the value shown in the dose counter, see Table 7-2. Once the target dose has been reached, the dose reminder card is only handed out as needed

- At V12 the investigator must ensure to instruct the subject that the dose/pen dose is dialled to adjust from 0.5 mg to 1.0 mg due to change in pen

Table 7-2 Dose escalation and maintenance of semaglutide 2.4 mg once weekly/semaglutide placebo

Trial product name	Dose	Volume	Value shown in dose counter*	Duration
Dose escalation period				
Semaglutide B 1.0 mg/mL PDS290/ semaglutide placebo	0.25 mg	0.25 mL	25*	4 weeks
Semaglutide B 1.0 mg/mL PDS290/ semaglutide placebo	0.5 mg	0.50 mL	50*	4 weeks
Semaglutide B 3.0 mg/mL PDS290/ semaglutide placebo	1.0 mg	0.34 mL	34*	4 weeks
Semaglutide B 3.0 mg/mL PDS290/ semaglutide placebo	1.7 mg	0.57 mL	57*	4 weeks
Maintenance period				
Semaglutide B 3.0 mg/mL PDS290/ semaglutide placebo	2.4 mg	0.80 mL	80*	52 weeks

* Conversion to dose is calculated based on 0.01 mL/value for both strengths.

- Subjects will be instructed to inject semaglutide/semaglutide placebo once-weekly at the same day of the week (to the extent possible) throughout the trial
- Injections should be administered by subcutaneous injections either in the abdomen, thigh or upper arm at any time of day irrespective of meals
- If a single dose of trial product 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 a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the subject should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week
- If ≥2 consecutive doses of trial product are missed, the subject should be encouraged to re-commence the treatment 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 continued as early as the situation allows. The missed doses should not affect the scheduled dosing day of the week. The start dose for re-initiation of trial product is at the investigator's discretion. In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk global medical expert

- For subject with T2D at screening or if diagnosed during the trial: If doses are missed, blood glucose (BG) should be more closely monitored if judged necessary by the investigator
- Auxiliary supplies will be provided in accordance with the trial materials manual (TMM) please see Table 7-3

Table 7-3 Auxiliary supplies provided by Novo Nordisk A/S

Auxiliary supply	Details
Needles	Needles for pre-filled pen system. Detail provided in the TMM. Only needles provided and approved by Novo Nordisk must be used for administration of trial product.
Direction for use (DFU)	DFU for 3 mL PDS290 pre-filled pen-injector. Not included in the dispensing unit and to be handed out separately.
BG meters	For subjects with T2D at screening or if diagnosed during the trial.

7.1.1 Medical device

Information about the PDS290 pre-filled pen-injector may be found in the IB[40] and any updates hereof.

Information about the use of the PDS290 pre-filled pen-injector for semaglutide 1.0 mg/mL, semaglutide 3.0 mg/mL, and semaglutide placebo can be found in the DFU.

Training in the PDS290 pre-filled pen-injector

The investigator must document that training in the DFU has been given to the subjects orally and in writing at the first dispensing visit. Training must be repeated during the trial at regular intervals in order to ensure correct use of the medical device. Training is the responsibility of the investigator or a delegate.

7.1.2 Diet counselling

All subjects (and parent(s)/LAR, as applicable) must receive individualised counselling in healthy nutrition with the goal of obtaining a weight loss. The counselling begins at run-in (week -12) and continues through the entire trial. The counselling must be done by a certified dietician or a similarly qualified health care professional according to local standard. The counselling can be done independently of the site visits within the visit window and flexibly as site visits, phone or video call.

The focus of the counselling in healthy nutrition must be to educate on healthier food choices. If a BMI corresponding to <85th percentile on CDC's growth charts is reached, subjects should be assigned a maintenance diet, at the discretion of the investigator. For details, refer to Appendix 9.

7.1.3 Physical activity counselling

At every site, there must be a qualified person (site staff trained in physical activity counselling) to provide instructions and advise on physical activity. The focus of the counselling in physical activity is to encourage and reinforce a goal of 60 minutes of moderate to high intensity physical activity per day[43]. The counselling can be done independently of the site visits within the visit window and flexibly as site visits, phone or video call. Activity trackers can be provided by Novo Nordisk in order to support the physical activity of the subjects. The use of these trackers is optional.

7.2 Dose modification

Not applicable for this trial. Please refer to Section 7.1 for description of missed dose(s).

7.3 Method of treatment assignment

All subjects will be centrally screened and 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. An 'end of treatment' session should be made in IWRS, when the subject completes the treatment or permanently discontinues trial product.

7.4 Blinding

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

- Semaglutide B 1.0 mg/mL PDS290/semaglutide placebo
- Semaglutide B 3.0 mg/mL PDS290/semaglutide placebo

The IWRS is used for blind-breaking. 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, record the reason 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 IWRS is not accessible at the time of blind break, the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

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 on-going 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 (see TMM) 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)
- Drug accountability should be performed on a pen level and must be documented in the IWRS according to "Drug handling" in the flowchart
- 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.

Compliance with trial product administration will be assessed and the assessment documented in source documents at each visit where information is available. If any suspicion of non-compliance arises, the site must enter into a dialogue with the patient, re-emphasizing the importance of

compliance and uncover barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Drug accountability information; counting returned trial product, visual inspection of pens, whether the used trial product Dispensing Unit Numbers (DUNs) have been administered by the subjects as expected at each visit (see 7.5)
- Review of PK diaries
- Questioning of subjects

Information about compliance and missed doses should be described in the subject's medical records and entered into the case report form (CRF).

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 the first visit or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates
- Dose for weight-related co-morbidities (diabetes, hypertension and dyslipidaemia)

During the trial, subjects should not initiate any anti-obesity 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 anti-obesity treatment.

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

7.8 Treatment after the end of the trial

After the end of the trial the subject should be treated at the discretion of the investigator.

8 Discontinuation/Withdrawal criteria

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

Efforts must be made to have subjects who discontinue trial product continue in the trial. Subjects must be educated about the continued scientific importance of their data, even if they discontinue trial product. Only subjects who withdraw consent will be considered as withdrawn from the trial.

8.1 Discontinuation of trial treatment

- Discontinuation of trial product can be decided by either the investigator, the subject or parent(s)/LAR
- Subjects who discontinue trial product should continue with the scheduled visits and assessments to ensure continued counselling and data collection
  - If the subject does not wish to attend the scheduled clinic visits, efforts should be made to have the visits converted to phone contacts or video calls. However all efforts should be made to have the subject attend at least the 'end of treatment' clinic visit (V30) containing the final data collection of primary and confirmatory secondary efficacy endpoints, and the 'end of trial' visit (V31) according to schedule.
  - If the subject refuses to attend the 'end of treatment' visit (V30) and/or 'end of trial' visit (V31), information about the attempts to follow up with the subject must be documented in the subject's medical record

The subject must be discontinued from trial product, if the following applies:

1. Safety concern as judged by the investigator
2. Calcitonin ≥50 ng/L (see Appendix 10)
3. Suspicion of pancreatitis
4. Pregnancy
5. Intention of becoming pregnant
6. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product[a]
7. Diagnosis of type 1 diabetes

[a] Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator's discretion without discontinuing trial product.

Ad. 3. If acute pancreatitis is suspected, appropriate actions should be initiated, including local measurement of amylase and lipase (see Appendix 4 for reporting).

Subjects meeting discontinuation criterion no. 3 are allowed to resume the trial product, if the Atlanta criteria[44] are not fulfilled and thus, the suspicion of pancreatitis is not confirmed. The trial product may be restarted for subjects with a gallstone-induced pancreatitis in case of cholecystectomy.

Subjects meeting discontinuation of trial product criteria no. 1, 4 or 5 are allowed to resume the trial product, if the criteria are no longer met (see Section 8.1.1).

Subjects who discontinue the trial product will be asked to follow the visit schedule and perform all assessments as planned.

The primary reason for discontinuation of trial product must be specified in the source data at the time of discontinuation, and subject should continue to follow the visit and assessment schedule. A change in 'treatment status' must be made in IWRS to discontinue trial product. If subject is not allowed to resume trial product, then the reason for discontinuation will be recorded in the 'end of treatment' form in the CRF, and final drug accountability must be performed. An 'end of treatment' session must be made in the IWRS.

8.1.1 Temporary discontinuation of trial treatment

If a subject has discontinued trial product and is allowed to resume, the subject should follow the guide for missed doses (Section 7.1).

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, or at the request of the subject's parent(s) or the subject's LAR. 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 assessment performed according to the 'end of treatment' visit. 'End of treatment' and 'end of trial' forms must be completed by the investigator and (as a minimum) BMI and safety assessments should be performed if the subject agrees. See the flowchart and Appendix 2 for data to be collected.

Final drug accountability must be performed even if the subject is not able to come to the trial site. The investigator must make a 'treatment status' session in IWRS to discontinue trial product.

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.

For country specific requirements, refer to Appendix 11.

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.

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 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). These contact attempts should be documented in the subject's source document
- Should the subject continue to be unreachable, 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 (Section 2) and in Appendix 2
- Refer to Appendix 8 for any investigations concerning subjects with T2D at screening or if diagnosed during the trial
- To ensure flexibility for the subjects, phone visits may be replaced by site visits or video calls
- Informed consent and informed assent (per local requirements) must be obtained before any trial related activity, see Appendix 3 and Appendix 7
- 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 the bias between assessments. The suggested order of the assessments:
  1. ECG and vital signs
  2. Blood samples
  3. COAs (see Sections 9.1.2 and 9.4.1)
  4. 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 recording to be considered source data includes, but is not limited to laboratory reports, ECG, diary recordings and COAs
- Subjects and/or the parent(s)/LAR must receive training in how to collect dosing information prior to PK sampling in a designated paper diary
- Only the subject and/or the parent(s)/LAR can make entries and corrections in the diaries, unless the section is specified for site staff
- Review of completed diaries, COAs, ECG and laboratory reports must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies is needed, the subject must be questioned and a conclusion made in the subject's source documents. Care must be taken not to bias the subject
- Approximately 115 mL blood will be collected from each subject during the entire trial period. Blood collection should be performed in accordance with the guidelines in EU Directive 2001/20/EC[45] unless stricter local requirements apply. According to EU Directive 2001/20/EC it is recommended not to draw more than 3% of the total blood volume in a 4-week period and 1% of total blood volume at any single occasion. The total volume of blood is estimated at 80 to

90 ml/kg body weight; 3% is 2.4 ml blood per kg body weight. If a subject weighs less than 33 kg a prioritisation of blood samples will be made on a case-by-case basis

- For subjects who have consented to have biosamples for future analysis collected, approximately additional 13 mL blood will be collected. If the subject's weight is lower than 41 kg, the regular blood samples must be prioritised and biosamples for future analysis should not be taken
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 for further details on laboratory samples
- According to the flowchart, the investigator will periodically evaluate the glycaemic status of subjects without T2D. This evaluation will be based on all available relevant information e.g. medical records, concomitant medication, BG parameters (HbA1c, Fasting plasma glucose (FPG)) and AEs. The subject's glycaemic status will be categorised as normo-glycaemia, prediabetes or diagnosed with T2D according to the American Diabetes Association's (ADA) definitions[46]

9.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart.

9.1.1 Body measurements

- Body weight should be measured at all site visits without shoes, with an empty bladder and only wearing light clothing. It should be measured on a digital scale and recorded in kilograms or pounds (one decimal) preferably using the same scale throughout the trial. The scale must be calibrated yearly as a minimum
- Height should be measured (centimetres or inches, one decimal) without shoes as two individual measurements performed by a single observer using identical technique with a Harpenden or other wall mounted stadiometer. The subject should be repositioned between the two measurements
- BMI will be calculated in the CRF every time the weight and height are measured. BMI SDS and height SDS will be calculated using the methods outlined in WHO 2007[47, 48]
- Waist circumference is defined as 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 0.5 cm or 0.2 inch. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally. The same measuring tape should be used throughout the trial. The measuring tape will be provided by Novo Nordisk to ensure standardisation.

9.1.2 Clinical outcome assessments

The Impact of Weight on Quality of Life-Kids (IWQOL-Kids) is a disease specific questionnaire which measures the impact of weight on quality of life in adolescents and is validated in youth ages 11 years and older[49]. The four concepts captured are:

- the impact of weight on an individual's physical mobility and comfort (Physical Comfort)
- how an individual feels about themselves and their body (Body Esteem)
- how an individual is treated in their social environment (Social Life)
- the individual's perception of what family members may think and feel about them (Family Relations)

The questionnaire has 27 items and a total, as well as domain specific score(s), can be derived. The scaled scores range from 1-5, with higher scores representing better health related quality of life.

IWQOL-Kids will be completed at V8, V20 and V30. Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. If the subject has difficulty reading the questionnaire, the site staff or the parent(s)/LAR can read the questions out loud, but should not help explaining the question or do anything else that might influence the subject's answer to the question. The questionnaire takes approximately 10 minutes to complete and should preferably be completed after fasting related activities (i.e. blood sampling) have been concluded.

Only subjects can make changes in the questionnaire.

After completion, the questionnaire must be reviewed by the investigator or delegated staff on the same day for potential AEs, including any overall change in health and concomitant medication. When reviewing the questionnaires, the investigator should not influence or question the subject on the content of the subject's response to the questionnaire questions. Review of questionnaires must be documented in the subject's medical record. Care must be taken not to bias the subject.

9.1.3 Clinical efficacy laboratory assessments

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

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 assent and until the 'end of trial' visit (V31), 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. The trial will be monitored by an external and un-blinded Data Monitoring Committee (DMC).

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, misuse and abuse observed during the trial. The relevant specific events are listed in Table 9-1 and the reporting timelines in Figure 9-1.

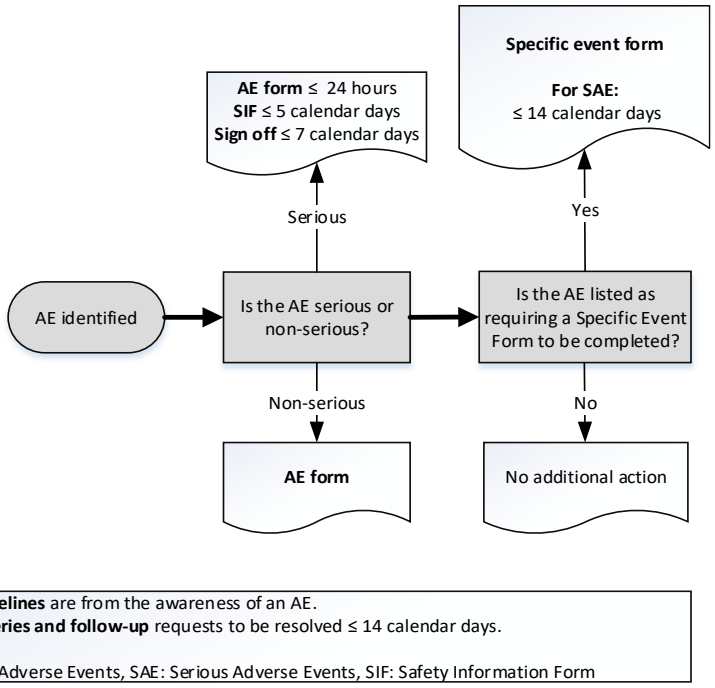


Figure 9-1 Decision tree for determining the event type and the respective forms to complete with associated timelines

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

Event type	AE via specific event form
Acute gallbladder disease	X
Acute pancreatitis	X
Malignant neoplasm	X
Hepatic event	X
Medication error	X
Misuse*	X
Abuse*	X
Diabetic retinopathy (T2D only)	X

* Additional data for misuse or abuse of trial product is reported on the medication error event form

For further information regarding AEs requiring additional data collection, refer to Appendix 4.

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, stabilization, 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, Institutional review board (IRB), Independent ethics committee (IEC), 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 an 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 Pregnancies and associated adverse events

Details of pregnancies in female subjects will be collected after the first-trial-related activity after obtaining informed consent and until pregnancy outcome.

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.

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.

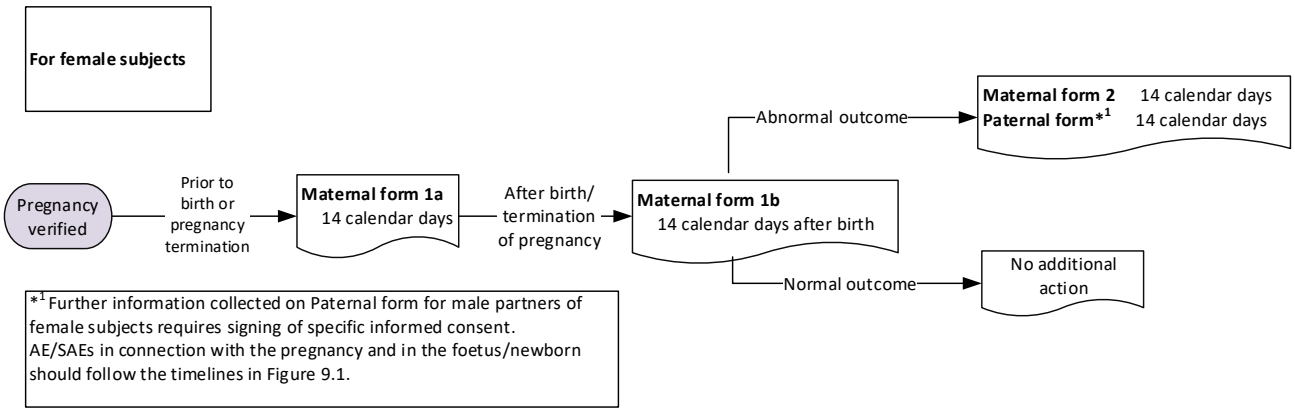


Figure 9-2 Decision tree for determining the forms to complete with associated timelines for pregnancy.

9.2.7 Medical device incidents (including malfunctions)

Section not applicable for this trial. Refer to technical complaints in Section 9.2.8.

9.2.8 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 9-3.

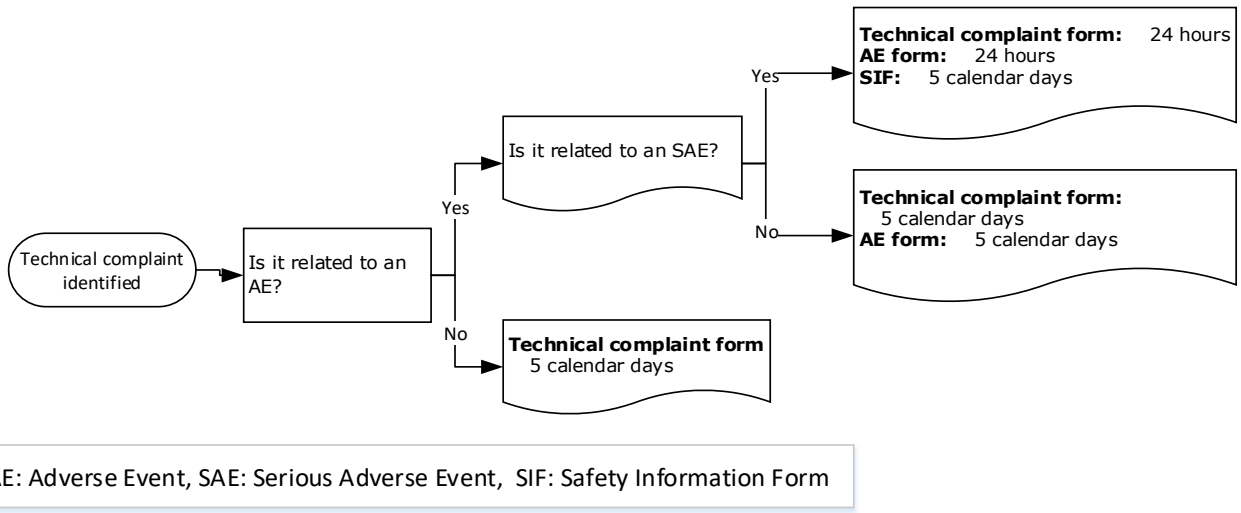


Figure 9-3 Decision tree for determining the forms to complete with associated timelines for technical complaints.

9.3 Treatment of overdose

Overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported AE was nausea. All subjects recovered without complications.

There is no specific antidote for overdose with semaglutide. In the event of an overdose, appropriate supportive treatment should be initiated according to subject's clinical signs and symptoms.

The overdose must be reported as a medication error. Intentional overdose must be reported as misuse or abuse (Appendix 4). For reporting timelines see Section 9.2.1 and Figure 9-1.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE and laboratory abnormalities. The long half-life of semaglutide of approximately one week should be taken into account.

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the subject.
For more information on overdose, also consult the current version of the current IB[40] and any updates hereof.

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.

Medical history is a medical event that the subject has experienced in the past. Any information of weight history, co-morbidities and history of psychiatric disorder must be recorded, otherwise only relevant and significant medical history should be recorded as judged by the investigator.

In case of an abnormal and clinically significant finding, the investigator must record the finding on the Medical history/Concomitant illness form if it is present at screening. Any new finding fulfilling the AE definition (see Appendix 4) during the trial and any clinically significant worsening from baseline (screening, V1) must be reported as an AE (see Section 9.2).

9.4.1 Clinical outcome assessments

The mental health assessment instruments PHQ-9 and C-SSRS will be completed at V1, V8, V20 and V30.

- PHQ-9[50] is a self-administered 9-item depression module of the patient health questionnaire used for assessment of mental disorders. The questionnaire will be available in a linguistically validated translated version
- C-SSRS[51] is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation. The questionnaire will be administered as an interview by the investigator or a qualified

delegate. The questionnaires (C-SSRS Baseline and C-SSRS Since Last Visit) will be available in a linguistically validated translated version. When answering the C-SSRS Since Last Visit questionnaire, the subjects should be instructed to answer the questions having the period since the last assessment in mind
- Prior to administering the C-SSRS questionnaire, the investigator or qualified delegate must complete sufficient training

A subject must be referred to a Mental Health Professional (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 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 it should be documented in the medical record and assessed if it is safe for the subject to continue on trial product and if the subject should continue in the trial.

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

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.

9.4.2 Physical examinations

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

9.4.3 Pubertal status

- Pubertal development must be assessed by the Tanner staging in accordance with stages 1-5[52]. The assessments must be conducted by site staff trained in pubertal assessments. For males, the assessment of testicular volume by orchidometer must be included
- Evidence of accelerated pubertal development at screening, as judged by the investigator must be recorded as Medical history/Concomitant illness in the CRF and in the subject's medical record

- Acceleration of pubertal development after screening as judged by the investigator must be reported as AEs in accordance with Section 9.2 and Appendix 4
- Tanner staging is not required once the subject reaches the Tanner stage 5, as judged by the investigator

9.4.4 Vital signs

- Pulse rate as well as diastolic and systolic blood pressure will be assessed.
- Blood pressure (diastolic and systolic) and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. television, cell phones)
- Blood pressure and pulse measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available

9.4.5 Bone age assessment (X-ray)

- An x-ray of left hand and wrist will be performed at randomisation (V8) and at 'end of treatment' (V30) for all subjects for evaluation of bone age. An x-ray will not be performed at V30 for subjects for whom the bone age evaluation at randomisation indicates that the epiphyses are fused
- The x-ray imaging data will be submitted to a supplier selected for central medical imaging services and will be analysed in a blinded manner by an independent paediatric radiology expert assigned by the supplier for bone age assessment

A bone age x-ray performed within 2 weeks prior to the scheduled assessments is acceptable.

9.4.6 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. The investigator should make an overall interpretation of the ECG

9.4.7 Clinical safety laboratory assessments

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

- Urine pregnancy tests must be performed for women of childbearing potential (WOCBP) at all site visits. Urine pregnancy test must be repeated at any time during the trial whenever a menstrual period is missed or if pregnancy is suspected. Please refer to Appendix 5. Further instructions can be found in the laboratory manual

9.4.8 Immunogenicity assessments

Blood samples for determination of serum antibodies against semaglutide, including cross reactivity to endogenous GLP-1, will be taken during the trial at visits specified in Appendix 2. Samples

which are positive for anti-semaglutide antibodies will be further characterised for in vitro neutralising effect towards semaglutide. In addition, if samples are also positive for cross-reactivity against endogenous GLP-1, the samples will be analysed for in vitro neutralising effect towards endogenous GLP-1. Samples which are positive for anti-semaglutide antibodies will also be titrated. The results of the analysis will only be disclosed after completion of the clinical trial report (CTR) if required by local regulation.

9.4.9 Severe hypersensitivity

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

In the event of an acute severe systemic hypersensitivity reaction possibly or probably related to trial product, the following sample should be taken 3-4 hours after the reaction, if possible:

- Tryptase

Furthermore, 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.

For both samples, the following assessments will be performed:

- Anti-semaglutide IgE antibodies
- Anti-semaglutide 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.

9.5 Pharmacokinetics

- Single blood samples for measuring plasma concentration of semaglutide will be drawn for all randomised subjects on visits specified in Appendix 2
- Subject must be instructed to withhold their trial product dose in the morning of the clinic visit until blood sampling has been performed
- The PK dosing information should be transcribed into the CRF for the last 2 doses of trial product prior to the PK assessment
- The exact timing of obtaining the PK sample must be recorded on the laboratory form

Samples will be used to evaluate the PK of semaglutide. Each plasma sample will be divided into 2 aliquots (e.g. one for PK and a backup) and may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial.

9.6 Pharmacodynamics

Not applicable for this trial

9.7 Genetics

A blood sample for genetic analysis will be collected from subjects who have consented to participate in the optional biobank component of the trial. Refer to Section 9.9 and Appendix 7 for further details.

9.8 Biomarkers

Collection of samples for biomarker research is part of this trial to support the safety objectives. The following samples must be taken in accordance with the laboratory manual and Appendix 2:

Biomarkers:

- Carcinoembryonic Antigen serum
- Serum Insulin-like growth factor 1

9.9 Biosamples for future analysis

Collection of biosamples for future analysis (stored in a biobank) is a component of this trial. The samples will allow for future analyses of biomarkers, both genetic and circulating when new knowledge or improved measurement technologies may have become available.

Participation is optional, and parent(s)/LAR, and if required by local legislation also the subject, will be asked to sign a separate informed consent form in order to participate in the biobank component. Subjects who do not wish to participate in the biobank component may still participate in the trial. For the biobank, blood samples will be collected according to Appendix 2 and stored for future use.

Genetic analyses may include analysis of candidate genes or genetic markers throughout the genome with the purpose of understanding and predicting response to semaglutide as well as to understand obesity or other related diseases.

Analyses of circulating biomarkers will measure hormones, metabolites or other non-genetic serum entity with the purpose of understanding and predicting response to semaglutide as well as understanding obesity or other related diseases.

These samples need to be frozen and should be sent in batches to the central laboratory. Results will not be part of the CTR. The biobank samples may be stored up to 15 years after end of trial at a central laboratory (see Appendix 7).

9.10 Subject diaries

Subjects will be provided with a paper diary to be completed at home. Only the subjects and/or the parent(s)/LAR must enter data in the diary. Subjects and the parent(s)/LAR will be instructed by the investigator on when and how to complete the diary. It is important to explain to the subjects and/or the parent(s)/LAR the necessity of accurate diary recording.

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

All data from the diary must be transcribed into the CRF.

9.10.1 PK diary

Trial product dosing diary pages should be completed by the subject before a visit including a blood sampling for semaglutide plasma concentration (see Section 9.5).

The last 2 doses of trial product should be recorded in the diary before a visit with PK sampling stating:

- Dose
- Date
- Exact time for dosing

9.10.2 Menstrual period diary

For female subjects of childbearing potential the following should be recorded:

- First date of recent menstrual period before the site visit of V8 (randomisation), V20, and V30 ('end of treatment')

If a subject experience a first menstrual period during the trial, the date for start of the period must be recorded.

9.10.3 Diabetes diary

Subjects with T2D at screening or if diagnosed during the trial will be provided with a diabetes diary on self-measured plasma glucose (SMPG) measurements and hypoglycaemic episodes. Refer to Appendix 8.

10 Statistical considerations

Taxonomy of week 68 assessments being available or missing

For each subject a given assessment at week 68 may be available or missing and Table 10-1 describes the taxonomy for this. Note, this is done per assessment not per subject; subjects may be a different type for different assessments (a subject may have "available on treatment (AT)" for weight but "missing on treatment (MT)" for waist circumference).

Table 10-1 Taxonomy for subjects based on week 68 assessments being available or missing

Assessment at week 68	On randomised treatment at week 68	**Type description**	**Type Abbreviation**
Available	Yes	**Available on randomised treatment**: Subjects who complete the trial on randomised treatment with an assessment at week 68: Includes those that stop and restart trial product.	AT
	No	**Available but discontinued** Subjects who discontinued randomised treatment prematurely but returned to have an assessment at week 68. 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 68: Includes those that stop and restart trial product.	MT
	No	**Missing and discontinued**: Subjects who discontinued randomised treatment prematurely and did not return to have an assessment at week 68. These are also called non-retrieved subjects	MD

10.1 Sample size determination

The tests of superiority of s.c. semaglutide 2.4 mg to semaglutide placebo for the primary and confirmatory secondary endpoints are performed using the fixed-sequence statistical strategy. This strategy tests the endpoints using a predefined hierarchical order, all at the significance level of 5%, moving to test the next endpoint only after a significant superiority result (two-sided p-value < 5%) on the previous endpoint. The test hierarchy is given in Table 10-2 with underlying assumptions, marginal power and effective power. The effective power is calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively.

In the analysis approach addressing the primary estimand, week 68 assessments from retrieved subjects (AD) are included. These data are also used to impute missing measurements at week 68 for non-retrieved subjects (MD). The imputation is done separately within each treatment arm (see description below). However, for the sample size calculations, missing values (MT and MD), regardless of treatment arm, are assumed to be similar to semaglutide placebo subjects. These

assumptions are likely conservative with respect to the power and correspond to the jump to reference sensitivity analysis described below.

Assumptions

The assumptions for the sample size calculations are:

- The significance level is 5%
- The randomisation ratio is 2:1
- The t-test on the mean difference assuming equal variances is used
- 35% of subjects discontinue permanently and ≥50% of these are retrieved (AD) at week 68
- All subjects in the semaglutide placebo arm are assumed to have same effect as subjects who complete the trial on semaglutide placebo (AT)
- Retrieved subjects (AD) in the semaglutide arm are assumed to have an effect corresponding to half the treatment difference (compared to semaglutide placebo) of subjects who complete the trial on semaglutide (AT)
- In the semaglutide arm, non-retrieved subjects (MD) and subjects with data missing on randomised treatment (MT) are assumed to have an effect corresponding to the semaglutide placebo arm

Further assumptions made to calculate the power for the primary and confirmatory secondary endpoints are conservatively based on findings from the s.c. semaglutide 0.1 mg and 0.2 mg once daily arms in trial NN9536-4153 and are presented in scenario 1 in Table 10-2. Alternate scenarios based on findings from the s.c. semaglutide 0.3 mg and 0.4 mg once daily arms (the latter expected to correspond to 2.4 mg once weekly) are presented in scenarios 2 and 3, respectively.

Given these assumptions, the sample size of 192 subjects (128 in the semaglutide 2.4 mg and 64 in the semaglutide placebo arm), gives a power of at least 90% for the primary endpoint and an effective power (marginal powers multiplied) of at least 72% for both endpoints in the hierarchical testing procedure. Furthermore, this sample size is selected to ensure an adequate amount of subject exposure to s.c. semaglutide to support safety.

Table 10-2 Assumptions and power for the primary and confirmatory secondary endpoints under various scenarios given an anticipated number of 192 randomised subjects

Scenario	Order	Endpoint	Assumed mean (±SD) or proportion for completers		Expected* mean (±SD) or proportion	Expected* difference or proportion ratio	Marginal power (%)	Effective power (%)
			Semaglutide 2.4 mg	Semaglutide placebo	Semaglutide 2.4 mg			
1	1	% change in BMI #	10.5 (±10)	3 (±10)	8.5 (±11)	5.5%-points	90	90
	2	≥5% responders in body weight	71%	42%	63%	1.5	80	72
2	1	% change in BMI #	12.5 (±10)	3 (±10)	10.0 (±11)	7.0%-points	98	98
	2	≥5% responders in body weight	77%	42%	68%	1.6	93	92
3	1	% change in BMI #	14 (±10)	3 (±10)	11.1 (±11)	8.1%-points	>99	>99
	2	≥5% responders in body weight	82%	42%	72%	1.7	97	97

shown as a positive number; *Accounting for reduced treatment effect among non-completers

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 database will be documented before database lock with the reason for exclusion provided.

Two 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

- On-treatment (with trial product): A time-point is considered as 'on-treatment' if any dose of trial product has been administered within the prior 2 weeks (14 days). The *on-treatment period* is defined as all times which are considered on-treatment
  - In general, 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 two consecutive missed doses
  - For the evaluation of AEs and hypoglycaemic episodes the lag time for each on-treatment time interval is 7 weeks (49 days)

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

As a complete description of the statistical analyses are provided in this section of the protocol, a separate statistical analysis plan (SAP) has not been written for this trial. However, if it is later found to be necessary, a SAP may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses, in which case the SAP will be finalised before database lock.

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

Results from statistical analyses will generally be accompanied by two -sided 95% confidence intervals and corresponding p-values.

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: % change in BMI

Change from baseline to week 68 in BMI (%) is defined as:

$$\%\ \text{change in BMI} = \frac{(\text{BMI at week 68} - \text{BMI at baseline})}{\text{BMI at baseline}} \times 100.$$

Analyses addressing the primary estimand

The following statistical analyses and imputation methods are designed to address the primary estimand, i.e. to assess the effectiveness of semaglutide 2.4 mg.

The analysis model for % change in BMI is a linear regression (ANCOVA) of % change in BMI on randomised treatment and stratification group (gender *Tanner stage group) as factors, and baseline BMI (kg/m2) as covariate. The estimated treatment difference between s.c. semaglutide 2.4 mg and semaglutide placebo will be reported together with the associated two-sided 95% CI and corresponding p-value.

The superiority tests of semaglutide 2.4 mg vs. semaglutide placebo will be carried out as follows.

Let $\mu_{semaglutide}$ and $\mu_{semaglutide\ placebo}$ denote the true mean of % change in BMI for s.c. semaglutide 2.4 mg and semaglutide placebo group, respectively. The null and alternative hypotheses tested are

$$H: \mu_{semaglutide} \geq \mu_{semaglutide\ placebo}\ vs$$
$$H_A: \mu_{semaglutide} < \mu_{semaglutide\ placebo}.$$

The hypothesis will be rejected and superiority claimed, if the upper limit of the estimated two-sided 95% CI is below 0.

Handling of missing week 68 values for the primary estimand

All available data at week 68 (AT and AD) are used and missing values (MT and MD) at week 68 will be imputed. Several approaches for imputation will be applied. First, a description of the primary imputation approach to address the primary 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 BMI development after discontinuation of randomised treatment impact the estimated treatment contrasts between s.c. semaglutide 2.4 mg and semaglutide placebo. An illustration of all imputation approaches for the effectiveness estimand is given in Figure 10-1.

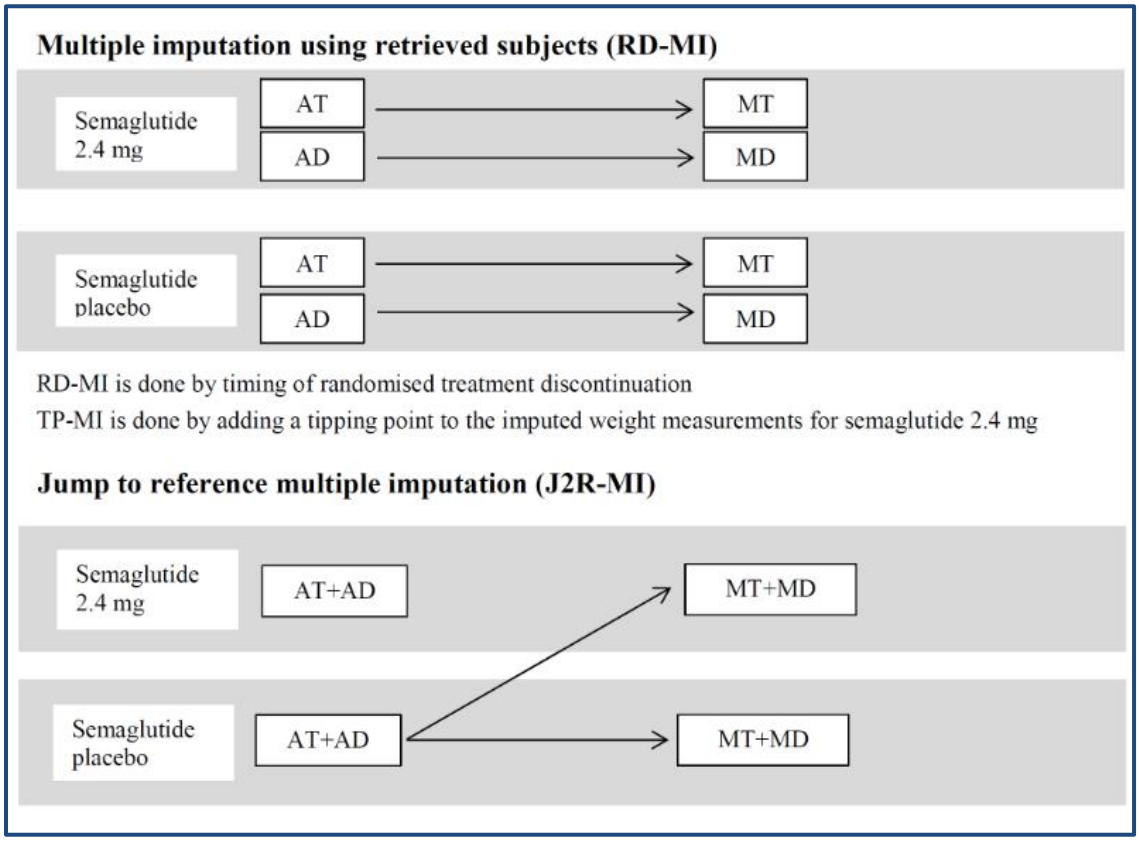


Figure 10-1 Illustration of imputation approaches for the effectiveness estimand

Primary imputation approach for the primary estimand

Multiple imputation approach using retrieved subjects (RD-MI): The primary imputation approach for the primary estimand is a multiple imputation similar to the one described by McEvoy[53].

Missing BMI measurements at week 68 for non-retrieved subjects (MD) are imputed using assessments from retrieved subjects (AD) in each randomised treatment arm. This will be done according to the timing (month) of last available observation during the on-treatment period (LAO-OT) of BMI. Missing BMI measurements at week 68 for subjects on randomised treatment (MT) are imputed by sampling from available measurements at week 68 from subjects on randomised treatment (AT) in the relevant randomised treatment arm. The multiple imputation approach is done in three steps:

1. **Imputation**: Defines an imputation model using retrieved subjects (AD) from FAS and done within groups defined by randomized treatment and the timing (month) of the LAO-OT of BMI (kg/m^2). The model will be a linear regression of BMI (kg/m^2) at week 68 on stratification group (gender *Tanner stage group) as a factor and baseline BMI (kg/m^2) and LAO-OT of BMI (kg/m^2) as covariates. No interactions will be included. If timing by month

is too restrictive, quarters, half-years, or excluding timing will be used. If any subjects are MT, an imputation model for missing BMI measurements at week 68 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 68 BMI values for each randomised treatment arm. This will be done 1000 times and result in 1000 complete data sets

2. **Analysis**: Analysis of each of the 1000 complete data sets, using the analysis model (ANCOVA), resulting in 1000 estimations
3. **Pooling**: Integrate the 1000 estimation results into a final result using Rubin's formula

Based on NN9536-4153 phase 2 results 1,000 copies should be sufficient to establish stable results. If 1,000 copies are insufficient, 10,000 copies will be used. The multiple imputations will be generated using Novo Nordisk trial number 95364451 as seed number.

Sensitivity analyses

Jump to reference multiple imputation approach (J2R-MI): Missing values of BMI at week 68 (MT and MD) for both the semaglutide 2.4 mg and semaglutide placebo group is by sampling among all available assessments at week 68 in the semaglutide placebo group (AT and AD). This approach makes the assumption that subjects instantly after discontinuation lose any effect of randomised treatment beyond what can be expected from semaglutide placebo treatment as adjunct to diet and physical activity[54].The multiple imputation approach is done as above with the first step replaced by:

1. Imputation: Defines an imputation model using semaglutide placebo subjects from FAS with a week 68 measurement (AT and AD). The model will be a linear regression of BMI (kg/m^2) at week 68 on stratification group (gender *Tanner stage group) as a factor and baseline BMI (kg/m^2) 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 68 BMI values for each randomised treatment arms. This will be done 1000 times and result in 1000 complete data sets.

The jump to reference approach is the basis for the sample size calculations.

Tipping-point multiple imputation analysis (TP-MI): This analysis will be performed only if superiority is concluded with respect to the primary endpoint. First, missing data are imputed according to the primary multiple imputation approach. Second, for the semaglutide 2.4 mg treatment arm a penalty will be added to the imputed values at week 68. The approach is to gradually increase this penalty until the conclusion from the primary analysis is reversed. The specific value of the penalty that reverses the conclusion will be used to evaluate the robustness of the primary analysis results. This sensitivity analysis evaluates the robustness of the superiority conclusion.

Mixed model for repeated measurements (MMRM): This 'MMRM for effectiveness' will use all assessments regardless of adherence to randomised treatment, including assessments at week 68 for retrieved drop-outs (AD). The MMRM for effectiveness will be fitted using the same factor and covariate as for the primary analyses all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

Analysis addressing the secondary estimand

The secondary estimand for % change in BMI addresses the efficacy of semaglutide 2.4 mg and will be assessed using a 'MMRM for efficacy'. Week 68 assessments for retrieved subjects (AD) are not used in this analysis. The MMRM for efficacy will use assessments only from subjects who are taking the randomised treatment until end of trial or at first discontinuation of randomised treatment. The derived date of the second consecutive missed dose will be used as the latest date for assessments included in this MMRM. The assessment closest in time and before the derived date of the second consecutive missed dose will be used as last assessment on randomised treatment. For subjects who initiate rescue interventions (weight management drugs or bariatric surgery) before completion or first discontinuation of randomised treatment, the date of starting weight management drugs or undergoing bariatric surgery will be used as last assessment on randomised treatment. The MMRM for efficacy will be fitted using % change in BMI and the same factor and covariate as for the primary analysis all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

10.3.2 Secondary endpoints

10.3.2.1 Confirmatory secondary endpoints

The confirmatory secondary endpoint is weight loss ≥ 5% at week 68 (Y/N) (≥5% body weight responder endpoint), and is included in the fixed-sequence statistical strategy described above.

Analysis addressing the primary estimand

The ≥5% body weight responder endpoint will be analysed using the same imputation approach as used for the primary endpoint and to address the primary estimand. The imputation model is the same as for the primary endpoint, with BMI replaced by body weight, and the resulting imputed values will then be dichotomized to derive the responder endpoint. The statistical model for the ≥5% body weight responder endpoint is a logistic regression using randomised treatment and stratification group (gender *Tanner stage group) as factors, and baseline body weight (kg) as a covariate. The estimated odds ratio (OR) between semaglutide 2.4 mg and semaglutide placebo will be reported together with the associated two-sided 95% CI and corresponding p-value.

The superiority tests of semaglutide 2.4 mg vs. semaglutide placebo will be carried out as follows for the two analysis models.

Let $OR_{semaglutide/placebo}$ denote the true odds ratio between semaglutide 2.4 mg and semaglutide placebo. The null and alternative hypotheses tested are

$$H: OR_{semaglutide/placebo} \leq 1 \; vs$$
$$H_A: OR_{semaglutide/placebo} > 1.$$

The hypothesis will be rejected and superiority claimed, if the lower limit of the estimated two-sided 95% CI is above 1.

Sensitivity analysis for the confirmatory secondary endpoint

A sensitivity analysis considering non-retrieved subjects as non-responders will be carried out.

Analyses addressing the secondary estimand

The secondary estimand for the ≥5% body weight responder endpoint will be assessed using the same MMRM as for the primary endpoint. Subjects who are missing week 68 body weight will be replaced by predicted values for % weight change at week 68 from the MMRM, and these predicted values will then be dichotomized to derive the responder endpoint. A logistic regression model with randomised treatment as a factor and baseline body weight (kg) as a covariate will then be used to analyse the 5% responder endpoint.

An overview of all analysis and imputation methods to address the effectiveness and efficacy estimands for the primary endpoints is given in Table 10-3.

Table 10-3 Analysis and imputation methods to address the effectiveness and efficacy estimands for the primary and confirmatory secondary endpoints in the statistical testing hierarchy

Objective	Endpoint	Test order	Endpoint type	Estimand	Analysis set	Statistical model	Imputation approach	Sensitivity analyses
Primary endpoint								
Primary	% change in BMI	1	Continuous	Primary	FAS	ANCOVA	RD-MI	J2R-MI TP-MI MMRM
				Secondary	FAS	MMRM	-	-
Confirmatory secondary endpoint								
Primary	≥5% body weight responders	2	Binary	Primary	FAS	LR	RD-MI	Non-responders
				Secondary	FAS	LR	MMRM	-

FAS = full analysis set; ANCOVA = analysis of covariance; RD-MI = multiple imputation using retrieved subjects; J2R-MI = jump to reference multiple imputation; TP-MI = tipping point multiple imputation; MMRM = mixed model for repeated measurements; LR = logistic regression

Test order refers to the order of the endpoint in the statistical test hierarchy outlined in Table 10-2.

10.3.2.2 Supportive secondary endpoints

Supportive secondary endpoints are listed in Section 4.

Analyses addressing the primary estimand

The effect-related supportive secondary endpoints will be analysed using the same imputation approach as used for the primary endpoint and to address the primary estimand. The imputation model is the same as for the primary endpoint with BMI replaced by assessments of the endpoint to be analysed. The statistical model for continuous endpoints will be ANCOVA with factor and covariate as for the primary endpoint % change in BMI with baseline BMI replaced by the baseline assessment of the endpoint to be analysed.

The statistical model for the responder endpoint relating to BMI will be logistic regression with randomised treatment as a factor and the baseline assessment of the endpoint to be analysed as covariate.

Analyses addressing the secondary estimand

The supportive secondary endpoints which relate to the primary objective will be analysed to address the secondary estimand using the same MMRM for efficacy described for the primary endpoint.

Analysis of safety endpoints

The safety endpoint pulse will be analysed using an MMRM for efficacy as described in Section 10.3.2.1. For amylase, lipase and calcitonin descriptive statistics will be provided. The analysis of calcitonin will be stratified by gender.

AEs 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). TEAEs and SAEs will be summarised by descriptive statistics, such as frequencies and rates. No formal statistical inference will be carried out based on the number of TEAEs and SAEs. AEs in the run-in period (prior to randomisation) will be presented in listings.

An overview of all analysis and imputation methods to address the effectiveness and efficacy estimands for supportive secondary endpoints is given in Table 10-4.

Table 10-4 Analysis and imputation methods to address the effectiveness and efficacy estimands for supportive secondary endpoints

Objective	Endpoint	Endpoint type	Estimand	Analysis set	Statistical model	Imputation approach
Supportive secondary endpoints (effect related)						
Primary	Weight change (kg)	Continuous	Primary	FAS	ANCOVA	RD-MI
			Secondary	FAS	MMRM	-
Primary	Weight change (%)	Continuous	Primary	FAS	ANCOVA	RD-MI
			Secondary	FAS	MMRM	-
Primary	BMI percentage of the 95th percentile (%)	Continuous	Primary	FAS	ANCOVA	RD-MI
			Secondary	FAS	MMRM	-
Primary	BMI (standard deviation score)	Continuous	Primary	FAS	ANCOVA	RD-MI
			Secondary	FAS	MMRM	-
Primary	Waist circumference change (cm)	Continuous	Primary	FAS	ANCOVA	RD-MI
			Secondary	FAS	MMRM	-
Primary	≥5% BMI responders	Binary	Primary	FAS	LR	RD-MI
			Secondary	FAS	LR	MMRM
Secondary	Systolic BP change (mmHg)	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	Diastolic BP change (mmHg)	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	HbA_{1c} change (%, mmol/mol)	Continuous	Primary	FAS	ANCOVA	RD-MI
Supportive secondary endpoints (safety related)						
Secondary	Number of TEAEs	Continuous	-	SAS	-	-
Secondary	Number of SAEs	Continuous	-	SAS	-	-
Secondary	Pulse change (bpm)	Continuous	-	SAS	MMRM	-
Secondary	Amylase change (U/L)	Continuous	-	SAS	Descriptive statistics	-
Secondary	Lipase change (U/L)	Continuous	-	SAS	Descriptive statistics	-
Secondary	Calcitonin change (ng/L)	Continuous	-	SAS	Descriptive statistics	-

FAS = full analysis set; ANCOVA = analysis of covariance; RD-MI = multiple imputation using retrieved subjects; MMRM = mixed model for repeated measurements; BMI = body mass index; HbA1c = Hemoglobin A1c; BP = blood pressure; TEAEs = treatment-emergent adverse events; SAEs = serious adverse events

10.3.3 Exploratory endpoints

Exploratory endpoints are listed in Section 4.

Analyses addressing the primary estimand

The effect-related exploratory endpoints will be analysed using the same imputation approach as used for the primary endpoint and to address the primary estimand. The imputation model is the same as for the primary endpoint with BMI replaced by assessments of the endpoint to be analysed. The statistical model for continuous endpoints will be ANCOVA with factor and covariate as for the primary endpoint % change in BMI with baseline BMI replaced by the baseline assessment of the endpoint to be analysed.

The statistical model for responder endpoints relating to body weight and COAs will be logistic regression with randomised treatment as a factor and the baseline assessment of the endpoint to be analysed as covariate.

For fasting insulin, lipids, as well as for HOMA-B and HOMA-IR, a multiplicative model will be used, i.e. the ratio between post randomisation measurements and baseline will be calculated instead of differences, and both the dependent variable and covariate will be log-transformed.

Analyses addressing the secondary estimand

The exploratory endpoints measured at week 68 which relate to the primary objective will be analysed to address the secondary estimand using the same MMRM for efficacy described for the primary endpoint.

An overview of all analysis and imputation methods to address the effectiveness and efficacy estimands for effect-related exploratory endpoints is given in Table 10-5.

Analysis of safety endpoints

Observed data for exploratory safety endpoints and other safety assessments will be summarised by descriptive statistics.

Hypoglycaemic episodes will be summarised by descriptive statistics, such as frequencies and rates. No formal statistical inference will be carried out based on the number of hypoglycaemic episodes.

Table 10-5 Analysis and imputation methods to address the effectiveness and efficacy estimands for exploratory endpoints

Objective	Endpoint	Endpoint type	Estimand	Analysis set	Statistical model	Imputation approach
Exploratory endpoints (effect related)						
Primary	BMI change (kg/m^2)	Continuous	Primary	FAS	ANCOVA	RD-MI
			Secondary	FAS	MMRM	-
Primary	≥10% body weight responders	Binary	Primary	FAS	LR	RD-MI
			Secondary	FAS	LR	MMRM
Primary	BMI change to week 52 (%)	Continuous	Primary	FAS	ANCOVA	RD-MI
Primary	BMI change to week 75 (%)	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	FPG change (mg/dL)	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	Fasting insulin change (mIU/L)	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	Total cholesterol change (mg/dL)	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	HDL change (mg/dL)	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	LDL change (mg/dL)	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	VLDL change (mg/dL)	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	Triglycerides change (mg/dL)	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	HOMA-B change (%)	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	HOMA-IR change (score)	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	IWQoL-Kids PCD score	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	IWQoL-Kids BED score change	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	IWQoL-Kids SLD score change	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	IWQoL-Kids FRD score change	Continuous	Primary	FAS	ANCOVA	RD-MI
Secondary	IWQoL-Kids total score change	Continuous	Primary	FAS	ANCOVA	RD-MI

FAS = full analysis set; ANCOVA = analysis of covariance; RD-MI = multiple imputation using retrieved subjects; MMRM = mixed model for repeated measurements; BMI = body mass index; FPG = fasting plasma glucose; HDL = high density lipoprotein; LDL = low density lipoprotein; VLDL = very low density lipoprotein; LR = logistic regression; IWQoL-Kids = Impact of Weight on Quality of Life-Kids for Clinical Trials; PCD = physical comfort domain; BED = body esteem domain; SLD = social life domain; FRD = family relations domain;

10.3.4 Other analyses

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

10.4 Pharmacokinetic and/or pharmacodynamic modelling

The population PK analysis will be performed by Quantitative Clinical Pharmacology, Novo Nordisk A/S. A more technical and detailed elaboration of the population PK analysis will be done in the modelling analysis plan, which will be finalised before database lock.

The population PK analysis will be reported in a separate modelling analysis report included as an appendix to the CTR. Selected results will be summarised in the CTR.

The objective of this modelling analysis is to study the semaglutide exposure in adolescents with obesity and to investigate the effects of pre-specified covariates on the semaglutide plasma concentration. Semaglutide concentrations based on sparse PK samples drawn at site visits will be included in the analysis together with dosing information, as well as relevant demographic data and other covariates. Data from pre-specified historical trials in relevant adult populations will be included in the analysis to allow for the comparison between populations.

A previously developed population PK model for semaglutide will be used in an analysis of data from the current paediatric trial including data and results from pre-specified historical trials with relevant adult patient populations. The pre-specified analysis will explore the effects of covariates on semaglutide exposure. The covariates of interest, such as body weight, gender and age group (paediatric subjects/adults) will be tested on CL/F.

Exposure-response analysis

The PK and PD data will be included in exploratory analyses of PK and exposure-response relationships, which may also include data from other trials.

11 Appendices

Appendix 1 Abbreviations and Trademarks

AD	available but discontinued
ADA	American Diabetes Association
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AT	available on randomised treatment
BG	blood glucose
BMI	body mass index
BUN	blood urea nitrogen
C_{max}	maximum concentration
CI	confidence interval
CLAE	clinical laboratory adverse event
CL/F	Apparent clearance
COA	clinical outcome assessment
CRF	case report form
C-SSRS	Columbia Suicidality Severity Rating Scale
CTR	clinical trial report
CTX1	type 1 C-telopeptide
DFU	direction for use
DHEAS	dehydroepiandrosterone sulfate
DMC	Data Monitoring Committee
DRE	disease-related event
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration

FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
HbA1c	glycated haemoglobin
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HOMA-B	homeostasis model assessment of beta-cell function
HOMA-IR	homeostasis model assessment of insulin resistance
IB	investigator's brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
ISPAD	International Society for Paediatric and Adolescent Diabetes
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWQOL-Kids	Impact of Weight on Quality of Life-Kids
IWRS	interactive web response system
J2R-MI	jump to reference multiple imputation
LAO-OT	last available observation on-treatment
LAR	legally acceptable representative
LDL	low-density lipoprotein
LH	luteinising hormone
LR	logistic regression
MD	missing and discontinued
MEN2	multiple endocrine neoplasia type 2
MHP	mental health professional

MMRM	mixed model for repeated measurements
MT	missing on randomised treatment
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
NTX1	type 1 collagen N-telopeptide
OAD	oral antidiabetic drug
OR	odds ratio
OSA	obstructive sleep apnoea
P1NP	procollagen 1 N-terminal propeptide
PCD	primary completion date
PD	pharmacodynamic
PDCO	European Paediatric Committee
PG	plasma glucose
PHQ-9	Patient Health Questionnaire 9
PK	pharmacokinetic
PYE	patient years of exposure
PYO	patient years of observation
RA	receptor agonist
RD-MI	multiple imputation using retrieved subjects
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous
SD	standard deviation
SDS	standard deviation score
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
T4	thyroxine
TEAE	treatment-emergent adverse event
TMM	trial materials manual

TP-MI	tipping-point multiple imputation
TSH	thyroid stimulating hormone
UNL	upper normal limit
UNR	upper normal range
VLDL	very low-density lipoprotein
WOCBP	woman of child bearing potential

Appendix 2 Clinical laboratory tests

- Laboratory samples specified in the protocol should be sent to the central laboratory for analysis
- The tests detailed in Table 11-1 and Table 11-2 will be performed by the central laboratory
- The tests detailed in Table 11-3 will be performed by a special laboratory
- 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 central lab will communicate to the investigator abnormal values of parameters not requested in the protocol, but identified by the laboratory equipment and/or their processes according to their lab SOPs. These data will not be transferred to the trial database. The investigator should review such values for AEs and report these according to this protocol.
- 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 antibody samples which will be stored until marketing authorisation or destroyed at the latest 15 years from end of trial
- Human biosamples for future analysis will be stored as described in Appendix 7
- For haematology samples (differential count) where the test result is not normal, a part of the sample may be kept for up to two years or according to local regulations

Table 11-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism (V2, V8, V20, V30)	• FPG[1] (also taken at V12 and V26 for subjects with T2D at screening or if diagnosed during the trial) • HbA1c (to be taken at V1, not V2. Also taken at V12, V16 and V26 for subjects with T2D at screening or if diagnosed during the trial) • Fasting serum insulin • Homeostasis model assessment (HOMA-B and HOMA-IR)
Lipids (V8,V20, V30)	• Total cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Very low density lipoprotein cholesterol (VLDL) • Triglycerides
NOTES : [1]A FPG result ≤3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator (Appendix 4).	

Table 11-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology (V1,V8,V20, V30)	• Haemoglobin • Haematocrit • Thrombocytes • Erythrocytes • Leucocytes • Eosinophils • Neutrophils • Basophils • Lymphocytes • Monocytes
Biochemistry[1] (V1,V8,V20, V30)	• Creatinine • Creatine kinase • Urea (BUN) • Albumin • Bilirubin (total) • Alanine aminotransferase (ALT)[2] • Aspartate aminotransferase (AST)[2] • Alkaline phosphatase (ALP) • Sodium • Potassium • Calcium total • Calcium (albumin corrected) • Gamma-glutamyltransferase (GGT) • Calcitonin • Amylase • Lipase
Hormones (V8,V20, V30)	• Thyroid stimulating hormone (TSH) (also taken at V1) • Free thyroxine (free T4) (also taken at V1) • Dehydroepiandrosterone sulfate (DHEAS) • Luteinising hormone (LH) • Follicle stimulating hormone (FSH) • Estradiol (females) • Testosterone (males) • Prolactin
Bone metabolism (V8, V30)	• Type 1 collagen N-telopeptide (NTX1) • Type 1 C-telopeptide (CTX1) • Procollagen 1 N-terminal propeptide (P1NP) • Alkaline phosphatase (bone)
Pregnancy Testing (V1, V2, V4, V6, V8, V10, V12, V14, V16, V18, V20, V22, V24, V26, V28, V30, V31)	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP), see Appendix 5 for further information.
Biomarkers	• Carcinoembryonic Antigen serum

(V8,V20, V30)	• Serum Insulin-like growth factor 1
Other tests	• Tryptase in case of acute severe systemic hypersensitivity, see Section 9.4.9. • Biosamples for future analysis (V8, V30)
Notes : [1]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 4 (Hy's Law) and Section 8.1. [2]If ALT or AST >3 upper normal limit (UNL) additional relevant blood samples should be taken by local laboratory (except at screening visit). Repeat testing of the abnormal lab assessments should be performed for the subject until abnormalities return to normal or baseline state.	

Table 11-3 Protocol-required special laboratory parameters

Laboratory assessments	Parameters
Antibodies (V8, V12, V16, V20, V26, V30, V31)	• Anti-semaglutide antibodies • Antibodies cross-reacting native GLP-1 • Semaglutide AB (Neutralising effect) • Antibodies neutralising native GLP-1 • Semaglutide anti bodies (Titer)
Antibodies (unscheduled)[1]	• Anti-semaglutide antibodies • Anti-semaglutide IgE antibodies
PK (V12, V16, V20, V22, V26, V30, V31)	• Semaglutide PK
NOTES : 1 Anti-semaglutide IgE antibodies and anti-semaglutide antibodies are analysed in case of suspicion of trial drug induced acute severe systemic hypersensitivity, see 9.4.9 and Appendix 4.	

Laboratory results that could unblind the trial (e.g. antibodies) will not be reported to the trial sites until the trial has been unblinded.

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[55] and applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[56]
  - 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

For country specific requirements, see Appendix 11.

2) Financial disclosure

Investigators and sub-investigators 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 the parent(s)/LAR and answer all questions regarding the trial
- The investigator must give the subject and the parent(s)/LAR verbal and written information according to his/her capacity to understand, always taking into consideration the subject's presumed willingness to participate in the trial
- The investigator must ensure the subject and their parent(s)/LAR ample time to come to a decision whether or not to participate in the trial
- Subjects and their parent(s)/LAR must be informed that their participation is voluntary
- Subjects or their parent(s)/LAR will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[56], Declaration of Helsinki[55] 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 and assent 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 and/or their parent(s)/LAR 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 or the subject's LAR
- If the minor reaches legal age while participating in the trial and has only signed an age specific informed consent/assent form, the subject has to re-consent to the informed consent form signed by the subject's LAR

4) Information to subjects during trial

The site will be offered a communication package for the subject and the parent(s)/LAR 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 or the parent(s)/LAR. The written information will be translated and adjusted to local requirements and distributed to the subject and the parent(s)/LAR at the discretion of the investigator.

The subject and the parent(s)/LAR may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further the subject and the parent(s)/LAR may receive other written information during the trial.

All written information to subjects and the parent(s)/LAR 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 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 and the parent(s)/LAR 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 and the parent(s)/LAR 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

For country specific requirements, refer to Appendix 11.

6) Committee structure

Novo Nordisk safety committee

Novo Nordisk will constitute an internal semaglutide s.c. safety committee to perform ongoing safety surveillance. The semaglutide s.c. 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.

Data monitoring committee

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

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

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 (or two) investigator(s) 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[57].

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[57].

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)[58], the Food and Drug Administration Amendment Act (FDAAA)[59], European Commission Requirements[60-62] 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 (LSFT) + 68 weeks corresponding to 'end of treatment' visit (V30). If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed 'end of treatment' visit (V30). The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

9) Data quality assurance

Case Report Forms (CRFs)

- 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
- The following will be provided as paper CRFs to be used when access to the electronic CRF is revoked or the electronic CRF is temporarily unavailable:
  - AE forms
  - Safety information forms
  - 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, 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 personnel 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 and PROs, 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
- The original of the completed diaries must not be removed from the trial site, unless they form part of the CRF and a copy is kept at the site
- 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
- 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 personnel 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: Please refer to Appendix 11.

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 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. • A "lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.
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** • 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. • 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 AEs 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 >3 x UNL and total bilirubin >2 x 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 are AEs where the additional data will benefit the evaluation of the safety of the trial product (see Table 9-1). The selection of these events is based on the non-clinical and clinical data with semaglutide, knowledge from the GLP-1 RA drug class as well as regulatory requirements.

Event type	Description
Acute gallbladder disease	Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis)
Acute pancreatitis	The diagnosis of acute pancreatitis requires two of the following three features: 1. abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) 2. serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal 3. characteristic findings of acute pancreatitis on imaging
Malignant neoplasm	Malignant neoplasm by histopathology or other substantial clinical evidence
Hepatic event	Hepatic event defined as: - Disorders of the liver including cholestatic conditions and liver related signs and symptoms - ALT or AST > 3x UNL and total bilirubin > 2x UNL* - ALT or AST > 3x UNL with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

		*Please note that in case of a hepatic event defined as ALT or AST > 3x UNL and total bilirubin > 2x UNL, where no alternative aetiology exists (Hy's law), this must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable.	
	Medication error	A medication error is an unintended failure in the trial drug treatment process that leads to, or has the potential to lead to, harm to the subject, such as: • Administration of wrong drug. • Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in administration of wrong drug. • Wrong route of administration, such as intramuscular instead of subcutaneous. • Accidental administration of more than 2.4 mg/week or a higher dose than intended during dose escalation, however, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.	
	Misuse	Misuse is when the trial product is intentionally and inappropriately used not in accordance with the protocol.	
	Abuse	Abuse of trial product is persistent or sporadic, intentional excessive use, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm)	
	Diabetic retinopathy (T2D only)	New onset or worsening of diabetic retinopathy	

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 safety information form. 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 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 the sequelae meet 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 form, safety information form and specific event form) 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 safety information form (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 safety information form (see box below) or to Novo Nordisk by telephone.

SAE reporting via paper CRF

• Relevant CRF forms (AE and safety information form) 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 safety information form within the designated reporting time frames (as illustrated in Figure 9-1):
  • AE form within 24 hours.
  • Safety information form 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

It must be recorded in the CRF whether female subjects are of childbearing potential (have had first menstrual period).

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

The childbearing potential of female subjects must be evaluated at every visit until the female subject becomes of childbearing potential.

Contraception guidance

Male subjects
No contraception measures are required for male subjects as the risk of teratogenicity/fetotoxicity caused by transfer of semaglutide in seminal fluid is unlikely.

Female subjects
Female subjects of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly as described in Table 11-4 below:

Table 11-4 Highly effective contraceptive methods (failure rate of <1% per year when used consistently and correctly)

Highly effective contraceptive methods that are user dependent [a and b]
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [b] • oral • intravaginal • transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • oral • injectable
Highly effective methods that are user independent [b]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine Device (IUD) • Intrauterine hormone-releasing System (IUS) • Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Sexual abstinence[b]
Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.
Notes: [a] Failure rates may differ from <1% per year, if not used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials. [b] Contraception should be utilised during the treatment period and for at least 49 days after the last dose of trial product.

In certain cases, it is accepted to use double barrier methods (a condom combined with an occlusive cap (e.g. diaphragm) with/without the use of spermicide). This should only be allowed in females with:

1. known intolerance to the highly effective methods mentioned in Table 11-4 or where the use of any of the listed highly effective contraceptive measures are contraindicated in the individual subject, and/or
2. if the risk of initiating treatment with a specific highly effective method outweighs the benefit for the female

Justification for accepting double barrier method should be at the discretion of the investigator taking into consideration his/hers knowledge about the female's obesity history, concomitant illness, concomitant medication and observed AEs. The justification must be stated in the medical records.

For country specific requirements, see Appendix 11.

Pregnancy testing

- WOCBP must only be included after a negative highly sensitive urine pregnancy test at screening (V1) and randomisation (V8)
- Urine pregnancy testing must be performed according to Appendix 2.
- If a girl becomes of childbearing potential (has first menstrual period) during the trial a urine pregnancy test must be performed as soon as possible or at the latest at the next site visit
- Pregnancy testing must be performed whenever a menstrual period is missed or when pregnancy is otherwise suspected
- Additional urine pregnancy testing must be performed at monthly intervals during the treatment period, if required locally (Appendix 11). Highly sensitive serum testing (sensitivity of 5-25 mIU/mL) is mandatory if required by local regulations or ethics committees, or to resolve an indeterminate test or to confirm a positive urine test

For country specific requirements, see Appendix 11.

Collection of pregnancy information

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 will 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 9-3. 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

- Antibody samples will be retained for potential later analysis for further characterisation of antibody responses towards drug, if required by health authorities or for safety reasons
- Only Novo Nordisk staff and personnel from the specialised laboratory will have access to the stored specimens
- The samples will be stored at the specialised laboratory or Novo Nordisk 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
- Samples might be transferred to other countries, 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 and the parent(s)/LAR can contact the investigator if they wish to be informed about results derived from stored biosamples obtained from their own body

Biosamples for future analysis

- In countries where applicable, the trial will involve collection of human biosamples to be stored in a central archive for future use
- The parent(s)/LAR, and if required by local legislation also the subject, must sign and date a separate informed consent form before biosamples are collected to be stored for future analysis
- The material to be collected at randomisation (V8) and 'end of treatment'(V30) is:
  - Whole blood (for genetic analysis)
  - Serum (for analysis of circulating biomarkers)
- As new biomarkers related to the disease and/or safety, efficacy or mechanism of action of semaglutide may evolve during the conduct of the trial, the analyses of the stored biosamples may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial
- The biosamples will be stored at a central laboratory for 6 months and at a central storage facility contracted by Novo Nordisk for up to 15 years after end of trial. Only Novo Nordisk and storage facility employees will be able to access the stored biosamples. The biosamples may be transferred to other countries for analysis and will be destroyed at the latest 15 years after end of trial

The subject or the parent(s)/LAR may request the stored biosamples to be destroyed by withdrawing the designated informed consent.

In case the subject or the parent(s)/LAR withdraws his/her informed consent for biosamples for future analysis and genetics, the monitor must contact the trial manager at Novo Nordisk as soon as possible in order to have the samples withdrawn from storage.

Appendix 8 Flowchart and assessments for subjects with T2D

Assessments relevant for subjects with T2D at screening or if diagnosed during the trial are described in this appendix. For these subjects, the flowchart in this appendix replaces the one in Section 2.

Medical history of the subjects with T2D must include diabetes history and complications. If the subject is diagnosed with T2D during the trial this must be recorded as an AE.

If the subject is on metformin the dose must be recorded in concomitant medication form.

Furthermore, evaluation of oral anti diabetes medication must be done according to the flowchart. The evaluation should be based on whether an overall change from randomisation until the time of the evaluation has occurred (i.e., either increase, decrease or no change) after reviewing all available relevant information e.g., changes in drug dose, drug class, number of drugs or a combination of these.

A diary on SMPG measurements and hypoglycaemic episodes will be handed out at randomisation (V8) or when diagnosed with T2D.

Flowchart for subjects with T2D at screening or if diagnosed during the trial.

	Screening	Run-in						Randomisation	Dose escalation								Maintenance												End of treatment	End of trial
Visit[a]	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	P25	V26	P27	V28	P29	V30	V31
Timing of Visit (Weeks)	-14	-12	-10	-8	-6	-4	-2	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7/0	±3	±7	±3	±7	±3	±7	±0	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	0/7
Attend visit fasting (6.5.1)		X						X				X								X						X				X	X
Informed consent, Informed assent and Demography[b] (Appendix 3)	X																														
Inclusion and exclusion criteria (6.1, 6.2)	X	X																													
Run-in criteria (6.3)			X	X	X	X	X																								
Randomisation criteria and randomisation (6.4)								X																							
Medical history/ Concomitant illness and Tobacco Use[c] (6.5.2, 9.4, Appendix 8)	X																														
Eye examination (Appendix 8)	X[l]							X[m]																						X	
Concomitant medication (7.7)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation Oral Anti Diabetes Medication (Appendix 8)																				X										X	
Childbearing potential[d], Menstrual cycle[e] and Pregnancy test[f] (9.2.6, 9.4.7, 9.10.2, Appendix 5)	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pubertal Status (9.4.3)	X							X												X										X	
ECG (9.4.6)	X							X																						X	
Vital Signs (9.4.4)	X							X		X		X		X		X		X		X		X		X		X		X		X	X
Laboratory assessments (Appendix 2)	X	X						X[g]				X[h]				X[h]				X[h]		X[h]				X[h]				X[h]	X
Biosamples for future analysis[i] (9.7, 9.9)								X																						X	
Clinical Outcome Assessments (9.1.2, 9.4.1)	X							X												X										X	
Physical examination (9.4.2)	X							X												X										X	
Height (9.1.1)	X							X						X						X				X		X				X	X

	Screening	Run-in						Randomisation	Dose escalation								Maintenance												End of treatment	End of trial
Visit[a]	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	P25	V26	P27	V28	P29	V30	V31
Timing of Visit (Weeks)	-14	-12	-10	-8	-6	-4	-2	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7/0	±3	±7	±3	±7	±3	±7	±0	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	0/7
Body Weight (9.1.1)	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	X
Waist Circumference (9.1.1)	X							X												X										X	
Bone age measurement (x-ray) (9.4.5)								X																						X	
Adverse event (9.2, Appendix 4, Appendix 6)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diet and physical activity counselling[j] (7.1.2, 7.1.3)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hand out and instruct in diary 9, Appendix 8)	X[k]							X		X		X		X		X		X		X		X		X		X		X		X	
Collect, review and transcribe diary (9.10, 9.10.1, 9.10.2, 9.10.3)								X[k]		X		X		X		X		X		X		X		X		X		X		X	X
Connect to IWRS (7.3)	X							X																						X	
Training in trial product, pen-handling (7.1.1)								X				X				X		X		X		X		X		X		X			
Drug handling (7.1, 7.3, 7.5)								X				X				X		X		X		X		X		X		X		X	
Trial product compliance (7.1, 7.6)									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Self-measured plasma glucose (SMPG) (Appendix 8)								X	X	X		X		X		X		X		X		X		X		X		X		X	X
Hand out and instruct in BG-meter (Appendix 8)								X																							
Hypoglycaemic episodes (Appendix 8)									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a) Visits marked as phone visits can be replaced by site visits or video calls to ensure flexibility for the subjects
b) Demography consists of date of birth, sex, ethnicity, and race (according to local regulation)
c) Smoking is defined as smoking at least one daily cigarette or equivalent (e.g. cigar, hookah or e-cigarette)
d) Only for females
e) Only for females that have started their menstrual period (of childbearing potential)
f) Only for females that have started their menstrual period (of childbearing potential): Urine pregnancy test should also be performed at any time during the trial if pregnancy is suspected, if a menstrual period is missed, and/or according to local regulations/law. If a female becomes of childbearing potential (has first menstrual period) during the trial a urine pregnancy test must be performed for that subject at the latest at the next site visit. For country specific requirements, see Appendix 11.

g) Blood samples should be taken prior to product dosing
h) Due to PK sampling, subjects must be instructed to withhold their trial product dose in the morning until blood sampling has been performed at the visit. This is not applicable for subjects that have discontinued trial product
i) Only for subjects where the separate informed consent for future research has been signed
j) The counselling can be done independent of the site visits within the visit window and flexibly as site visits or phone or video call
k) Only for females (for menstrual period record in run-in period)
l) Fundus examination can be performed up to 90 days prior to and until screening (V1)
m) Fundus examination can be performed up to 30 days prior to and until randomisation (V8)

Eye examination

Subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy are not eligible as this indicates retinopathy that has recently progressed to a level that requires intervention or is approaching intervention, but has yet to be brought under control.

Results of an eye examination performed by an ophthalmologist or another suitably qualified health care provider must be available and evaluated by the investigator at screening and before randomisation to assess eligibility. If T2D is diagnosed during the trial, an eye examination should be performed as soon as possible.

The eye examination should be performed as a fundus photography (e.g. 2-field 60 degree or better, colour or red-free) or by slit-lamp biomicroscopy examination (e.g. using a pre-corneal or corneal contact lens examination) and performed with pharmacologically dilated pupils.

If the subject had such an eye examination performed within 90 days prior to screening, the investigator may base his/her evaluation upon the results of that examination. The examination must be repeated before randomisation if the subject has experienced worsening of visual function since the last examination. If the applicable eye examination was performed before the subject signed the informed consent form, it must be documented that the reason for performing the examination was not related to this trial. A second examination must be repeated within 30 days prior to randomisation (V8).

After randomisation an eye examination performed according to above must be performed as per the flowchart in this appendix. The investigator should indicate the outcome of each eye examination. Relevant findings prior to randomisation must be recorded as concomitant illness/medical history. While relevant findings occurring after randomisation should be reported as an AE, if applicable according to Appendix 4.

Self-measured plasma glucose (SMPG)

Subjects will be provided with a BG meter including auxiliaries as well as instructions for use at randomisation or if diagnosed with T2D during the trial. The subjects will be instructed in how to use the device. Investigator should ensure throughout the trial that the subject is able to correctly measure BG at any time.

The BG meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display.

The BG meter provided by Novo Nordisk should be used for the measurements required in the protocol.

SMPG measurements should be taken fasting (at least 8 hours overnight before the visit), and prior to taking any diabetes medication. SMPG should be taken either on the day of the clinic visit or on the day before, according to the flowchart. In case of suspicion of a hypoglycaemic event a SMPG should also be taken. Subjects should be instructed in how to record the results of the SMPG values in the diaries. The record of each SMPG value should include date, time and value. All data from the diary must be transcribed into the CRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the CRF must be corrected.

Rescue criteria

If the confirmatory HbA1c exceeds the values described below then the subject should be offered treatment intensification (rescue medication) at the discretion of the investigator and according to the recommendations below. To allow for observation of the expected effect of trial product, rescue criteria will be applied from week 8 (V12) to week 68 (V30). Below rescue criteria applies to all subjects regardless if on active treatment or placebo.

- subjects with a central HbA1c value above 8.5% (69 mmol/mol), who have experienced deterioration in glycaemic control, as expressed by an increase in HbA1c equal to or above 1% from randomisation (or lowest level post-randomisation) that is confirmed within 30 days by the central laboratory*
- subjects with persistent poor glycaemic control, as expressed by a stable HbA1c value above 8.5% (69 mmol/mol) that is confirmed at the next planned visit and by the central laboratory and considered unacceptably high according to investigator's assessment*

* with no intercurrent illness or explanation including non-compliance according to investigator's assessment.

Rescue medication

Glycaemic rescue medication, i.e. intensification of background oral antidiabetic drug (OAD) treatment or addition of new background OADs, should be implemented at the discretion of the investigator in case of persistent hyperglycaemia.

The following guidelines should be used:

Rescue medication according to ADA/International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines[63, 64] (excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues). Rescue medication should preferably be weight-neutral.

If deemed necessary at the discretion of the investigator, insulin rescue therapy can be initiated, if so it should be according to ADA/ISPAD guidelines[63, 64] and as short duration as possible.

Subjects that are started on rescue medication should continue to follow the protocol-specified visit schedule and stay on randomised treatment unless the investigator judge that it jeopardise safety. Rescue medication should be documented in medical records and reported as concomitant medication.

Rescue medication will not be supplied by Novo Nordisk, but reimbursed as long as subject is participating in the trial, if required according to local regulations Appendix 11.

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

The following Disease-Related Event (DRE) is common in subjects with T2D and can be serious/life threatening:

- Hypoglycaemic episodes

Non-serious hypoglycaemia must be reported on a hypoglycaemic episode form only.

If the hypoglycaemic episode fulfils the criteria for an SAE then in addition to the above, an AE form and a safety information form must also be filled in. One AE form and safety information form can cover several hypoglycaemic episode forms, if the subject has not recovered between the episodes.

Hypoglycaemic episodes

Novo Nordisk classification of hypoglycaemia in paediatrics

Hypoglycaemic episodes are classified according to ISPAD's definition of severe hypoglycaemia[65], as well as the Novo Nordisk classification of hypoglycaemia and the ADA classification of hypoglycaemia (Figure 11-1).

In normal physiology, symptoms of hypoglycaemia occur below a Plasma Glucose (PG) level of 3.1 mmol/L (56 mg/dL)[66]. Therefore, Novo Nordisk has included hypoglycaemia with PG levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

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

1. Severe hypoglycaemia according to the ISPAD classification[65]: Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?
2. Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia
3. Severe or BG confirmed symptomatic hypoglycaemia: The union of 1. and 2

ADA/ISPAD classification of hypoglycaemia in paediatrics[65, 66]

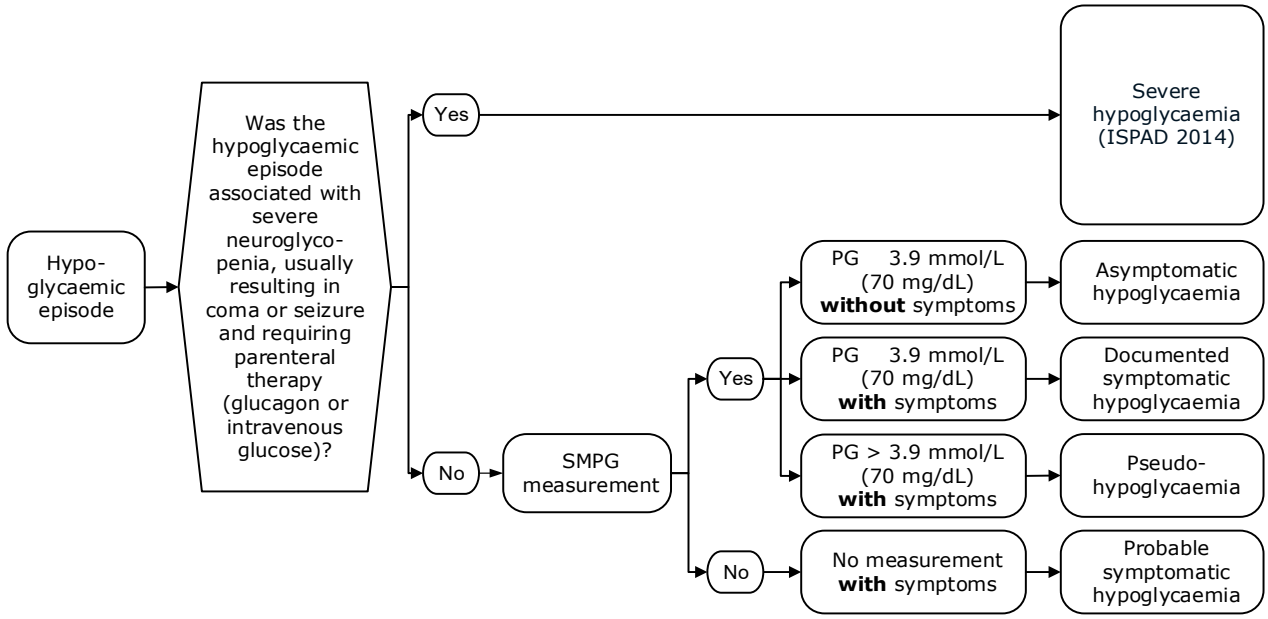
- Severe hypoglycaemia according to the ISPAD classification[65]: Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured PG concentration ≤3.9 mmol/L (70 mg/dL)
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration ≤3.9 mmol/L (70 mg/dL)
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured PG concentration >3.9 mmol/L (70 mg/dL) but approaching that level
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a PG determination but that was presumably caused by a PG concentration ≤3.9 mmol/L (70 mg/dL)

For hypoglycaemic episodes reported with missing information related to the classification, the following applies when classifying the episode according to the ADA/ISPAD classification:

- A hypoglycaemic episode with missing information on severe neuroglycopenia will be classified as no severe neuroglycopenia
- A hypoglycaemic episode with missing information on symptoms will be classified as without symptoms

Episodes that cannot be classified according to the above, are included in the following category:

- 'ADA/ISPAD unclassifiable' includes episodes where subjects did not have severe neuroglycopenia with PG>3.9 mmol/L (70 mg/dL) or missing PG, and with missing information on symptoms



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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 11-1 ADA/ISPAD classification of hypoglycaemia in paediatrics[65, 66]

Treatment-emergent: hypoglycaemic episodes will be defined as treatment-emergent, if the onset of the episode occurs in the on-treatment period (see definition in Section10.2).

Nocturnal hypoglycaemic episodes: episodes occurring between 23:00 and 07:00 both inclusive.

Hypoglycaemic episodes are classified according to ISPAD's definition of severe hypoglycaemia[65], as well as the Novo Nordisk classification of hypoglycaemia and the ADA classification of hypoglycaemia (Figure 11-1).

Reporting of hypoglycaemic episodes:

PG should always be measured and recorded when a hypoglycaemic episode is suspected.
All PG values:
≤3.9 mmol/L (70 mg/dL) or
>3.9 mmol/L (70 mg/dL) occurring in conjunction with hypoglycaemic symptoms should be reported as a hypoglycaemic episode according to the flowchart and instructions below. When a subject experiences a hypoglycaemic episode, subject or the parent(s)/LAR should record the general information in relation to the hypoglycaemia (timing, PG measurements, symptoms etc. as described in the diary). In case a subject is not able to fill in the diary (e.g. in case of hospitalisation

or at the 'follow-up phone contact'), then investigator should report the hypoglycaemic episode directly in the CRF.

The hypoglycaemic episode diary pages should be completed if the subject recognises a hypoglycaemic episode in between visits.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines[66].

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

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

The lowest value measured during the hypoglycaemic episode will be reported as the PG value for the episode. The remaining values will be kept as source data in the diary.

A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode.
If the severity of a hypoglycaemic episode worsens, only one hypoglycaemic episode should be reported, reflecting the most severe degree of hypoglycaemia.

If the question "Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?" is answered "YES", the hypoglycaemic episode is classified as "severe[65]". The subject or the parent(s)/LAR should be instructed to contact the investigator as soon as possible after recovery for further guidance.

Additional information (e.g. description of symptoms, alleviation of symptoms, seizure, coma, fatal) in relation to these severe hypoglycaemic episodes must be recorded.
Oral carbohydrates must not be given if the subject is unconscious.

The investigator must review the diary for low SMPG values not reported as hypoglycaemic episodes. The subject must be questioned whether any of the low values were severe, i.e. whether the subject was able to self-treat or not. If the subject was not able to self-treat, it has to be reported as a severe hypoglycaemic episode.

For low SMPG values for hypoglycaemic episodes where the subject was able to self-treat: If a hypoglycaemic episode form is not completed within 7 calendar days of the SMPG measurement, the episode should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data[67, 68].

The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies low SMPG values not reported as hypoglycaemic episodes.

Appendix 9 Clinical Charts for Body Mass Index by gender and age

Age calculated from CDC.gov: https://www.cdc.gov/growthcharts/percentile_data_files.htm

In Table 11-5 BMI cut-off points are listed for the entire month; for example, 17:1 (age:months) represent 17 years and 1 month up to but not including 17 years and 2 months of age.

According to the protocol inclusion criterion (Section 6.1) and the protocol randomisation criterion (Section 6.4), subjects must have a BMI corresponding to ≥95th percentile OR ≥85th percentile with ≥1 weight related comorbidity, on gender and age-specific growth charts (CDC.gov). Table 11-5 must be used to determine subjects' eligibility.

If a BMI corresponding to <85th percentile on gender and age-specific growth charts (CDC.gov) (Table 11-5) is reached during the trial, subjects should be assigned a maintenance diet, at the discretion of the investigator (see Section 7.1.2).

If subjects becomes 18 years of age during the trial (after signing the Informed Consent Form), the definition for obesity is BMI ≥30 kg/m^2 and the definition for overweight is BMI ≥27 kg/m^2, while if a BMI corresponding to <25 kg/m^2 is reached during the trial, subjects should be assigned a maintenance diet, at the discretion of the investigator (see Section 7.1.2).

Table 11-5 Cut-off points for BMI (Weight in kg/Height in m^2) for obesity (≥95th percentile) and for overweight (≥85th percentile) and for diet maintenance (<85th percentile) by gender for children from 12 and <18 years of age

Age (Year: Month)	Obesity (95th percentile)		Overweight (85th percentile)	
	BMI for Males	BMI for Females	BMI for Males	BMI for Females
12:0	24.23	25.26	21.02	21.74
12:1	24.31	25.35	21.09	21.81
12:2	24.39	25.43	21.16	21.88
12:3	24.47	25.52	21.23	21.96
12:4	24.55	25.61	21.30	22.03
12:5	24.63	25.70	21.37	22.10
12:6	24.71	25.79	21.44	22.17
12:7	24.79	25.87	21.51	22.23
12:8	24.87	25.96	21.58	22.30
12:9	24.95	26.05	21.65	22.37
12:10	25.03	26.13	21.71	22.44
12:11	25.10	26.22	21.78	22.51
13:0	25.18	26.30	21.85	22.58
13:1	25.25	26.38	21.92	22.64
13:2	25.33	26.46	21.99	22.71
13:3	25.40	26.55	22.06	22.77
13:4	25.48	26.63	22.12	22.84
13:5	25.55	26.71	22.19	22.90
13:6	25.62	26.79	22.26	22.97
13:7	25.69	26.87	22.33	23.03
13:8	25.77	26.95	22.39	23.10
13:9	25.84	27.03	22.46	23.16
13:10	25.91	27.10	22.53	23.22
13:11	25.98	27.18	22.60	23.29
14:0	26.05	27.26	22.66	23.35
14:1	26.12	27.33	22.73	23.41
14:2	26.18	27.41	22.80	23.47
14:3	26.25	27.48	22.86	23.53
14:4	26.32	27.55	22.93	23.59
14:5	26.38	27.63	22.99	23.65
14:6	26.45	27.70	23.06	23.71
14:7	26.52	27.77	23.13	23.76
14:8	26.58	27.84	23.19	23.82
14:9	26.65	27.91	23.26	23.88
14:10	26.71	27.99	23.32	23.93
14:11	26.77	28.05	23.39	23.99

Age (Year: Month)	Obesity (95th percentile)		Overweight (85th percentile)	
	BMI for Males	BMI for Females	BMI for Males	BMI for Females
15:0	26.84	28.12	23.45	24.05
15:1	26.90	28.19	23.52	24.10
15:2	26.96	28.26	23.58	24.15
15:3	27.02	28.33	23.64	24.21
15:4	27.09	28.39	23.71	24.26
15:5	27.15	28.46	23.77	24.31
15:6	27.21	28.53	23.83	24.36
15:7	27.27	28.59	23.90	24.42
15:8	27.33	28.66	23.96	24.47
15:9	27.39	28.72	24.02	24.52
15:10	27.45	28.78	24.09	24.57
15:11	27.51	28.85	24.15	24.62
16:0	27.56	28.91	24.21	24.66
16:1	27.62	28.97	24.27	24.71
16:2	27.68	29.03	24.33	24.76
16:3	27.74	29.10	24.40	24.81
16:4	27.80	29.16	24.46	24.85
16:5	27.85	29.22	24.52	24.90
16:6	27.91	29.28	24.58	24.94
16:7	27.97	29.34	24.64	24.99
16:8	28.03	29.40	24.70	25.03
16:9	28.08	29.46	24.76	25.08
16:10	28.14	29.52	24.82	25.12
16:11	28.20	29.57	24.88	25.16
17:0	28.26	29.63	24.94	25.20
17:1	28.31	29.69	25.00	25.25
17:2	28.37	29.75	25.06	25.29
17:3	28.43	29.81	25.12	25.33
17:4	28.49	29.87	25.18	25.37
17:5	28.55	29.92	25.24	25.41
17:6	28.60	29.98	25.30	25.45
17:7	28.66	30.04	25.36	25.49
17:8	28.72	30.10	25.42	25.53
17:9	28.78	30.15	25.48	25.57
17:10	28.84	30.21	25.54	25.60
17:11	28.90	30.27	25.60	25.64

Appendix 10 Monitoring of calcitonin

Background

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

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

There is little information available on normal calcitonin levels in children. The available information suggests that children in the age range included in this clinical trial (10 to less than 18 years) will have calcitonin levels indistinguishable from adults[69].

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

- renal dysfunction
- tobacco use
- autoimmune thyroiditis
- several drug classes (e.g. proton pump inhibitors, beta-blockers, H2-blockers and glucocorticoids)

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

Calcitonin monitoring

Subjects with a personal or family (family is defined as a first degree relative) history of MTC or multiple endocrine neoplasia syndrome type 2 (MEN 2) or with a screening calcitonin ≥50 ng/L at visit 1 must be excluded from the trial.

In case a subject has a calcitonin value ≥ 10 ng/L, the algorithm outlined in Figure 11-2 and described below should be followed. The algorithm applies for all calcitonin values in the trial.

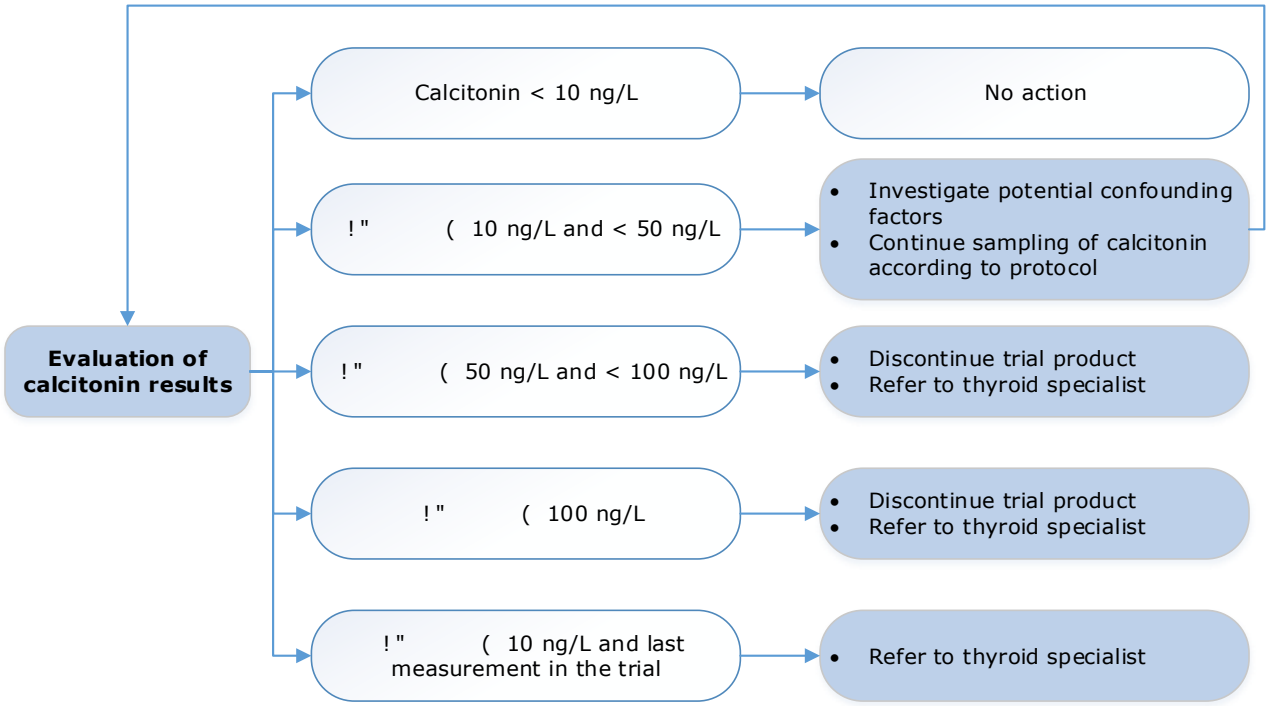


Figure 11-2 Flowchart of calcitonin monitoring

Calcitonin ≥ 100 ng/L

Action: The subject (even if a screen failure) must immediately be referred to a paediatric endocrinologist or thyroid specialist for further evaluation and the trial product must be discontinued (Section 8.1.1). The subject should remain in the trial; however, all medications suspected to relate to this condition must be discontinued until diagnosis has been established.

Background: These values were found in 9 (0.15%) of a population of 5817 patients with thyroid nodular disease[70]. All of these patients were diagnosed with MTC, resulting in a positive predictive value of 100%.

Diagnostic evaluation should include:

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

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

Calcitonin ≥ 50 and < 100 ng/L

Action: The subject (even if a screen failure) should be referred to a paediatric endocrinologist or thyroid specialist for further evaluation. The subject should remain in the trial but must discontinue from trial product.

Background: These values were found in 8 (0.14%) of the population of 5817 patients with thyroid nodular disease[70]. Two of these subjects were diagnosed with MTC and two were diagnosed with C cell hyperplasia, resulting in a positive predictive value of a C-cell anomaly of 50%.

Diagnostic evaluation should include:

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

Calcitonin ≥ 10 and < 50 ng/L

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

If the subject is a screen failure, or if the value is from the last sample taken in the trial, the subject should be referred to a paediatric endocrinologist or thyroid specialist for further evaluation.

Background: Calcitonin values from 20-50 ng/L were found in up to 1% of subjects of the population of 5817 patients with thyroid nodular disease[70]. The predictive value of a C-cell anomaly for this calcitonin level was 8.3%. However, the likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.

For calcitonin values between 10-20 ng/L, Costante et al.[70] identified 216 (3.7%) patients. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin value of 33 ng/L, and had C-cell hyperplasia at surgery. Two other studies used a cut-off of calcitonin > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT > 10 and < 20 ng/L to allow conclusions[71, 72].

Appendix 11 Country-specific requirements

For Austria:

Section 2 and Appendix 5 Pregnancy testing

A monthly pregnancy test is mandatory for female subjects of childbearing potential. , i.e. at P19, P21, P23, P25, P27 and P29 the subject must perform a pregnancy urine test at home and results must be recorded in the medical record.

Appendix 3 section 14 Indemnity statement

Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBl. I Nr. 40/2017.

For Belgium:

Appendix 3 section 14 Indemnity statement

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.

For Ireland:

Section 6.1 inclusion criterion no. 5

In line with the SPC in Ireland, metformin is contraindicated in patients with severe renal failure (creatinine clearance below 30 ml/min) and therefore creatinine clearance needs to be established (glomerular filtration rate below 30 ml/min, calculated by the Cockroft & Gault formula).

For Mexico:

Section 8.2 Withdrawal from the trial

Should the subject, his/her family members, parents or legal representative decide to withdraw the consent for participation in the trial, the subject will be entitled to receive appropriate, free of charge medical care and/or trial drug during the follow up period of the protocol when it will be established with certainty that no untoward medical consequences of the subject´s participation in the research occurred.

Appendix 3 section 1 Regulatory and ethical considerations

In the case of Mexico, the following responsibilities for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility:

a) Investigation follow-up
b) Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the Subject;
c) Timely compliance of the terms in which the authorization of a research for health in human beings had been issued;

d) To present in a timely manner the information required by the Health Authority.

Appendix 3 section 14 Indemnity statement

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

b) If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the study medication and/or a study procedure that otherwise would not have been part of his/her regular medical care, the subject will receive from the institution or medical care establishment and free of charge, the appropriate medical treatment as required. In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by the trial sponsor in accordance with the terms provided by all applicable regulations; even if the subject discontinues his/her participation in the study by his own will or by a decision from the investigator.

c) By signing the informed consent, the subject will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the trial; any additional expense resulting from the subject's participation in the trial will be covered by the trial sponsor.

For Russia:

Appendix 3 section 1 Regulatory and ethical considerations

The trial should be conducted in compliance with the protocol and Ministry of Healthcare of Russian Federation' order #200н from April, 01, 2016 "Approval of rules of good clinical practice".

For UK:

Contraceptive measures considered adequate include highly effective contraceptive methods as listed in Table 11-4 'Highly effective contraceptive methods' in Appendix 5. This means that the use of double barrier methods is not applicable for UK.

Appendix 3 section 5 Data protection

In the UK the IRB/IEC do not have access to the patients' medical records.

12 References

1. 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. 2001.
2. Smith KB, Smith MS. Obesity Statistics. Prim Care. 2016;43(1):121-35, ix.
3. Kolsgaard ML, Joner G, Brunborg C, Anderssen SA, Tonstad S, Andersen LF. Reduction in BMI z-score and improvement in cardiometabolic risk factors in obese children and adolescents. The Oslo Adiposity Intervention Study - a hospital/public health nurse combined treatment. BMC Pediatr. 2011;11:47.
4. Ford AL, Hunt LP, Cooper A, Shield JP. What reduction in BMI SDS is required in obese adolescents to improve body composition and cardiometabolic health? Arch Dis Child. 2010;95(4):256-61.
5. Reinehr T, Kleber M, Toschke AM. Lifestyle intervention in obese children is associated with a decrease of the metabolic syndrome prevalence. Atherosclerosis. 2009;207(1):174-80.
6. Whitlock EP, O'Connor EA, Williams SB, Beil TL, Lutz KW. Effectiveness of Weight Management Interventions in Children: A Targeted Systematic Review for the USPSTF. Pediatrics. 2010;125(2):E396-E418.
7. Chao AM, Wadden TA, Berkowitz RI. The safety of pharmacologic treatment for pediatric obesity. Expert Opin Drug Saf. 2018;17(4):379-85.
8. The American Society for Metabolic and Bariatric Surgery, The Obesity Society, The American Society of Bariatric Physicians and the American Association of Clinical Endocrinologists. Obesity is a Disease: Leading Obesity Groups Agree (Joint Press Release). 19 June 2013.
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. Ferguson C, David S, Divine L, Kahan S, Gallagher C, Gooding M, et al. Obesity Drug Outcome Measures. A Consensus Report of Considerations Regarding Pharmacologic Intervention. Avaliable from: https://publichealth.gwu.edu/pdf/obesitydrugmeasures.pdf. 2012.
14. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, et al. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med. 2011;365(17):1597-604.

15. Schwartz A, Doucet E. Relative changes in resting energy expenditure during weight loss: a systematic review. Obes Rev. 2010;11(7):531-47.
16. Pasman WJ, Saris WH, Westerterp-Plantenga MS. Predictors of weight maintenance. Obes Res. 1999;7(1):43-50.
17. Dombrowski SU, Knittle K, Avenell A, Araujo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. BMJ. 2014;348:g2646.
18. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: Summary report. Pediatrics. 2007;120:S164-S92.
19. Kumar S, Kelly AS. Review of Childhood Obesity: From Epidemiology, Etiology, and Comorbidities to Clinical Assessment and Treatment. Mayo Clin Proc. 2017;92(2):251-65.
20. Durkin N, Desai AP. What Is the Evidence for Paediatric/Adolescent Bariatric Surgery? Curr Obes Rep. 2017;6(3):278-85.
21. Brethauer SA, Chand B, Schauer PR. Risks and benefits of bariatric surgery: current evidence. Cleve Clin J Med. 2006;73(11):993-1007.
22. Schauer PR, Ikramuddin S, Gourash W, Ramanathan R, Luketich J. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Ann Surg. 2000;232(4):515-29.
23. Miller JL, Silverstein JH. Management approaches for pediatric obesity. Nat Clin Pract Endocrinol Metab. 2007;3(12):810-8.
24. Viner RM, Hsia Y, Tomsic T, Wong IC. Efficacy and safety of anti-obesity drugs in children and adolescents: systematic review and meta-analysis. Obes Rev. 2010;11(8):593-602.
25. 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.
26. Kelly AS, Fox CK, Rudser KD, Gross AC, Ryder JR. Pediatric obesity pharmacotherapy: current state of the field, review of the literature and clinical trial considerations. Int J Obes (Lond). 2016;40(7):1043-50.
27. Sorli C, Harashima SI, Tsoukas GM, Unger J, Karsbøl JD, Hansen T, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol. 2017;5(4):251-60.
28. Gutzwiller JP, Drewe J, Goke B, Schmidt H, Rohrer B, Lareida J, et al. Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. Am J Physiol. 1999;276(5 Pt 2):R1541-4.
29. Aroda VR, Bain SC, Cariou B, Piletič M, Rose L, Axelsen M, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol. 2017;5(5):355-66.
30. Ahrén B, Masmiquel L, Kumar H, Sargin M, Karsbøl JD, Jacobsen SH, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol. 2017;5(5):341-54.

31. Ahmann A, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, et al. Efficacy and safety of once-weekly semaglutide vs exenatide ER after 56 Weeks in subjects with type 2 diabetes (SUSTAIN 3). European Association for the Study of Diabetes, 52nd meeting 2016, Oral Presentation #1472016.
32. Rodbard H, Lingvay I, Reed J, de la Rosa R, Rose L, Sugimoto D, et al. Efficacy and safety of semaglutide once-weekly vs placebo as add-on to basal insulin alone or in combination with metformin in subjects with type 2 diabetes (SUSTAIN 5) [abstract]. Diabetologia. 2016;59(Suppl 1):364-5.
33. Blundell J, Finlayson G, Axelsen M, Flint A, Gibbons C, Kvist T, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab. 2017;19(9):1242-51.
34. Lu TT, Secher A JJ, Alanentalo T, Juel Paulsen S, Hecksher-Sørensen J, Larsen JN, Baquero A, Knudsen LB. Semaglutide interacts with hypothalamic neurons and lowers body weight in mice. Poster discussion 1072-P. American Diabetes Association, 77th Scientific Sessions, San Diego, CA, USA.9–13 June 2017.
35. O'Neil PM, Birkenfeld AL, McGowan B, Mosenzon O, Pedersen SD, Wharton S, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. Lancet. 2018;392(10148):637-49.
36. Novo Nordisk A/S. Investigator's Brochure, Semaglutide subcutaneous administration, Project NN9536 (edition 6). 03 Dec 2020.
37. Twig G, Yaniv G, Levine H, Leiba A, Goldberger N, Derazne E, et al. Body-Mass Index in 2.3 Million Adolescents and Cardiovascular Death in Adulthood. N Engl J Med. 2016;374(25):2430-40.
38. European Medicines Agency. EMA/CHMP/311805/2014; Guideline on clinical evaluation of medicinal products used in weight management. 01 Jan 2017.
39. Food and Drug Administration. FDA Guidance for Industry: Developing products for weight management. 2007.
40. Novo Nordisk A/S. Investigator's Brochure, Semaglutide subcutaneous administration, Project NN9536 and NN9931, (edition 3).
41. World Health Organisation. Growth reference 5-19 years, BMI-for-age. 2011.
42. Carlsson Petri KC, Ingwersen SH, Flint A, Zacho J, Overgaard RV. Semaglutide s.c. Once-Weekly in Type 2 Diabetes: A Population Pharmacokinetic Analysis. Diabetes Ther. 2018;9(4):1533-47.
43. World Health Organization, Global Strategy on Diet, Physical Activity and Health 2015.
44. 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.
45. The European Commission. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population - Recommendations of the adhoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. 2008.
46. American Diabetes Association. Standards of medical care in diabetes - 2017. Diabetes Care. 2017;40(Suppl 1):S1-135.

47. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007;85(9):660-7.
48. Organization WH. Growth reference data for 5-19 years 2016 [cited 2016 03 June].
49. Kolotkin RL, Zeller M, Modi AC, Samsa GP, Quinlan NP, Yanovski JA, et al. Assessing weight-related quality of life in adolescents. Obesity (Silver Spring). 2006;14(3):448-57.
50. 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.
51. 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.
52. Tanner JM. Normal growth and techniques of growth assessment. Clin Endocrinol Metab. 1986;15(3):411-51.
53. McEvoy BW. Missing data in clinical trials for weight management. J Biopharm Stat. 2016;26(1):30-6.
54. Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat. 2013;23(6):1352-71.
55. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.
56. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R2), Step 4 version. 09 Nov 2016.
57. 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.
58. 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.
59. U.S. Department of Health and Human Services, 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.
60. 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.
61. 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.
62. The European Parliament and the Council of the European Council. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on

medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, article 41. Official Journal of the European Communities. 27 Dec 2006.

63. Association AD. 12. Children and Adolescents:. Diabetes Care. 2018;41(Suppl 1):S126-S36.
64. International Diabetes Federation. Global IDF/ISPAD guideline for Diabetes in Childhood and Adolescence. 2011.
65. Ly TT, Maahs DM, Rewers A, Dunger D, Oduwole A, Jones TW, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes. 2014;15 Suppl 20:180-92.
66. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95.
67. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Avaliable from: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. 2009.
68. Stull DE, Leidy NK, Parasuraman B, Chassany O. Optimal recall periods for patient-reported outcomes: challenges and potential solutions. Curr Med Res Opin. 2009;25(4):929-42.
69. Basuyau JP, Mallet E, Leroy M, Brunelle P. Reference intervals for serum calcitonin in men, women, and children. Clin Chem. 2004;50(10):1828-30.
70. Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab. 2007;92(2):450-5.
71. Scheuba C, Kaserer K, Moritz A, Drosten R, Vierhapper H, Bieglmayer C, et al. Sporadic hypercalcitoninemia: clinical and therapeutic consequences. Endocr Relat Cancer. 2009;16(1):243-53.
72. Verga U, Ferrero S, Vicentini L, Brambilla T, Cirello V, Muzza M, et al. Histopathological and molecular studies in patients with goiter and hypercalcitoninemia: reactive or neoplastic C-cell hyperplasia? Endocr Relat Cancer. 2007;14(2):393-403.

16.1.01 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

If applicable, Protocol Attachment II is also located in the Trial Master File.

Content: Global key staff and Country key staff.

Protocol Amendment

no 1

to Protocol, version 1.0 dated 09 Apr 2019

Trial ID: NN9536-4451

Effect and safety of semaglutide 2.4 mg once weekly on weight management in adolescents with overweight or obesity

Trial phase: IIIa
Applicable to Ireland

Table of Contents

1 Introduction including rationale for the protocol amendment

This amendment was prepared to update protocol NN9536-4451 version 1.0 dated 09 Apr 2019 with the following change:

- To correct typographical error in appendix 11
- To update contraceptive requirements for subjects in Ireland as per request from the Irish regulatory authority, the Health Products Regulatory Authority on 30 Sep 2019

In this protocol amendment:

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

2 Changes

Appendix 11 Country Specific Requirements

For Ireland:

Section 6.1 ~~exclusion~~ *inclusion* criteria no. 5

In line with the SPC in Ireland, metformin is contraindicated in patients with severe renal failure (creatinine clearance below 30 ml/min) and therefore creatinine clearance needs to be established (glomerular filtration rate below 30 ml/min, calculated by the Cockroft & Gault formula).

Appendix 5 Contraceptive guidance and collection of pregnancy information

Contraceptive measures considered adequate include highly effective contraceptive methods as listed in Table 11-4 'Highly effective contraceptive methods' in Appendix 5. This means that the use of double barrier methods is not applicable for Ireland.

Protocol Amendment

no 1 IE

to protocol, version 2

dated 06 January 2021

Trial ID: NN9536-4451

Effect and safety of semaglutide 2.4 mg once weekly on weight management in adolescents with overweight or obesity

Trial phase: IIIa

Applicable to Ireland

Table of contents

Page

1 Introduction including rationale for the protocol amendment

This amendment was prepared to update protocol NN9536-4451 version 2.0 dated 06 January 2021 with the following change:

- To update contraceptive requirements for subjects in Ireland as per request from the Irish regulatory authority, the Health Products Regulatory Authority on 30 Sep 2019

In this protocol amendment:

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

2 Changes

Appendix 11 Country Specific Requirements

For Ireland:

Appendix 5 Contraceptive guidance and collection of pregnancy information

Contraceptive measures considered adequate include highly effective contraceptive methods as listed in Table 11-4 'Highly effective contraceptive methods' in Appendix 5. This means that the use of double barrier methods is not applicable for Ireland.