

Cover Page for Protocol

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Protocol

Protocol title: PIONEER TEENS

Efficacy and safety of oral semaglutide versus placebo both in combination with metformin and/or basal insulin in children and adolescents with type 2 diabetes

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Protocol amendment summary of changes table

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Protocol version 9.0 (21 May 2025)

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014.¹

Overall rationale for preparing protocol, version 9.0

This version of the protocol was primarily prepared to implement the suggestions received from the FDA to Section [10](#) Statistical considerations.

Section # and name	Description of change	Brief rationale
Section 10.3.1	For the primary analysis of primary estimand, the multiple imputation method using stepwise collapsing of group method to handle the missing data has been replaced with wash-out multiple imputation approach (WO-MI) method.	Based on FDA feedback
Section 10.3.1.1	For the sensitivity analyses, the method for the comparator multiple imputation analysis I is replaced with the previous imputation method for primary analysis. The comparator multiple imputation analysis II is removed as it is similar to the WO-MI method.	Based on FDA feedback
Section 10.3.2.2	Stratification factors in logistic regression model were added as suggested by the FDA.	Based on FDA's feedback
Section 4.2.3.2 and 10.3.2.2	The below additional supportive secondary endpoints were added: - Change in BMI (kg/m²) - Percent change in BMI (%) - Change in BMI percentage of the 95th percentile (% points)	Based on FDA's feedback

Section # and name	Description of change	Brief rationale
Section 10.3.2.2	Under treatment policy estimand, for the time to additional anti-diabetic medication endpoint analysis, an additional analysis after censoring the subjects who withdraw or are lost to follow-up has been added.	Based on FDA' feedback
Section 10.3.6	Subgroup analyses has been added to the primary endpoint based on race, sex, region, ethnicity and age group.	Based on FDA's feedback
Section 1 Section 4.2.3.1 Section 4.2.3.2 Section 4.2.4 Section 10.3.2.1 Section 10.3.2.2 Section 10.3.3	The unit for FPG has been changed from mmol/L to mg/dL.	Based on FDA's feedback

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Attachment I Global list of key staff and relevant departments and suppliers

Attachment II Country list of key staff and relevant departments

1 Synopsis

Rationale

PIONEER TEENS (NN9924-4437) will be conducted to confirm the efficacy and safety of oral semaglutide in the paediatric population to address the unmet need for treatment of children and adolescents 10 to <18 years of age with type 2 diabetes. Further, the trial will explore the beta-cell-function-preserving effects of oral semaglutide during treatment and after a period of 12 weeks off-trial product following the 52-week treatment period.

Objectives and endpoints

Primary objective

To confirm superiority of oral semaglutide at the maximum tolerated dose* (3 mg, 7 mg or 14 mg) versus placebo on glycaemic control in children and adolescents (age 10 to <18 years) with type 2 diabetes on a background treatment of metformin or basal insulin or both.

*maximum tolerated dose is defined as maximum dose level defined according to individual glycaemic response and tolerability as assessed by the investigator

Primary endpoint

Change from baseline (week 0) to week 26 in glycosylated haemoglobin (HbA_{1c}) (%-point and mmol/mol)

Key secondary objectives

To assess and compare the efficacy of oral semaglutide at the maximum tolerated dose (3 mg, 7 mg or 14 mg) versus placebo on a background treatment of metformin or basal insulin or both on

- parameters of body composition

To assess and compare the safety and tolerability of oral semaglutide at the maximum tolerated dose (3 mg, 7 mg or 14 mg) versus placebo on a background treatment of metformin or basal insulin or both.

Key secondary endpoints

Change from baseline to week 26 and 52 in:

- HbA_{1c} (%-point and mmol/mol) (only at week 52)
- Fasting plasma glucose (FPG) (mg/dL)
- Body weight (kg)
- Body weight (relative change in %)
- Body mass index (BMI) standard deviation score (SDS)

Estimands

For each efficacy endpoint, a primary (treatment policy) and a secondary estimand (hypothetical) are defined. The estimands are used to address the trial objectives in terms of two different aspects of the treatment effect of oral semaglutide.

Treatment policy estimand:

The treatment policy estimand evaluates the treatment effect (oral semaglutide vs placebo) including the effect of any additional anti-diabetic medication for all randomised subjects regardless of premature discontinuation of trial product.

Hypothetical estimand:

The hypothetical estimand evaluates the treatment effect (oral semaglutide vs placebo) for all randomised subjects assuming that all subjects remained on trial product and did not use rescue medication.

Overall design:

This is a randomised, double-blind, placebo-controlled, parallel-group, multi-national, and multi-centre clinical trial that includes a 52-week treatment period followed by a 12-week off-trial product follow-up period.

The subjects aged 10 to <18 years with type 2 diabetes must be on a background treatment of metformin or basal insulin or both, in addition to diet and exercise. Subjects will, after a 2-week screening period, be randomised in a 1:1 manner to receive either oral semaglutide or placebo. All subjects will follow a dose escalation regimen to an individualised maximum tolerated dose. The end-of-treatment visit will be at week 52. After the 52-week treatment period, all subjects will continue a 12-week off-trial product follow-up period with visits at week 57 and week 64 (end-of-trial visit).

Key inclusion criteria:

- Informed consent from parent(s) or legally acceptable representative (LAR) and child assent from the subject 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, aged 10 to <18 years at the day of randomisation
- HbA_{1c} 6.5%–11.0% (47–97 mmol/mol) (both inclusive)
- Diagnosed with type 2 diabetes mellitus according to the American Diabetes Association criteria² and treated with:
 - stable metformin dose* or
 - stable metformin dose* and a stable dose of basal insulin** or
 - stable dose of basal insulin**

*stable metformin dose is defined as at least 1000 mg daily or the maximum tolerated dose for 56 days or longer prior to screening.

**stable dose of basal insulin is defined as basal insulin treatment ≥ 30 days prior to screening, compared to the dose at screening, dose adjustments of $\pm 25\%$ are allowed.

Key exclusion criterion:

- Diagnosis of type 1 diabetes
- Maturity onset diabetes of the young (MODY)

- Positive insulinoma associated-protein 2 (IA-2) antibodies or anti-glutamic acid decarboxylase (anti-GAD) antibodies.

Key assessments:

Efficacy:

- HbA_{1c}
- Fasting Plasma Glucose
- Body weight

Safety:

- Adverse events

Number of subjects:

A total number of 132 subjects are planned to be randomised. 330 subjects are planned to be screened.

Treatment groups and duration:

The investigational medicinal products (trial products) will be provided by Novo Nordisk:

- Test product: Oral semaglutide 3 mg, 7 mg and 14 mg, tablets.
- Reference therapy: Placebo, tablets.

The maximum duration of the trial including the 2-week screening and the 12-week follow-up period will be up to 66 weeks (2+52+12 weeks), with an additional 2 weeks if the visit window is fully used. If prematurely discontinuing trial product, the subject should continue on background medication until the end-of-trial visit (week 64). After the end of trial, the subject should be transferred to a suitable marketed product at the discretion of the investigator.

2 Flowchart

Trial periods	Protocol section	Screening	Randomisation	Treatment															End of treatment	5-week follow-up visit	End of trial
Visit (V)/phone contact (P) ^a		V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	V19	V20
Timing of visit (weeks)		-2	0	2	4	6	8	10	12	15	18	22	26	30	34	38	42	47	52	57	64
Visit window (days)		±7		±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	+7	±7
Informed consent/informed assent and demography ^b	Appendix 3	X																			
In/exclusion criteria	6.1, 6.2	X	X																		
Randomisation	7.3		X																		
Attend visit fasting	6.3.1		X ^c						X ^c				X ^c						X ^c	X ^d	X ^c
Concomitant medication	7.7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history/concomitant illness and tobacco use	9.4.1, 6.3.2	X																			
Diagnosis of diabetes, diabetes history and diabetes complications and hypoglycaemic unawareness ^e	9.4.1	X																			
Childbearing potential and menstrual cycle (first day of last menstrual period) ^f	Appendix 5	X	X		X		X		X		X		X		X		X		X	X	X
Rescue criteria	8.1.1						X		X		X		X		X		X		X	X	X
Discontinuation criteria	8.1			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Glucose metabolism	Appendix 2		X						X				X						X	X	X
Lipids	Appendix 2		X						X				X						X		
HbA _{1c}	Appendix 2	X	X				X		X		X		X		X		X		X	X	X
C-peptide ^g	Appendix 2	X																			
Body measurements	9.1.2		X						X				X				X		X	X	X

Trial periods	Protocol section	Screening	Randomisation	Treatment															End of treatment	5-week follow-up visit	End of trial
				P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17			
Visit (V)/phone contact (P) ^a		V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	V19	V20
Timing of visit (weeks)		-2	0	2	4	6	8	10	12	15	18	22	26	30	34	38	42	47	52	57	64
Visit window (days)		±7		±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	±7	±3	+7	±7
Adverse events	9.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	Appendix 8		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaints	Appendix 6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Physical examination, ECG	9.4.4, 9.4.6	X											X						X		
Eye examination	9.4.7	X																	X		
Vital signs	9.4.5	X	X						X				X						X	X	
Pubertal status ^h	9.4.8		X										X						X		
Anti-semaglutide antibodies	9.4.10, Appendix 2		X		X		X		X				X				X		X	X	
Anti-GAD antibodies and IA-2 antibodies	6.2, Appendix 2	X																			
Biochemistry ALT, creatinine and bilirubin only	Appendix 2	X																			
Biochemistry, biomarkers, hormones and haematology	Appendix 2		X						X				X						X		
Adiponectin, total and high molecular weight (HMW)	Appendix 2		X										X						X		X
Calcitonin	Appendix 2, Appendix 11	X	X						X				X						X		

[illegible]

[illegible]

2.1 Flowchart explanatory description

Footer	Description
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	Fasting is defined as no food or liquid for at least 8 hours prior to blood sampling, however water is allowed up until 2 hours prior to the blood sampling. The trial product dose, glucose lowering agents and any medication which should be taken with or after a meal should be withheld on the day of the fasting visit until the fasting assessments have been performed. See section 6.3.1 .
d	For visit 19: Fasting is defined as having consumed only water within the last 6 hours prior to blood sampling. See section 6.3.1 .
e	Information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8 ³ . The investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" Subjects answering 'never, rarely or sometimes' are considered as having impaired awareness of hypoglycaemia.
f	Childbearing potential is only for female subjects. If a subject experience a first menstrual period during the trial, the date for start of the period must be recorded and contraceptive consideration should be taken according to Appendix 5 .
g	C-peptide at visit 1 can be non-fasting.
h	Pubertal status will be performed by Tanner staging, see section 9.4.8 . A Tanner staging assessment performed 2 weeks prior to the scheduled visit is acceptable as the respective visit assessment.
i	Only for females that have reached menarche (of childbearing potential), see Appendix 5 : - Urine-stick pregnancy test should be performed at any time during the trial if a menstrual period is missed, and/or according to local regulations/law. - If a girl becomes of childbearing potential (has first menstrual period) during the trial a urine-stick pregnancy test must be performed for that subject as soon as possible or at the latest at the next site visit.
j	Bone age is assessed by X-ray, see section 9.4.9 .
k	Fasting SMPG measurements should be performed and captured in the diary on three consecutive days prior to the site visit.
l	The swallowability questionnaire should be completed immediately after administration of trial product, see section 9.6.2 .
m	Semaglutide PK samples can be taken at any time during the visit. (Except for visit 8 and 12, where sampling should be done together with sampling for SNAC PK and lactate at the following time points: pre-dosing, 25 ($\pm$ 5) minutes post dosing and 40 ($\pm$ 5) minutes post dosing). See section 9.5.1.2 .
n	SNAC PK samples should be taken pre-dosing, 25 ($\pm$ 5) minutes post dosing and 40 ($\pm$ 5) minutes post dosing. See section 9.5.1.1 .
o	Lactate samples should be taken pre-dosing, 25 ($\pm$ 5) minutes post dosing and 40 ($\pm$ 5) minutes post-dosing. See section 9.4.11 .
p	At visit 4, 6 and 10 blood samples drawn for semaglutide PK will also be used for SNAC PK analysis. Instructions on handling and shipment of samples are found in the laboratory manual.
q	For OGTT, samples for plasma glucose, C-peptide, insulin and glucagon should be taken at timepoints -15, 0, 30 and 120 minutes. See section 9.1.3 .
r	At visit 2 training in trial product handling (including dosing instruction) is mandatory, see section 7.1 .

3 Introduction

Semaglutide is a potent, long-acting GLP-1 analogue with 94% sequence homology to human GLP-1. Treatment of patients with type 2 diabetes (T2D) with GLP-1 RAs has been shown to result in improved glycaemic control and meaningful weight loss^{4,7}. In addition, the drug class has a well described safety profile including a low risk of hypoglycaemia.

For once-daily oral administration, semaglutide has been co-formulated with an absorption enhancer (SNAC, **CC** mg) to provide the established benefits of a GLP-1 RA in a tablet formulation. Oral semaglutide (under the brand name Rybelsus[®]) is currently approved in multiple regions, including the US and EU, for the treatment of adults with T2D. Semaglutide is also approved worldwide as a once-weekly subcutaneous injection for the treatment of adults with T2D (Ozempic[®]).

3.1 Trial rationale

The PIONEER (Peptide InnOvation for Early diabEtes tReatment) phase 3a programme investigated the efficacy, safety and tolerability of oral semaglutide (3 mg, 7 mg and 14 mg) in a large and broad population of adult subjects with T2D. The PIONEER programme confirmed superiority of oral semaglutide on glycaemic control and body weight versus relevant active comparators, and the acceptable safety and tolerability profile were similar to those of other GLP-1 RAs including s.c. injectable semaglutide (Ozempic[®]). Compared with injectable therapies, orally administered drugs are considered attractive by a large group of patients with T2D and may help alleviate treatment inertia. Oral semaglutide may therefore enable more children and adolescents to achieve the benefits of a GLP-1 RA given that the benefits are confirmed in the paediatric population with T2D.

Based on the development of oral semaglutide in adults with T2D, trial NN9924-4437 (PIONEER TEENS) will be conducted to confirm the efficacy and safety of oral semaglutide in the paediatric population to address the unmet need for treatment of children and adolescents 10 to <18 years of age with T2D. Further, the trial will explore the beta-cell-preserving-effects of oral semaglutide during treatment and after a period of 12 weeks off-trial product following the 52-week treatment period.

The trial will also fulfil the regulatory requirements for paediatric trials from the U.S. Food and Drug Administration (FDA) and the Paediatric Committee (PDCO) of the European Medicines Agency (EMA).

3.2 Background

Despite the increased prevalence and the potential short-term and long-term risks associated with early onset of T2D, optimal regimens to treat children and adolescents with T2D are not established. Treatment approaches are often extrapolated from those used for adults⁸. For many years, metformin was the only globally approved non-insulin treatment for children and adolescents with T2D^{9,10}. In the TODAY study (The Treatment Options for Type 2 Diabetes in Adolescents and Youth)⁸, metformin monotherapy failed to maintain glycaemic control in 52% of the 10–17-year-old participants, indicating that combination therapy may be required within a few years after diagnosis. The study showed that β -cell function in youth-onset type 2 diabetes declined at a rate of

20–35% per year, considerably accelerated compared with adult diabetes.^{11,12} (3,4 adopt and 2013 Today)

The Restoring Insulin Secretion (RISE) Adult Medication Study and Pediatric Medication Study compared interventions to improve or preserve beta-cell function. Temporal changes in beta-cell function was distinctly different. In youth, beta-cell function deteriorated during treatment and after treatment withdrawal, with no differences between treatment groups. In adults, beta-cell function improved during treatment, but this was not sustained after treatment withdrawal. The difference in beta-cell function outcomes in response to medications in youth versus adults supports a more adverse trajectory of beta-cell deterioration in youth.^{13,14} This evidence outlines an unmet medical need for effective therapies that preserve or sustainably improve beta-cell function in young patients with T2D.

Insulins are approved for the treatment of paediatric T2D; however, insulins are associated with hypoglycaemia and weight gain and are therefore subject to considerable clinical inertia, i.e. the failure to in a timely manner initiate insulin or intensify the dose.

GLP-1 RAs have therefore been suggested as another treatment option when glycaemic control is not achieved with metformin and insulin alone¹⁵.

Recently, the GLP-1 RA liraglutide (Victoza®) was approved in the US and EU for use in patients 10 years and older with T2D¹⁶. To date, no studies in children or adolescents with T2D have evaluated whether improvements in beta-cell function (and other parameters central to the pathophysiology of diabetes) gained while on treatment with GLP-1 RAs in clinical trials persist after treatment cessation.

Information about oral semaglutide is available in the current edition of the Investigator's Brochure (IB) and any updates hereof¹⁷.

3.3 Benefit-risk assessment

3.3.1 Benefits

In clinical trials, oral semaglutide has provided superior long-term glycaemic control in adults with T2D and clinically relevant reductions in body weight as compared to commonly used marketed products and placebo. In this trial, subjects will be randomised to either continue on their current treatment of metformin or basal insulin or both (placebo treatment) or to continue on their current treatment with add on of a treatment expected to be more efficacious (oral semaglutide treatment) than the treatment they receive at the time of entry into the trial. It is expected that all subjects regardless of randomised treatment will benefit from participation in the trial through frequent contact with the site, close follow-up of their diabetes, and frequent medical examinations.

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

3.3.2 Risks

The sections below describe identified and potential risks associated with oral semaglutide treatment. For classification and further details of the risks, please refer to the current version of the IB or any updates hereof¹⁷. The identified/potential risks are based on findings in non-clinical

studies and clinical trials with semaglutide (both s.c. and oral) as well as other GLP-1 RAs. For each of these risks, mitigating actions have been implemented to minimise the risks for subjects enrolled in this trial.

Gastrointestinal adverse events

Consistent with the other GLP-1 RAs, the most frequent adverse events (AEs) with oral semaglutide are gastrointestinal AEs (nausea, vomiting, diarrhoea). In general, these reactions are mild or moderate in severity, of short duration, and dose dependent. Clinical trials have shown that a low starting dose and gradual dose escalation mitigate the risk of developing gastrointestinal symptoms.

In subjects treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating patients with impaired renal function as significant dehydration may cause a deterioration of renal function. Impaired renal function induced by treatment with GLP-1 RAs may increase the risk of metformin-associated lactic acidosis.

Subjects with gastrointestinal symptoms are recommended to drink plenty of fluids to avoid volume depletion.

Hypoglycaemia

There is a low risk of hypoglycaemic episodes when semaglutide is used as monotherapy. Subjects treated with semaglutide in combination with a sulfonylurea (not included in this trial) 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. To mitigate the risk, investigators should instruct subjects and their legally acceptable representatives (LARs) on recognition of signs and symptoms of hypoglycaemia and treatment.

Acute gallstone disease (cholelithiasis)

Patients with T2D are often overweight or obese and have an inherent risk of developing gallstones (cholelithiasis). Events of cholelithiasis have been associated with the use of GLP-1 RAs including semaglutide. In the clinical development programme, events of cholelithiasis were mainly mild and non-serious and did not lead to an increased risk of complication such as cholecystitis or pancreatitis.

Diabetic retinopathy complications

A 2-year clinical trial with s.c. semaglutide investigated 3,297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with s.c. semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. Systematic evaluation of diabetic retinopathy complication was only performed in the cardiovascular outcomes trial with s.c. semaglutide. In clinical trials with oral semaglutide of up to 18 months duration involving 6,352 patients with type 2 diabetes, adverse events related to diabetic retinopathy were reported in similar proportions in subjects treated with semaglutide (4.2%) and comparators (3.8%).

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Long-term glycaemic control decreases the risk of diabetic retinopathy.

As a precaution, subjects with 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 will be performed according to flowchart (see section [2](#) and [9.4.7](#))

Allergic reactions

As with all protein-based pharmaceuticals, treatment with oral semaglutide may evoke allergic reactions including serious allergic reactions such as angioedema and anaphylactic reactions. As a precaution, subjects with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this trial. In addition, subjects will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the trial product occurs.

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 RA drug class. In the completed phase 3 trials with semaglutide s.c. and oral semaglutide, both the event rate and the proportion of subjects experiencing confirmed pancreatitis were similar with semaglutide and comparator. Few events were confirmed; the events occurred throughout the trial periods and the overall rates were similar to the rates reported in background populations. As a precaution, subjects with a history or presence of pancreatitis (acute or chronic) will not be enrolled in the trial. In addition, subjects should be informed of the characteristic symptoms of acute pancreatitis and if pancreatitis is suspected, semaglutide should be discontinued. If confirmed, semaglutide should not be restarted in accordance to section [8.1](#).

Pancreatic cancer

Patients with T2D have an increased risk of certain types of cancer such as 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.

However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies. In the completed phase 3 trials, there is no indication of an increased relative risk in the semaglutide treatment groups versus comparator, including placebo. The rates of pancreatic cancer events, confirmed by the event adjudicated committee, were consistently low across trials. Subjects with presence or history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this trial.

Medullary thyroid cancer (MTC) (based on non-clinical data)

Thyroid C-cell tumors were seen in the mice and rat carcinogenicity studies, after the daily exposure to semaglutide for two years. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. No C-cell tumours were observed in monkeys after 52 weeks of exposure up to 52-fold above the clinical plasma exposure at 14 mg/day. The GLP-1 receptor is not expressed in the normal human thyroid

and therefore, clinical relevance of the findings is considered to be low. To mitigate this risk, subjects with a family or personal history of medullary thyroid carcinoma and subjects with MEN2 will be excluded from clinical trials with semaglutide. Moreover, calcitonin levels will be measured regularly.

Pregnancy and fertility

Studies in animals have shown reproductive toxicity. There are limited data from the use of oral semaglutide in pregnant women. Therefore, female subjects of childbearing potential are required to use highly effective contraceptive methods when participating in this trial, refer to [Appendix 5](#).

If a subject wish to become pregnant, or pregnancy occurs, treatment with oral semaglutide should be discontinued immediately. Exclusion and discontinuation criteria related to pregnancy have been implemented in the trial.

Aspiration in association with general anesthesia or deep sedation

There is currently insufficient evidence that GLP-1 RAs increase the risk of aspiration in association with general anesthesia or deep sedation. However, given that the GLP-1 RAs may cause a delay in gastric emptying leading to retention of gastric contents, there is a theoretical risk of aspiration in patients undergoing operative procedures under general anesthesia or deep sedation. Aspiration in association with general anesthesia or deep sedation is potentially serious as it may result in severe complications.

Patients should be informed about the risk of aspiration in association with general anesthesia or deep sedation and inform their doctor that they are taking GLP-1 RA when undergoing planned general anesthesia or deep sedation. Doctors should follow local anesthesiologic guidelines on preoperative management of patients treated with GLP-1 RAs when possible. If anesthesia-related aspiration is suspected appropriate clinical follow-up is to be initiated at the investigator's discretion.

Intestinal obstruction

There have been post marketing cases of intestinal obstruction reported with semaglutide. Intestinal obstruction is a severe form of constipation with blocked passage of food, liquid, and stool with additional symptoms such as stomachache, bloating, vomiting etc. In serious cases, intestinal obstruction can lead to bowel ischemia and perforation.

Please refer to the mitigations of gastrointestinal adverse events. Furthermore, participants should be informed of the characteristic symptoms of intestinal obstruction. If intestinal obstruction is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.

Risk related to COVID-19:

Risk related to trial treatment: Available data does not suggest an increased risk of infection or a more severe progression of infection when treated with oral semaglutide. More detailed information about the known risks for oral semaglutide may be found in the current version of the IB or any updates hereof [17](#).

Risk related to trial procedures: Subjects may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country.

The risk of COVID-19 transmission in relation to site visits is overall considered to be low, however this may vary between geographical areas. To minimize the risk as much as possible, the following measures have been taken:

- Cautious subject recruitment planning will ensure controlled subject enrolment in countries where the COVID-19 pandemic is evaluated to be sufficiently under control, and at sites where health care resources are evaluated to be adequate.
- The number of physical on-site visits has been limited to the extent possible. Phone visits have to the extent possible replaced on-site visits.
- On-site visits will be well-prepared and as short as possible. Physical contact between subjects and site staff will be limited to the extent possible, and protective measures will be implemented.

3.3.3 Benefit and risk conclusion

Data from the oral semaglutide clinical development programme in adults with T2D has not revealed any safety issues that outweigh the benefits. As the trial population will consist of children and adolescents with T2D, an external independent Data Monitoring Committee (DMC) will monitor unblinded subject safety data on an ongoing basis. Assessment of diabetes control and adherence to standard of care treatment will be provided throughout the trial. It is therefore concluded that the potential benefits from participating in the trial outweigh the risks for oral semaglutide as well as placebo treated subjects.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of semaglutide may be found in the current version of the IB or any updates hereof [17](#).

4 Objectives and endpoints

4.1 Primary, secondary and exploratory objectives

4.1.1 Primary objective

To confirm superiority of oral semaglutide at the maximum tolerated dose* (3 mg, 7 mg or 14 mg) versus placebo on glycaemic control in children and adolescents (age 10 to <18 years) with type 2 diabetes on a background treatment of metformin or basal insulin or both.

*maximum tolerated dose is defined as maximum dose level defined according to individual glycaemic response and tolerability as assessed by the investigator

4.1.2 Secondary objectives

To assess and compare the efficacy of oral semaglutide at the maximum tolerated dose (3 mg, 7 mg or 14 mg) versus placebo on a background treatment of metformin or basal insulin or both on:

- Other parameters of glycaemic control
- Parameters of body composition
- Growth parameters
- Cardio-metabolic parameters

To assess and compare the safety and tolerability of oral semaglutide at the maximum tolerated dose (3 mg, 7 mg or 14 mg) versus placebo on a background treatment of metformin or basal insulin or both.

4.1.3 Exploratory objectives

To evaluate swallowability of tablet.

To assess and compare the efficacy of oral semaglutide at the maximum tolerated dose (3 mg, 7 mg or 14 mg) versus placebo on a background treatment of metformin or basal insulin or both on:

- Glucose metabolism parameters
- Oral glucose tolerance test (OGTT) parameters
- Adiponectin
- Lipid profile

To explore the beta-cell-preserving effect of oral semaglutide treatment in children and adolescents with type 2 diabetes on parameters derived from OGTT after the 12 weeks off-trial product period.

4.1.4 Estimands

For each efficacy endpoint, a primary (treatment policy) and a secondary estimand (hypothetical) are defined. The estimands are used to address the trial objectives in terms of two different aspects of the treatment effect of oral semaglutide. The purpose of each estimand is introduced below.

The treatment policy estimand evaluates the treatment effect (oral semaglutide vs placebo) including the effect of any additional anti-diabetic medication for all randomised subjects regardless

of trial product discontinuation. For the treatment policy estimand, the occurrence of either intercurrent event is irrelevant; i.e. all randomised subjects contribute with baseline and landmark data regardless of whether treatment with trial product was initiated, whether trial product was discontinued or whether additional anti-diabetic medication was initiated (in-trial observation period).

The hypothetical estimand evaluates the treatment effect (oral semaglutide vs placebo) for all randomised subjects assuming that all subjects remained on trial product and did not use additional anti-diabetic medication (on-treatment principle). This assumes that neither intercurrent event will occur; i.e. all randomised subjects contribute with baseline data and with data collected from first dose of trial product until last dose of trial product or initiation of rescue medication (on-treatment without rescue medication observation period). The hypothetical estimand aims at estimating the achievable treatment effect without a confounding effect of rescue medication.

4.2 Primary, secondary and exploratory endpoints

4.2.1 Endpoints

For each assessment, the baseline assessment is defined as the latest available measurement obtained at either the randomisation visit (visit 2) or screening visit (visit 1). Thus, if a visit 2 assessment is missing (whether it was planned or not) then the assessment from visit 1, if available, will be used as the baseline assessment.

4.2.2 Primary endpoint

Change from baseline (week 0) to week 26 in glycosylated haemoglobin (HbA_{1c}) (%-point and mmol/mol)

4.2.3 Secondary endpoints

4.2.3.1 Confirmatory secondary endpoints

Change from baseline (week 0) to week 26 in:

- Fasting plasma glucose (FPG) (mg/dL)
- Body mass index (BMI) standard deviation score (SDS)

4.2.3.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

Change from baseline (week 0) to week 26 and to week 52 in:

- HbA_{1c} (%-point and mmol/mol) (only at week 52)
- FPG (mg/dL) (only at week 52)
- Body weight (kg)
- Body weight (relative change, %)
- Waist circumference (cm)
- BMI SDS (only at week 52)
- BMI percentile (age and gender adjusted) (%)
- BMI (kg/m²)
- BMI (Percent change, %)

- BMI percentage of the 95th percentile (% points)
- Systolic and diastolic blood pressure (mmHg)

HbA_{1c} targets:

- HbA_{1c} <7.0% (53 mmol/mol) at week 26 (yes/no), American Diabetes Association (ADA) target and International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines from 2018¹⁸
- HbA_{1c} ≤6.5% (48 mmol/mol) at week 26 (yes/no), American Association of Clinical Endocrinologists (AACE) target
- HbA_{1c} <7.0% (53 mmol/mol) at week 52 (yes/no), ADA target and ISPAD guidelines from 2018¹⁸
- HbA_{1c} ≤6.5% (48 mmol/mol) at week 52 (yes/no), AACE target

Time to event:

- Time to additional anti-diabetic medication (to support the treatment policy estimand)
- Time to rescue medication (to support the hypothetical estimand)

Supportive secondary safety endpoints

Number of treatment-emergent adverse events (TEAEs) during exposure to trial product, assessed up to approximately 57 weeks

Hypoglycaemic episodes:

- Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes from randomisation to week 26
- Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks
- Treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episode from randomisation to week 26 (yes/no)
- Treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episode during exposure to trial product, assessed up to approximately 57 weeks (yes/no)

Change from baseline (week 0) to week 26 and week 52 in:

- Biochemistry
 - amylase (U/L)
 - lipase (U/L)
- Biomarkers
 - insulin-like growth factor 1 (IGF-1) (ng/mL)
 - insulin-like growth factor binding protein 3 (IGFBP 3) (ng/mL)
- Hormones
 - calcitonin (pmol/L)
 - estradiol (for girls) (pmol/L)
 - testosterone (for boys) (nmol/L)
 - prolactin (mIU/L)
 - thyroid stimulating hormone (TSH/thyrotropin) (mIU/L)
 - follicle stimulating hormone (FSH) (mIU/mL)

- luteinizing hormone (LH) (mIU/mL)
- dehydroepiandrosterone sulfate (DHEAS) ($\mu\text{mol/L}$)

Anti-semaglutide antibodies endpoints during 57 weeks:

- Anti-semaglutide antibody status.
- Anti-semaglutide antibody titer.
- Anti-semaglutide antibodies with *in vitro* neutralising effect to semaglutide
- Anti-semaglutide antibodies cross reacting with endogenous GLP-1
- Cross reacting antibodies with *in vitro* neutralising effect to endogenous GLP-1

Other supportive safety endpoints

The following will be assessed at week 26 and week 52:

- Height velocity (cm/year)

Safety assessments

The safety assessments are change from baseline (week 0) to week 26 and week 52 in:

- Height SDS
- Bone age assessment, X-ray (only at week 52) (years)
- Pubertal assessment (Tanner staging) (stage 1-5 where 5 is full sexual maturity)
- Pulse rate (beats/minute)

Change from pre-dose to post-dose (25 and 40 min) at week 12 and week 26 in:

- Lactate (mmol/L)

Supportive secondary pharmacokinetic endpoints

Pharmacokinetic (PK) sampling of semaglutide from eight visits over the treatment period of 52 weeks with three samples performed during the dose escalation period will be included in an analysis comparing the following PK properties to historical adult data, at steady state:

- Apparent clearance (CL/F) (L/h)
- Average concentration (C_{avg}) (nmol/L)

SNAC PK samples collected in this trial will be evaluated using relevant summary statistics and compared to historical adult data:

- SNAC plasma concentrations (ng/mL)

4.2.4 Exploratory endpoints

Exploratory efficacy endpoints

Evaluated after intake of first tablet (week 0) and after 26 weeks:

- Swallowability of semaglutide tablet (questionnaire)

Change from baseline (week 0) to week 26 and week 52 in:

- Fasting lipid profile
- cholesterol, low density lipoprotein (LDL), very low density lipoprotein (VLDL), high density lipoprotein (HDL) and triglycerides (mmol/L)

Change from baseline (week 0) to week 26, week 52 and week 64 in:

- Adiponectin
- total (ng/mL)
- high molecular weight (HMW) (ng/mL)

Change from baseline (week 0) to week 26, week 52, week 57, and week 64 in:

- Glucose metabolism
- fasting insulin (pmol/L)
- fasting pro-insulin (pmol/L)
- pro-insulin to insulin ratio (%)
- fasting glucagon (pg/mL)
- fasting C-peptide (nmol/L)
- homeostasis model assessment (HOMA-B and HOMA-IR) (ratio to baseline)

Change from baseline (week 0) to week 57 and to week 64 in:

- HbA_{1c} (%-point and mmol/mol)
- FPG (mg/dL)
- Body weight (kg)
- Body weight (relative change, %)
- Waist circumference (cm)
- BMI SDS
- BMI percentile (age and gender adjusted) (%)

The following endpoints are evaluated as change from baseline (week 0) to week 52 and to week 64 in:

- OGTT-derived endpoints
- Incremental C-peptide (iAUC_{cp,0-120 min}) (nmol/L)
- Incremental insulin (iAUC_{ins,0-120 min}) (pmol/L)
- Incremental glucose (iAUC_{g,0-120 min}) (mmol/L)
- 2-hour glucose value (mmol/L)
- C-peptide index: Δ C-peptide from 0-30 minutes/ Δ glucose from 0-30 minutes [$\Delta C_{30}/\Delta G_{30}$] (nmol/mmol)
- Insulinogenic index: Δ insulin from 0-30 minutes/ Δ glucose from 0-30 minutes [$\Delta I_{30}/\Delta G_{30}$] (pmol/mmol)
- C-peptide derived oral disposition index (DIO; C-peptide index adjusted for insulin sensitivity [$\Delta C_{30}/\Delta G_{30}$] x 1/I_F) (1/nM)
- Insulin derived oral disposition index (DIO; insulinogenic index adjusted for insulin sensitivity [$\Delta I_{30}/\Delta G_{30}$] x 1/I_F) (1/nM)
- Incremental glucagon relative to glucose (iAUC_{glucagon,0-120 min}) (pg/mL)
- Early phase glucagon response relative to glucose after oral glucose ingestion (Δ glucagon from 0-30 minutes x Δ glucose from 0-30 minutes [$\Delta \text{Glucagon}_{30} \times \Delta G_{30}$]) (pg/mL x mmol)

5 Trial design

5.1 Overall design

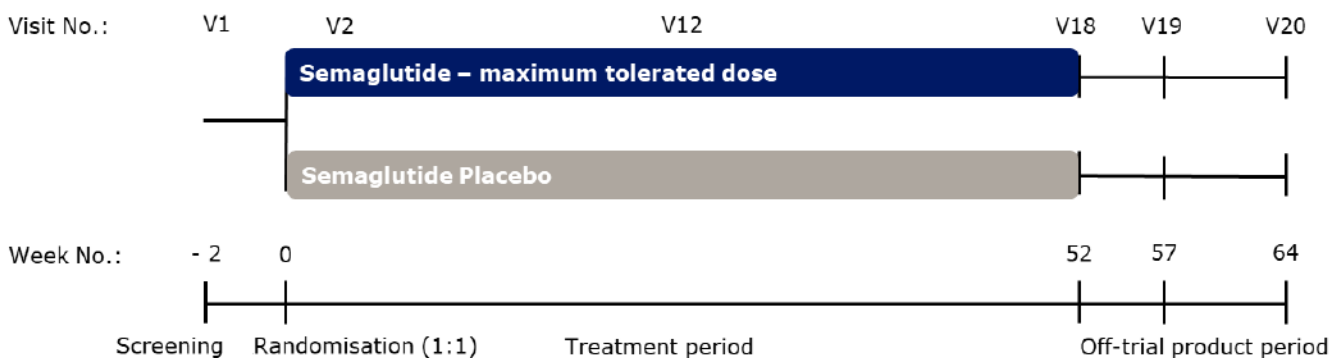
This is a randomised, double-blind, placebo-controlled, parallel-group, multi-national, and multi-centre clinical trial that includes a 52-week treatment period followed by a 12-week off-trial product follow-up period in subjects aged 10 to <18 years (at randomisation) with T2D diagnosed according to the most recent ADA criteria². Subjects will be randomised in a 1:1 manner to receive either oral semaglutide or oral semaglutide placebo (hereafter referred to as placebo) once daily in addition to background treatment with metformin or basal insulin or both, in addition to diet and exercise for 52 weeks. Randomisation will be stratified by sex (male or female) and by age (<14 years of age or ≥14 years of age). The stratification is done to ensure an even distribution of males vs. females and age groups across treatment groups.

The trial consists of a 2-week screening period during which time all screening parameters must be assessed. If eligible according to the inclusion and exclusion criteria, subjects are to be randomised to either oral semaglutide or placebo treatment for 52 weeks. All subjects will be dose-escalated to an individual maximum tolerated dose. For the duration of the trial, subjects should be on stable background treatment with either metformin, basal insulin or a combination of both, all in addition to diet and exercise. After the 52-week treatment period, all subjects will continue in a 12-week follow-up period with visits at week 57 and week 64 (end-of-trial visit). The maximum duration of the trial including the 2-week screening and the 12-week follow-up period will be up to 66 weeks (2+52+12 weeks), with an additional 2 weeks if the visit window is fully used.

No interim analyses will be performed during the trial.

The trial design is illustrated in [Figure 5-1](#). Refer to section [7.1](#) for dosing instruction of trial product.

Figure 5-1 Trial design



The follow-up period is 12 weeks plus a 7-day visit window.

5.2 Subject and trial completion

Approximately 330 subjects will be screened to achieve 132 subjects randomly assigned to trial product. A screen failure rate of 60% is expected.

Discontinuation of trial products, withdrawal or initiation of rescue treatment at week 26 is expected to occur at a rate of 35% based on experience from a paediatric trial with liraglutide in T2D.

To fulfil regulatory requirements, each sex must be represented by at least 30% and at least 30% of the randomised subjects must be 10 to <14 years old at time of randomisation. At least 30% of patients must be included from EU countries or countries with lifestyle and diabetes care similar to those of EU member states.

Trial period completion for a subject:

Trial period completion is defined as when the randomised subject has completed the final scheduled visit, visit 20 ('end-of-trial' week 64 according to the flowchart, section 2).

'Date of trial completion' is the date the subject completed the final scheduled visit (visit 20).

Treatment period completion for a subject:

Treatment period completion is defined as when the randomised subject has received the required treatment (52 weeks with oral semaglutide/placebo) and attended the 'end-of-treatment' visit (visit 18) according to the flowchart, section 2.

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 (LSLV).

5.4 Scientific rationale for trial design

5.4.1 Trial population

Children and adolescent aged 10 to <18 years are the target population for this trial since the mean age for diagnosis of T2D in children and adolescents is 13.5 years^{15,19} and the incidence of T2D in children less than 10 years old is low²⁰. The trial population includes children and adolescents with T2D who do not achieve sufficient glycaemic control on metformin or basal insulin or both, in addition to diet and exercise. To ensure subjects are achieving acceptable metformin treatment effects, a minimum dose requirement of metformin is chosen. Insulin therapy is a key component in the treatment of children and adolescents with T2D²¹. The inclusion of subjects on basal insulin is consistent with current clinical practice. This trial will be carried out globally for best representation of the intended target population. Additionally, subjects with serious concomitant conditions which could interfere with trial schedule, procedures, or affect the interpretation of efficacy and safety results are excluded from participating in this clinical trial.

5.4.2 Trial design

A randomised, double-blind, placebo-controlled design was chosen to limit potential bias in the conduct and interpretation of the trial and results. Stratification (<14 and ≥14 years of age at randomisation and by sex) has been implemented to ensure an even distribution of age groups and sex across treatments. The full effect of oral semaglutide on HbA_{1c} is expected by 26 weeks of treatment which is why the primary endpoint is evaluated at week 26²². Subjects will stay on their randomised treatment and continue the double-blind treatment period to 52 weeks to facilitate the

collection of blinded, placebo-controlled safety data. The global standard of care for this population is metformin and/or insulin treatment, if glycaemic control cannot be achieved by metformin treatment alone²³. When entering the trial, subjects on metformin will continue treatment with metformin at a dose of ≥ 1000 mg (or maximum tolerated dose). The dose should not be changed during the trial. This metformin dose is generally approved for children and adolescents.

After the 52-week treatment period, a 12-week follow-up period is included where subjects are not exposed to trial products. Evaluation of anti-semaglutide antibody response is performed 5 weeks after the 52-week treatment period. To explore effect on beta-cell function during active treatment OGTTs are conducted at baseline and at week 52. At the end of the 12 weeks follow-up period (i.e. 64 weeks after randomisation), the OGTT will be repeated to explore the durability of the effects of the 52-week treatment period on beta-cell function. If subjects experience unacceptable hyperglycaemia, rescue criteria have been defined, see section [8.1.1](#).

5.5 Justification for dose

Oral semaglutide is a long-acting GLP-1 RA to be administered orally once daily. The dose range of oral semaglutide (3 mg, 7 mg and 14 mg) was selected based on the NN9924-**CC1** dose-finding phase 2 trial and has been evaluated in a comprehensive phase 3a programme in adult subjects including a 4-week dose-escalation regimen to mitigate gastrointestinal AEs.

Data from finalised trials have suggested a positive benefit risk profile. Thus the same oral semaglutide doses (3 mg, 7 mg and 14 mg) and the same 4-week dose-escalation regimen will be used in this trial in paediatric subjects, refer to section [7.2](#) for details.

Previous studies have demonstrated similar exposure of the same doses of oral diabetes drugs in paediatric subjects with T2D and adults matched for sex and weight²⁴. This is supported by studies with liraglutide in PK/pharmacodynamic (PD) trials in a paediatric population of 10 to <18 years with T2D (NN2211-**CC1**)²⁵, an adolescent obese population of 12 to <18 years (NN8022-**CC1**)²⁶ and an efficacy and safety study in children and adolescents (NN2211-**CC1**). Thus, oral semaglutide exposure is expected to be the same in adults and paediatric subjects.

6 Trial population

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

6.1 Inclusion criteria

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

1. Informed consent from parent(s) or legally acceptable representative (LAR) and child assent from the subject obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, aged 10 to <18 years at the day of randomisation
3. Diagnosed with type 2 diabetes mellitus according to the ADA criteria and treated with:
 - stable metformin dose* or
 - stable metformin dose* and a stable dose of basal insulin** or
 - stable dose of basal insulin**

*stable metformin dose is defined as at least 1000 mg daily or the maximum tolerated dose for 56 days or longer prior to screening.

**stable dose of basal insulin is defined as basal insulin treatment ≥ 30 days prior to screening, compared to the dose at screening, dose adjustments of $\pm 25\%$ are allowed.

4. HbA_{1c} 6.5%–11.0% (47–97 mmol/mol) (both inclusive)
5. Ability and willingness to adhere to the protocol including self-measurement of plasma glucose according to the protocol.

6.2 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as randomisation. Re-screening is allowed, however there must be at least 90 days between screenings.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using highly effective contraceptive methods, refer to [Appendix 5](#).
4. Receipt of any investigational medicinal product within 30 days before screening.
5. Any disorder, which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol.
6. Any laboratory safety parameter at screening outside the below extended laboratory ranges:
 - creatinine > upper normal limit (UNL) for age in children unless renal function is proven normal by further assessments at the discretion of the investigator
 - C-peptide <0.6 ng/mL
 - calcitonin ≥ 50 ng/L

- For subjects without Gilbert's Syndrome:
 - ALT ≥ 5 times UNL
 - For subjects with ALT ≥ 3 - <5 times UNL, aetiologies other than non-alcoholic fatty liver disease (NAFLD) must have been ruled out.
 - Bilirubin $> \text{UNL}$
- For subjects with Gilbert's Syndrome
 - ALT ≥ 3 times UNL
 - Bilirubin ≥ 1.5 times UNL
- 7. Personal or first degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.
- 8. History or presence of pancreatitis (acute or chronic).
- 9. Known history of heart disease (including history of clinically significant arrhythmias or conduction delays on ECG) within 180 days of visit 1, new clinically significant arrhythmias or conduction delays on ECG identified at visit 1.
- 10. Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8³.
- 11. Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator.
- 12. Uncontrolled hypertension, treated or untreated, >99 th percentile for age and gender in children and adolescents. If "white coat hypertension" is suspected at visit 1 a repeat blood pressure measurement either during visit 1 or at visit 2 prior to other trial related activities is allowed, with the last measurement being conclusive.
- 13. Treatment with any medication for the indication of diabetes other than stated in the inclusion criteria in a period of 90 days before screening. However, short-term treatment with bolus insulin for a metabolic decompensation/intercurrent illness for a maximum of 14 days prior to the day of visit 1 is allowed.
- 14. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy documented by an ophthalmologic examination of the retina preferably supported by a fundus photography or optical coherence tomography within the past 90 days prior to screening or in the period between screening and randomisation (visit 2). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.
- 15. Presence or history of malignant neoplasm within 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ is allowed.
- 16. Diagnosis of type 1 diabetes
- 17. Positive insulinoma associated-protein 2 (IA-2) antibodies or anti-glutamic acid decarboxylase (anti-GAD) antibodies.
- 18. Maturity onset diabetes of the young (MODY).
- 19. History of major surgical procedures involving the stomach potentially affecting absorption of trial product (e.g. subtotal and total gastrectomy, sleeve gastrectomy or gastric bypass surgery).

6.3 Lifestyle restrictions

Diet and physical activity counselling will be provided according to local practice. The investigator may provide the subject with an activity tracker to support physical activity.

6.3.1 Meals and dietary restrictions

Fasting visits

The subjects should attend six visits in the fasting state according to the flowchart, section [2](#). Fasting is defined as no food or liquid for at least 8 hours prior to blood sampling, however water is allowed up until 2 hours prior to the blood sampling. Trial product, glucose lowering agents and any medication which should be taken with or after a meal should be withheld on the day of the fasting visit until the fasting assessments have been performed.

Visit 2:

At visit 2, the subjects need to be fasting, as per above definition, for blood sampling and the OGTT. The subjects will also take the first trial product dose at site to assess the swallowability questionnaire, please refer to section [9.6.2](#) for further guidance. Subjects must be instructed to stop background medication (metformin and/or basal insulin) 24-36 hours prior to initiation of the OGTT, refer to section [9.1.3](#).

Visits 18 and 20:

At visits 18 and 20 the subjects need to be fasting, as per above definition, for blood sampling and the OGTT. Subjects must be instructed to stop background medication (metformin and/or basal insulin) 24-36 hours prior to initiation of the OGTT, refer to section [9.1.3](#).

Visit 19:

At visit 19 the subjects need to be fasting for blood sampling. Fasting for this visit is defined as having consumed only water within the last 6 hours prior to blood sampling. Glucose lowering agents and any medication which should be taken with or after a meal should be withheld on the day of visit 19 until blood samples have been obtained.

If the subject does not attend the visit in a fasting state, the subject should be asked to attend a re-scheduled visit within the visit window to have the fasting-dependent assessments performed.

The subject must be fasting for the following assessments:

- OGTT
- glucose metabolism (except C-peptide at visit 1 and HbA_{1c})
- lipids
- SNAC PK sampling
- lactate
- anti-semaglutide antibody sampling (visit 19 only)

6.3.2 Tobacco use

Smoking is defined as smoking at least one daily cigarette or equivalent daily (e.g. cigar, hookah or e-cigarette).

Smoking status should be recorded in the electronic case report form (eCRF) at visit 1 as never smoked, previous smoker (smoking stop date) or current smoker.

Smoking is not allowed for at least 8 hours before the OGTT and during the OGTT.

6.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to in/exclusion 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).

If subjects withdraw their consent prior to randomisation or do not return for randomisation, a screen failure session must be made in the IWRS. The reason for failure will in all cases be captured in the eCRF.

Re-screening

Subjects who have previously screen failed solely due to the previous exclusion criteria for ALT (≥ 2.5 times the upper limit) and/or C-peptide (< 1.5 ng/mL), can be rescreened to assess if they are eligible according to the updated exclusion criterium 6 (see section [6.2](#)).

However, there is no possibility for screened subjects to be rescreened if the subject meets the updated exclusion criteria for c-peptide, ALT, or bilirubin.

Re-screening of screen failures is allowed if the screening visits are at least 90 days apart. In case of re-screening, a new informed consent from the subject's LAR and assent from the subject must be obtained. Furthermore, the subject must be allocated a new subject number and all samples and assessments must be performed again in accordance with the screening procedures.

7 Treatments

7.1 Treatments administered

The following trial products are considered as investigational medicinal products (IMPs) and will be provided by Novo Nordisk A/S:

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

Trial product	Strength	Dosage form	Route of administration	Container/delivery device
Semaglutide 3 mg tablet (IMP, test product)	3 mg	Tablet	Oral	Dose-pack ^a
Semaglutide 7 mg tablet (IMP, test product)	7 mg			
Semaglutide 14 mg tablet (IMP, test product)	14 mg			
Placebo tablet (IMP, reference therapy)	NA			

a A dose-pack contains one blister card with 7 tablets

For details regarding the trial products, please refer to the most recent version of European Medicines Agency (EMA) summary of product characteristics.^{[27](#)}

The semaglutide tablets and the placebo tablets are identical with regards to visual appearance irrespective of dose levels. Placebo tablets include the same excipients as the oral semaglutide trial product except for the active component (semaglutide) and the absorption enhancer (SNAC).

All baseline assessments must be done prior to administration of the first dose of trial product.

Dosing instructions

Subjects will be instructed to take trial product once-daily. Absorption of oral semaglutide is substantially affected by food and fluid in the stomach, hence dosing should be in the morning in a fasting state and at least 30 minutes before the first meal or drink of the day. Oral semaglutide can be taken with up to half a glass of water (approximately 120 mL/4 fluid oz). The tablet must be swallowed whole. Other oral medication can be taken 30 minutes after oral semaglutide.

The investigator must document that training in dosing instructions has been given to subject orally at the first dispensing visit (visit 2) and training should be repeated at all dispensing visits.

Auxiliary supply

Novo Nordisk will provide subjects with a blood glucose (BG) meter including related auxiliaries. The BG meters must be handed out to the subjects at visit 2 and the subject should be instructed in how to use and handle the device. Training should be repeated at visit 4 and during the trial as needed.

7.2 Dose modification

As a safety precaution, dose-escalation in the paediatric subjects will be approached cautiously depending on pre-defined criteria for glycaemic control and the subjects' tolerability to trial product. Subjects will receive a starting dose of 3 mg for 4 weeks and then the dose will be escalated with minimum 4-week intervals to 7 mg and then to 14 mg.

The dose will only be escalated if the pre-defined criteria for glycaemic control are met: mean of three fasting self-measured plasma glucose (SMPG) measurements > 6.1 mmol/L [>110 mg/dL] taken on three consecutive days prior the visit and the individual subject's tolerability for the trial product. For subjects not reaching the dose of 14 mg of trial product as assessed by the criterion for glycaemic control within the initial 8 weeks of the trial, the dose will be assessed for escalation as per above criterion during the remaining part of trial according to the visits listed in the flowchart, section [2](#).

Doses should not be decreased during the trial unless a subject experiences severe intolerance (e.g. gastro-intestinal side-effects) or other clinically meaningful side-effects (e.g. hypoglycaemia), as judged by the investigator. Subjects, who experience severe intolerance, as judged by investigator, may have the dose lowered to the next lower dose level. Subjects on the lowest dose level who continue to have severe intolerance will be discontinued from the trial product.

The reason for lowering the dose of trial product must be documented in the subject's medical record and transferred to the eCRF.

Subjects treated with insulin and experiencing hypoglycaemia should have their insulin doses decreased before decreasing the trial product dose.

If the pre-defined criterion for glycaemic control is met and it is deemed safe by the investigator, the dose of trial products may be increased again later in the trial.

7.3 Method of treatment assignment

All subjects will be centrally randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Only eligible subjects are allowed to be randomised. Trial product will be dispensed at the trial visits as indicated in the flowchart, section [2](#).

At screening, each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial (for re-screening, see section [6.4](#)).

The subjects will be randomised to oral semaglutide or placebo both once-daily. A randomisation session will be carried out for all subjects at visit 2 in a 1:1 manner. Subjects will be stratified at randomisation by sex and according to age (<14 years and ≥ 14 years). Stratification will be controlled by the IWRS. The strata are listed in [Table 7-2](#).

Table 7-2 Strata used for randomisation

Female	<14 years
Female	≥ 14 years
Male	<14 years
Male	≥ 14 years

Age is on the day of randomisation

7.4 Blinding

The active drug and placebo drug are visually identical and will be packed to maintain the blinding.

The IWRS is used for blind-breaking instructions. The blind may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Novo Nordisk will be notified immediately after breaking the blind. The date when and reason why the blind was broken must be recorded in the source documentation.

Whenever the blind is broken, the person breaking the blind must print the "code break confirmation" notification generated by the IWRS, 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](#).

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

The special laboratories responsible for anti-semaglutide antibody analysis and PK of semaglutide and SNAC will have access to an unblinding report in the IWRS.

7.5 Preparation/Handling/Storage/Accountability

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

Trial product storage, in-use time and in-use conditions will be available in the trial materials manual (TMM) and on the trial product labels.

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 first shipment will be triggered by the first subject screened.

The investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and any discrepancies are reported and resolved before use of the trial products. All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the TMM. Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk.

Subjects must be instructed to return all used, partly used and unused trial products including empty packaging material as instructed by the investigator. The investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records). Drug accountability should be performed in IWRS. Drug accountability must be done on tablet level.

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.

Drug treatment compliance

When subjects self-administer trial product at home, 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 a dialogue with the subject, re-emphasising the importance of compliance and uncover barriers to compliance. This dialogue must be documented.

Compliance will be assessed by crosschecking the following sources and comparing these to the expected use:

- Drug accountability information; amount of trial products returned compared to what was dispensed at the last dispensing visit
- Review of diaries
- Discussing treatment compliance and dosing conditions with the subject

Compliance is defined as taking between 80%-120% of the dose as prescribed between visits. If the subject has been off treatment for more than 10 consecutive days, then Novo Nordisk should be contacted for guidance regarding continuation of trial medication.

When subjects are dosed at the site (at visit 2, visit 8 and visit 12), they will receive trial product directly from the investigator or his/her representative. The date and time of each dose administered at the site will be recorded in the source documents (see section [9.5.1.1](#) and [9.6.2](#)).

7.7 Concomitant medication

Any medication 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
- Only applicable for diabetes medication: start date of current dose and total daily dose

Details of background medication must be recorded at visit 1. Changes in concomitant medication must be recorded at each visit. If a change is due to an AE, then this must be reported according to section [9.2](#). If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

Belgium: For country-specific requirements, please refer to [Appendix 12](#).

7.7.1 Background medication

Oral semaglutide or placebo will be added to background treatment of metformin or basal insulin or a combination of both, in addition to diet and exercise.

All background medications are considered to be non-investigational products (NIMPs) and will not be supplied by Novo Nordisk. However, in the 64-week duration of the trial, the subjects' de-facto cost (actual patient cost, not covered by the Health Authorities/any insurance) of metformin and basal insulin may be reimbursed in accordance with local legislation and institutional review board (IRB)/independent ethics committee (IEC) approval.

Metformin

Metformin should be used in accordance with standard of care, for the age group 10 – 18 years, in the individual country according to the investigator.

The dose of metformin should not be changed during the trial, unless the rescue criteria are met (see section [7.7.2](#) and [8.1.1](#)) or in case of safety concern.

Basal insulin

Basal insulin should be used in accordance with standard of care, for the age group 10–18 years, in the individual country according to the investigator. No shifts in type of insulin will be allowed during the trial and for the 30 days prior to screening.

Subjects who enter the trial on basal insulin with $HbA_{1c} \leq 8\%$ should have their insulin dose decreased by 20-30% at randomisation. This is to limit the potential risk of hypoglycaemia induced by the combination of insulin and semaglutide. The exact decrease in basal insulin should be transcribed to the eCRF.

The basal insulin dose can be up-titrated to the pre-randomised dose level at the discretion of the investigator in accordance with [Table 12-5](#) in [Appendix 9](#) and based on the mean of three fasting SMPG values measured three consecutive days prior site visits. Increasing the dose of insulin back to baseline level before week 8 should preferably be avoided, unless required to control

hyperglycaemia or to prevent acute diabetic complications. Increasing the basal insulin dose to the pre-randomisation dose level is not considered rescue treatment.

The dose of basal insulin can be decreased at any time during the trial in the event of unexplained recurrent or unexplained hypoglycaemia as judged by the investigator in accordance with [Table 12-6](#) in [Appendix 9](#).

7.7.2 Rescue medication

Rescue medications and changes hereof should be prescribed as add-on to randomised treatment and be captured on the concomitant medication form in the eCRF if rescue criteria are met. Subjects on rescue medication should be kept in the trial and follow protocol procedures.

It is important to note that rescue medication should not be added until the highest tolerable dose of trial product has been reached, see pre-defined criteria for glycaemic control in section [7.2](#).

Addition of rescue medication will be at the discretion of the investigator and in accordance with section [8.1.1](#). For subjects on metformin, it is recommended to up-titrate metformin to the maximum approved dose if tolerated or to add basal insulin. For subjects already on basal insulin it is recommended to up-titrate the dose of basal insulin or add bolus insulin.

Note: If an intercurrent illness with metabolic decompensation as assessed by the investigator occurs from week 0–52, then a short-term treatment with insulin, basal or bolus, (≤ 14 days) is permitted (this is not considered rescue therapy).

Rescue medication is considered a NIMP and will not be supplied by Novo Nordisk.

Belgium: For country-specific requirements, please refer to [Appendix 12](#).

7.8 Treatment after discontinuation of trial product

Subjects who discontinue trial product should remain in the trial and continue to follow the protocol (see section [8.1](#)).

When discontinuing trial product, the subject should continue on background medication until the end-of-trial visit (week 64). If additional treatment is needed, refer to section [7.7.2](#) for rescue medication and [8.1.1](#) for rescue criteria.

7.9 Treatment after the end of the trial

After the end of trial (visit 20) the subject should be transferred to a suitable marketed product 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 attend and complete all scheduled visit procedures after discontinuation of trial product. Subjects and their LARs 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

If any criteria for discontinuation of trial product apply, the subject must discontinue from trial product but should remain in the trial. The subject must be discontinued from trial product, if the following applies:

1. Pregnancy
2. Intention of becoming pregnant
3. Receipt of any investigational medicinal product in another clinical trial
4. Safety concern at the discretion of the investigator
5. Calcitonin ≥ 50 ng/L
6. Diagnosis of acute pancreatitis*
7. Subjects treated with 3 mg of trial product who experience severe intolerance, or unexplained recurrent or unexplained severe hypoglycaemia as judged by the investigator.

*In case of suspicion of acute pancreatitis, the trial product should promptly be discontinued. No treatment discontinuation call should be made in IWRS before diagnosis of acute pancreatitis is confirmed. If acute pancreatitis is ruled out, trial product should be re-initiated. If acute pancreatitis is confirmed, criterion no 6 above applies and appropriate treatment and careful monitoring of the subject should be initiated. For diagnosis of acute pancreatitis, refer to [Appendix 4](#).

Efforts must be made to have subjects attend and complete all scheduled visit procedures after discontinuation of trial product. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after treatment discontinuation. However, as a minimum, these subjects must be asked to attend visit 12, the planned end-of-treatment visit (visit 18), the planned 5-week follow-up visit (visit 19) and the end-of-trial visit (visit 20) at site.

The primary reason for discontinuation of trial product must be specified in the end-of-treatment-form in the CRF, and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS.

8.1.1 Rescue criteria

If the confirmatory HbA_{1c} exceeds the values described below, then the subject should be offered treatment intensification (rescue medication, see section [7.7.2](#)) 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 (visit 6) and onwards.

Rescue medication must be offered from week 8 to week 26 to:

- Subjects with a HbA_{1c} value above 8.5% (69 mmol/mol), who have experienced deterioration in glycaemic control, as expressed by an increase in HbA_{1c} 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 HbA_{1c} 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*

Rescue medication must be offered from week 26 to week 64 to:

- Subjects with a HbA_{1c} value above 8.5% (69 mmol/mol) that is confirmed within 30 days by the central laboratory*

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

In addition, the subject should be offered rescue medication if:

Any of the FPG values (including fasting SMPG) exceeds the values outlined below and is supported by a confirmatory FPG at the central laboratory, by calling the subject for a re-test.

- Subjects with a FPG value above 14.4 mmol/L (260 mg/dL) from week 8 to week 14 that is confirmed by a FPG at the central laboratory*
- Subjects with a FPG value above 13.3 mmol/L (240 mg/dL) from week 14 to week 26 that is confirmed by a FPG at the central laboratory*
- Subjects with a FPG value above 11.1 mmol/L (200 mg/dL) from week 26 to week 52 that is confirmed by a FPG at the central laboratory*
- Subjects with a FPG value above 13.3 mmol/L (240 mg/dL) from week 52 to week 64 that is confirmed by a FPG at the central laboratory*

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

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.

If a subject withdraws consent, the investigator must make every effort to collect AEs from last visit to withdrawal.

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

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.

Mexico only: For country specific requirements, please see [Appendix 12](#).

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

The following sections describe the assessments and procedures, while their timing are summarised in the flowchart, section [2](#).

- Informed consent and assent must be obtained before any trial related activity, see [Appendix 3](#).
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- The investigator should inform the subjects' primary physician about the subjects' participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
- Adherence to the trial design requirements, including those specified in the flowchart, section [2](#), is essential and required for trial conduct.
- It is the responsibility of the investigator to schedule the visits including laboratory assessments and contacts as per protocol (flowchart, section [2](#)) and to ensure they take place.
- At any time during the trial site visits can be performed as home/off-site location visits and phone contacts can be converted into site visits at the discretion of the investigator. It is a prerequisite for conversion of visits that assessments can be performed in accordance with the protocol.
- 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.
- Review of completed diaries, electrocardiograms (ECG), laboratory reports etc. must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the diary 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.
- The investigator may provide the subject with a mobile phone at visit 2. The site personnel should consider sending text messages to the subjects to remind them of site visits, dosing of trial products, and other trial requirements. Novo Nordisk will ensure the availability of pre-paid phone cards or similar.

Volume of blood

Approximately 255 mL blood will be collected from each subject during the entire trial period of 66 weeks. Blood collection should be performed in accordance with the guidelines in EU Directive 2001/20/EC²⁷. 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 per visit. The total volume of blood is estimated at 90 mL/kg body weight. Please refer to [Table 9-1](#).

Based on experience from a finalised paediatric trial (NN2211-**CCI**) with a similar population as this trial, it is not expected that subjects will weigh less than 41 kg as the range observed was 41.8–201.7 kg with an average of 91.4 kg.

Table 9-1 Volume of blood

Body weight	Total amount of blood allowed per visit (1% of total blood volume)	Maximum amount of blood required per visit	Total amount of blood allowed in a 4-week period (3% of total blood volume)	Maximum amount of blood required in a 4-week period during the trial	Total amount of blood required during 66-week trial period
41 kg	36.9 mL	36.5 mL (visit 2)*	108 mL	48.5 mL	228 mL
50 kg	45 mL	45 mL (visit 2)	135 mL	57 mL	255 mL
91 kg	81.9 mL	45 mL (visit 2)	245.7mL	58 mL	255 mL

* If a subject weigh <50 kg and ≥41 kg then the following samples should not be drawn throughout the trial: HMW adiponectin and glucagon in connection with the OGTT.

If a subject weigh less than 41 kg a further prioritisation of blood samples will be made on a case-by-case basis by Sponsor.

9.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart, section [2](#).

9.1.1 Clinical efficacy laboratory assessments

All protocol-required laboratory assessments, as defined in [Appendix 2](#), must be conducted in accordance with the flowchart, section [2](#) and the laboratory manual.

9.1.2 Body measurements

The body measurements below should be performed in accordance with the flowchart, section [2](#).

Height, body weight and body mass index

Height should be measured 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. The height should be measured in centimetre or inch [cm/in], with a precision of 1/10 unit (e.g. 150.3 cm) and both measurements should be recorded in the eCRF.

Body weight should be measured without shoes and only wearing light clothing and recorded in the eCRF in kilogram or pound [kg/lb], with a precision of 1/10 unit (e.g. 45.2 kg / 137.2 lb).

BMI will be calculated in the eCRF every time the weight and height are measured. BMI SDS and height SDS will be calculated using the methods outlined in WHO 2007 reference^{[27, 28](#)}.

Waist circumference

The circumference should be measured using a non-stretchable measuring tape and preferably the same throughout the trial. The circumference should be measured to the nearest ½ cm or 0.2 inch and recorded in the eCRF.

Waist circumference is defined as the minimal abdominal circumferences located midway between the lower rib margin and the iliac crest. It should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject should be standing with arms down their side and feet together. The measuring tape should touch the skin but not compress soft tissue. The subject should be asked to breathe normally, and the measurement should be taken when the subject is breathing out gently.

9.1.3 Oral glucose tolerance test (OGTT)

OGTTs will be performed 3 times during the trial in accordance with the flowchart, section [2](#).

Subjects must be fasting for at least 8 hours before the test (for fasting requirements, see section [6.3.1](#)) and during this period, smoking is not allowed.

The last dose of metformin should be stopped 24 hours before the OGTT. The last dose of basal insulin should be stopped 24-36 hours before the OGTT, depending on whether the basal insulin is taken in the morning or in the evening. Fast-acting insulin must be stopped at least 4 hours prior to the OGTT.

The subjects should empty their bladder and then rest for at least 15 minutes before the first blood sample is drawn. During the test, the subjects must not be physically active, have intake of fluids or food or be allowed to smoke.

Samples for assessment of plasma glucose, C-peptide, insulin and glucagon should be drawn at the following time points in relation to glucose administration:

- -15 minutes (before glucose administration)
- 0 minutes (just before glucose administration)
- 30 ($\pm$ 2) minutes (post glucose administration)
- 120 ($\pm$ 2) minutes (post glucose administration)

Immediately after the blood draw at time point 0 minutes, the subject will be asked to drink a fluid containing a 75 grams glucose load (supplied by Novo Nordisk) over a maximum of 5 minutes. If the subject weighs less than 43 kg the amount of glucose and fluid will be calculated based on weight (as described in the OGTT site manual).

The time when subject starts to drink the glucose load will be recorded in the eCRF as start time for glucose administration (this is time 0). The time when the subject has finished drinking will also be recorded in the eCRF as stop time for glucose administration. The date and exact time of blood sampling must be recorded at the laboratory requisition form.

Further requirements and details will be described in the OGTT site manual. For handling of samples, please refer to 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/assent and until the end-of-trial visit (visit 20) at the time points specified in the flowchart, section [2](#).

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

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

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

Timelines for reporting of AEs are listed in [Figure 9-1](#).

9.2.1.1 Adverse events requiring additional data collection

Some AEs require additional data collection via a specific event form. This includes medication errors observed during the trial. The relevant specific events are listed in [Table 9-2](#) and the reporting timelines in [Figure 9-1](#).

Figure 9-1 Safety reporting timelines

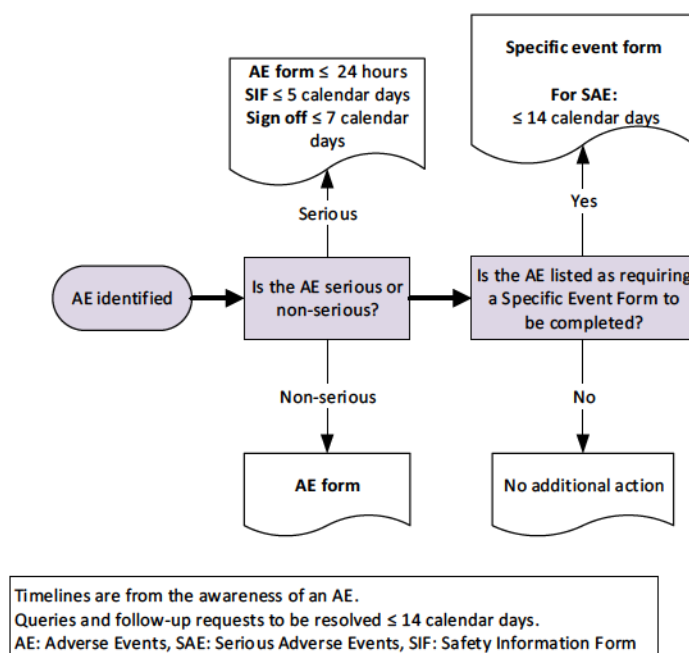


Table 9-2 AEs requiring additional data collection (via specific event form)

Event type
Acute gallstone disease
Hepatic event defined as: ALT or AST >5x UNL and total bilirubin ≤2x UNL, regardless of baseline level of ALT or AST* ALT or AST >3x UNL and total bilirubin >2x UNL, regardless of baseline level of ALT or AST** ALT or AST >2x baseline level if baseline was abnormal*** Hepatic event leading to trial product discontinuation.
Hypersensitivity reaction
Neoplasm
Pancreatitis
Renal events
Diabetic retinopathy and related complications
Medication error
Lactic acidosis
Creatinine kinase (CK) > 10x UNL

*Baseline level is considered to be the ALT/AST measurement at V2.

**Please note that in case of a hepatic event defined as ALT or AST > 3 x UNL and total bilirubin > 2 x 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.

***Abnormal is defined as values >UNL.

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

9.2.5 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to AE/SAEs description in section [9.2.1](#).

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

The following Disease-Related Events (DREs) are common in subjects with T2D and can be serious/life threatening:

- Hypoglycaemic episodes

Definitions, classification and reporting requirements are described in [Appendix 8](#).

Hypoglycaemia

Non-serious hypoglycaemia must be reported on a hypoglycaemic episode form in the eCRF.

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.

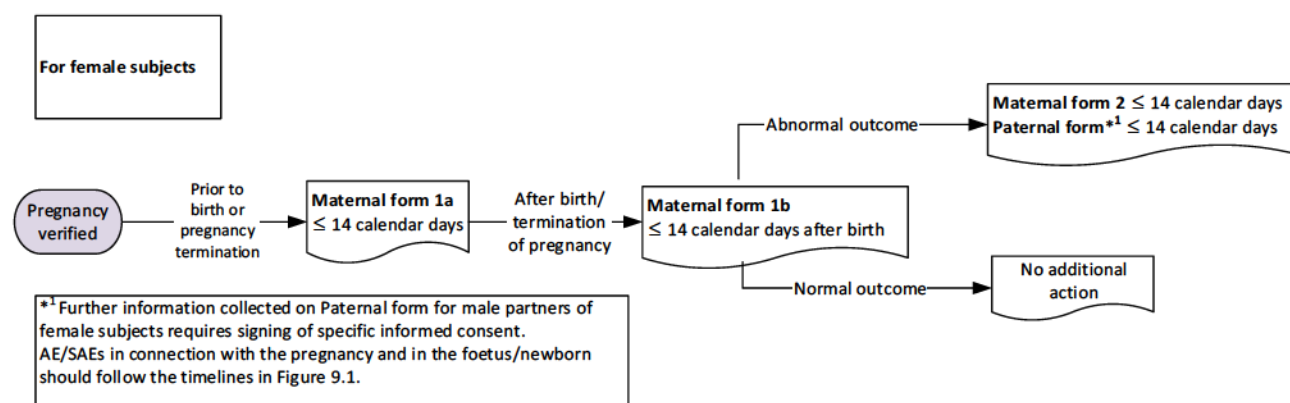
9.2.7 Pregnancies and associated adverse events

Details of pregnancies in female subjects will be collected after the first-trial-related activity after obtaining informed assent/consent and until end of trial visit.

If a pregnancy is reported in female subjects, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in [Figure 9-2 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 Safety reporting timelines for pregnancy



The investigator must report information on the subject and the pregnancy outcome until the newborn infant is one month of age in accordance with EMA and Committee for Medicinal Products for Human Use (CHMP²⁹). Information about the pregnancy and pregnancy outcome/health of the newborn infant has to be reported on paper pregnancy forms.

9.2.8 Medical device incidents (including malfunctions)

Section not applicable for this trial. Refer to technical complaints in [9.2.9](#).

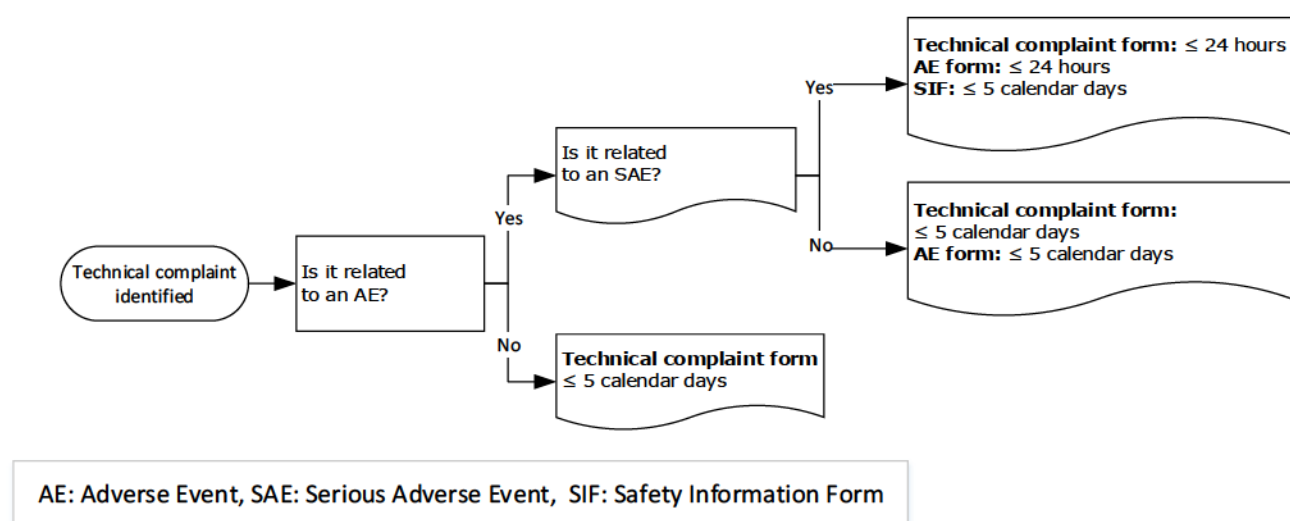
9.2.9 Technical complaints

The investigator must assess whether a technical complaint is related to an AE.

The definitions and reporting process for technical complaints can be found in [Appendix 6](#).

Timelines for reporting technical complaints are listed in [Figure 9-3](#).

Figure 9-3 Safety reporting timelines for technical complaints



9.3 Treatment of overdose

There is no specific antidote for overdose with oral semaglutide. Limited data are available with regard to overdose in subjects treated with oral semaglutide. Based on data from treatment with semaglutide s.c., the most commonly reported adverse reaction was nausea and all subjects recovered without complications. In the event of overdose, appropriate supportive treatment should be initiated according to the subjects' clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of oral semaglutide of approximately one week. Accidental overdose must be reported as a medication error. Refer to section [9.2.1](#) for further details.

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 oral semaglutide IB¹⁷.

9.4 Safety assessments

Planned time points for all safety assessments are provided in the flowchart, section [2](#).

9.4.1 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at visit 1) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

According to the updated exclusion criteria (Section [6.2](#)), for subjects with ALT ≥ 3 -<5 times the UNL, aetiologies other than NAFLD must have been ruled out as documented in medical records and a relevant concomitant illness should be reported.

Date of diagnosis of T2D should be reported separately in the Diabetes History Form in the eCRF.

Diabetes complications will be recorded at screening as part of the Concomitant illness and medical history form and consists of:

Information regarding diabetes complications including date of onset:

- Diabetic retinopathy
- Diabetic neuropathy
- Diabetic nephropathy
- Macroangiopathy (including peripheral vascular disease)

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

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

It must be possible to verify the subject's medical history in source documents such as subject's medical record. If a subject is not from the investigators own practice; the investigator must make reasonable effort to obtain a copy of subject's medical record from relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted in the subject's source data.

In case of an abnormal and clinically significant finding, the investigator must record the finding on the Concomitant illness and medical history 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 visit 1 must be reported as an AE (see Section [9.2](#)).

9.4.2 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 in section [2](#).

9.4.3 Self-measured plasma glucose

At visit 2 subjects will be provided with a BG meter including auxiliaries as well as instructions for use. The subjects will be instructed in how to use the device and the instruction will be repeated at visit 4 and at regular intervals as needed throughout the trial.

The BG meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display. The BG meter provided by Novo Nordisk should be used for the measurements required in the protocol.

Measurements of fasting SMPG (fasting for 6 hours) should be performed and captured in the diary on three consecutive days prior to the site visits (see section [2](#)).

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

Occasional review by the investigator of the BG meter values stored in the memory of the BG meter and correct reporting of these in the diary is advised in order to ensure adequacy of the data reported in the trial database.

9.4.4 Physical examinations

Physical examination should be performed according to local procedures and will include assessments of the:

- General appearance
- Head, ears, eyes, nose, throat, neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- Thyroid gland
- Lymph node palpitation
- Pubertal status by Tanner staging, see section [9.4.8](#).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.5 Vital signs

Pulse rate as well as diastolic and systolic blood pressure will be assessed.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. television, cell phones). The 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.

Blood pressure (diastolic and systolic) and pulse rate will at screening consist of three measurements with intervals of at least 1 minute. All three readings must be entered in the CRF and the average of the three readings will be calculated in the CRF. At the subsequent visits, the blood pressure and pulse should only be measured once.

If exclusion criteria number 12 is met and if “white coat hypertension” is suspected at visit 1 a repeat blood pressure measurement either during visit 1 or at visit 2 prior to other trial related activities is allowed, with the last measurement being conclusive.

9.4.6 Electrocardiograms

12-lead ECG will be obtained as outlined in the flowchart (section [2](#)) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals.

The ECG will be performed and interpreted locally by the investigator. The evaluation must be documented, signed and dated on the ECG print-out.

The ECG can be performed up to 90 days prior to and until randomisation if results are available for evaluation at visit 2. If the ECG was performed before the subject signed the informed consent and assent form, it must be documented in the medical notes that the reason for performing the examination was not related to the trial.

9.4.7 Eye examination

Subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy are not eligible for participation in this trial as this indicates retinopathy that has 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 must be available and evaluated by the investigator before randomisation to assess eligibility. The eye examination should preferably be performed by slit-lamp biomicroscopy examination and supported with a fundus photography (e.g. 2-field 60 degree or better, colour or red-free) and optical coherence tomography (OCT) as appropriate. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

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 informed assent/consent forms were signed, it must be documented that the reason for performing the examination was not related to this trial.

Eye examinations must be performed per the flowchart in section [2](#) in accordance with above guidance. The investigator must indicate the outcome of each examination. Relevant findings prior to randomisation must be recorded as concomitant illness/medical history, while findings occurring after randomisation should be reported as an AE, if applicable according to section [9.2](#).

The subject must be informed that pharmacologically pupil-dilated fundus examination may make the eyes more sensitive to light and cause blurry vision. Therefore, the subject may not be able to attend school or drive a car for up to 6 hours.

The eye examination performed as part of the visit 18 assessments can be performed in the period between visit 18 and visit 19 (including the visit windows).

9.4.8 Pubertal status (Tanner staging)

Pubertal development will be assessed by the Tanner staging in accordance with the stages I–V^{[30](#)}.

Assessment of testicular volume (by orchidometer) for boys will be included. The assessment must be conducted by personnel trained in pubertal assessments.

A Tanner staging assessment performed 2 weeks prior to the scheduled visit is acceptable as the respective visit assessment. The Tanner staging assessments is no longer required to be performed, once the subject reaches the Tanner stage V, as judged by the investigator.

Evidence of accelerated pubertal development, as judged by the investigator, at visit 2 should be recorded as concomitant illness. Acceleration of pubertal development after visit 2, as judged by the investigator, should be recorded as an AE. Pubertal status will be recorded in the eCRF.

9.4.9 Bone age assessment

An X-ray of the left hand and wrist will be performed at randomisation and at the end of treatment visit for all subjects for evaluation of bone age. A repeat bone age assessment will not be performed at subsequent visits for subjects for whom the bone age assessment at the randomisation visit 2 indicates that all the epiphyses are fused.

The X-rays will be analysed by a central reader for determination of bone age. Further requirements and details will be described in the X-ray site manual.

An X-ray for bone age assessment performed within 2 weeks prior to the relevant visits is acceptable.

9.4.10 Immunogenicity assessments (anti-semaglutide antibodies)

Blood samples will be drawn at the site for measurement of serum anti-semaglutide antibodies according to the flowchart, section [2](#).

The samples will be analysed at special laboratories, please refer to [Attachment I](#). Positive anti-semaglutide antibody samples will be further characterised for titer and cross reactivity to native GLP-1 and for in vitro neutralising effect towards semaglutide. In addition, samples which are positive for cross-reactivity against native GLP-1 will be further analysed for in vitro neutralising effect towards native GLP-1.

All samples from oral semaglutide treated subjects are analysed for anti-semaglutide antibodies. Samples from the randomisation visit (baseline, visit 2) from all subjects may be used for determination of cut point in the antibody analysis and for assay maintenance.

For storage of antibody samples after the end-of-trial, please see [Appendix 7](#).

9.4.11 Lactate sampling

Assessment of lactate levels at selected time points around peak concentrations of SNAC will be included with the intention to document that SNAC does not impair cellular respiration in children and adolescents. In the PIONEER programme in adults treated with oral semaglutide, no correlation between blood concentrations of SNAC and lactate was identified, please refer to the current version of the IB or any updates hereof^{f17}.

At visit 8 and 12 where sampling for lactate is performed, trial product must be taken at site and the subject must be fasting and not take any other oral medication until last sample has been taken (see section [6.3.1](#)).

Samples for lactate should be drawn together with SNAC PK (see section [9.5.1.1](#)) at the following time points in relation to dosing of trial product:

- pre-dose*
- 25 ($\pm$ 5) minutes post dosing
- 40 ($\pm$ 5) minutes post dosing

The date and exact time of sampling must be recorded at the laboratory requisition form.

*Trial product can be taken from the dose pack dispensed at the previous visit or at the current visit.

Correct pre-analytical handling of these samples is extremely important to ensure valid results.

The subject must be fasting for the assessment and remain fasting until the last sample has been taken, that is, at least 40 minutes after dosing. Also, the subject should have rested for at least 30 minutes in a sitting position prior to sampling and should remain resting until the last sample has been taken. During sampling, use of tourniquet should be avoided (if possible). If blood pressure measurement has been performed prior to sampling, blood should preferably be drawn from the opposite arm.

9.5 Pharmacokinetics

Samples will be used to evaluate the pharmacokinetics of oral semaglutide. Blood samples for the PK bioanalysis will be drawn at selected visits (see flowchart, section [2](#)) and must be collected, handled and shipped according to the description in the laboratory manual supplied by the central laboratory (see [Attachment I](#)). The investigator must record the exact time for sampling the blood in the laboratory requisition form.

The PK bioanalysis is outlined in the special laboratory study plan.

9.5.1.1 SNAC PK sampling

At visit 8 and 12 where sampling for SNAC PK is performed, trial product must be taken at site and the subject must be fasting and not take any other oral medication until last sample has been taken (see section [6.3.1](#)).

Samples for SNAC PK should be drawn at the following time points in relation to dosing of trial product:

- Pre-dosing
- 25 ($\pm$ 5) minutes post-dosing
- 40 ($\pm$ 5) minutes post-dosing

The date, the exact time and dose of trial product must be recorded in the medical record and entered into the eCRF. The date and exact time of sampling must be recorded at the laboratory requisition form.

9.5.1.2 Semaglutide PK sampling

Samples can be drawn at any time during the visit (except for visit 8 and visit 12, see below). For simplicity it is recommended to take the samples for semaglutide PK together with biochemistry samples.

The date and exact time of the latest trial product administration prior to semaglutide PK sampling must be recorded in the diary and entered into the eCRF. The date and time of sampling must be recorded at the laboratory requisition form.

For visit 8 and visit 12 only: Trial product must be taken at site and the subject must be fasting and not take any other oral medication until last sample has been taken (see section [6.3.1](#)).

Blood sampling should be done together with sampling for SNAC PK and lactate and drawn at the following time points in relation to dosing of trial product:

- Pre-dosing
- 25 ($\pm$ 5) minutes post-dosing
- 40 ($\pm$ 5) minutes post-dosing

The date and exact time of dosing of trial product must be recorded in the medical record and entered into the eCRF. The date and exact time of sampling must be recorded at the laboratory requisition form.

9.6 Other assessments

9.6.1 Subject diary

The subject must be provided with a diary to be completed at home for all visits and other data applicable according to the flowchart, section [2](#). Only the subjects and/or the subject's parent(s)/LAR must enter data in the diary.

The investigator should instruct the subject and subject's LAR in entering the following data in the diary:

- Date, time and dose of first trial product dose
- Date, time and dose of last dose of trial product before each visit, both site and phone visits (not applicable after visit 18)
- Date and dose of last dose of metformin before the site visit, if applicable
- Date and dose of last dose of basal insulin before the site visit, if applicable
- Measurements of fasting SMPG for three consecutive days prior to the site visit (not applicable after visit 16)
- Details on hypoglycaemic episodes, as described in [Appendix 8](#)
- AEs and concomitant medications (health issues)

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

- First day of last menstrual period before the site visit

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

It is important to explain to the subjects the necessity of accurate diary recording. The subject should bring the diary to the site at every visit during the trial.

9.6.2 Swallowability questionnaire

The questionnaire is designed to evaluate the subject's experience taking the trial product and focuses on tablet related factors which may affect the acceptability.

The questionnaire should be completed two times during the trial: after first administration of trial product (on site at visit 2) and at week 26 (on site at visit 12) according to the flowchart, section [2](#). The investigator or his/her representative and the subject should complete the questionnaire together immediately after the subject's intake of trial product. Thus, the subject needs to be fasting at the visits and take the tablet in front of the investigator or his/her representative.

At visit 2, the subject will have an OGTT performed. The 2-hour OGTT should be done prior to trial product administration.

The questionnaire takes approximately 3 minutes to complete and all the results must be transferred into the eCRF.

10 Statistical considerations

General considerations

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

Data from all sites will be analysed and reported together.

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

Results from a statistical analysis will as a minimum be presented by the estimated treatment contrasts with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference with no multiplicity adjustments.

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

The two different estimands defined in section 4 are described in more details below and they will be used for the evaluation of the efficacy endpoints.

Primary and secondary estimands

To address the trial objectives in terms of the two different aspects of the treatment effect of oral semaglutide, two estimands will be used as outlined below.

Intercurrent events

For both estimands, the following will be considered intercurrent events:

- Premature discontinuation of trial product
- Initiation of additional anti-diabetic medication

Primary estimand – ‘Treatment policy estimand’

- Treatment effect (oral semaglutide versus placebo) at week 26 including the effect of any additional anti-diabetic medication for all randomised subjects regardless of trial product discontinuation.

For the treatment policy estimand, the occurrence of either intercurrent event is irrelevant; i.e. all randomised subjects contribute with baseline and week 26 data regardless of whether treatment with trial product is initiated, whether trial product is prematurely discontinued or whether additional anti-diabetic medication is initiated (i.e. the evaluation of the treatment policy estimand is based on data collected during the in-trial observation period).

Secondary estimand – ‘Hypothetical estimand’

- Treatment effect (oral semaglutide versus placebo) at week 26 for all randomised subjects assuming, that all subjects remain on treatment with trial product and do not use rescue medication.

The hypothetical estimand reflects a scenario where neither intercurrent event occur; i.e. all randomised subjects contribute with baseline data and with data collected from first dose of trial product to last dose of trial product or initiation of rescue medication (i.e. the evaluation of the hypothetical estimand is based on data collected during the on-treatment without rescue medication observation period). The extent of and timing of intercurrent events, will be displayed graphically.

Missing data consideration

The primary efficacy results will be evaluated at week 26. This approach will result in a lower proportion of missing data, use of rescue medication and premature trial product discontinuation, compared to the expected proportion at week 52. For the primary estimand, data collected regardless of premature discontinuation of trial product or initiation of rescue medication(s) will be used to draw inference, missing data will therefore mainly be due to withdrawal from trial or lost to follow-up. When estimating the secondary estimand, the proportion of missing data is expected to be higher compared to the primary estimand, since data collected after premature discontinuation of trial product or initiation of rescue medication(s) will be set to missing as well.

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

10.1 Sample size determination

The primary endpoint is change from baseline to week 26 in HbA_{1c}. The confirmatory secondary endpoints are; change from baseline to week 26 in FPG and change from baseline to week 26 in BMI SDS.

The sample size is based on calculations for the primary endpoint alone and has been determined to demonstrate superiority of oral semaglutide versus placebo in change from baseline at week 26 in HbA_{1c}.

A hierarchical statistical testing strategy will be used starting with the primary endpoint and only after having established glycaemic efficacy by HbA_{1c} the confirmatory secondary endpoints will be tested in the below order:

- change from baseline (week 0) to week 26 in FPG
- change from baseline (week 0) to week 26 in BMI SDS

The sample size assumptions for treatment effects (TE), and the standard deviation (SD) for both the primary endpoint and the secondary endpoints are given in [Table 10-1](#). These are primarily based on oral semaglutide phase 3 results. For the primary endpoint also the adjusted treatment effect is provided.

For HbA_{1c} a treatment effect of 0.8%-point and a SD of 1.2 are chosen as assumptions for the sample size calculation in this paediatric trial. In the sample size calculation, the assumed treatment effect will be adjusted for the anticipated use of rescue medication and trial product discontinuation. Collectively, the proportion of subjects who will discontinue trial product, initiate rescue medication or have missing data at week 26 is assumed to be up to 35%. The assumed treatment effect will be adjusted according to a 75% smaller effect in those subjects.

The adjusted treatment effect is described as below:

CCI

CCI

Table 10-1 Assumptions for the sample size and power calculation

Endpoint	Treatment effect (TE)	Adjusted TE	SD	Marginal power	Conditional power
Change in HbA1c (%-point)	0.8	CCI	1.2	80%	80%
Change in FPG (mmol/L)	1.1	NA	2.5	71%	57%
Change in BMI SDS	0.1	NA	0.3	48%	27%

Based on the above assumptions and a two-sided t-test using a 0.05 significance level, a total of 132 subjects will have to be randomised in a 1:1 ratio to have at least 80% power to confirm HbA_{1c} superiority of oral semaglutide versus placebo.

Assuming a screening failure rate of 60%, 330 subjects will need to be screened.

Table 10-2 show different scenarios to evaluate the robustness of the sample size calculation and the impact of the number of randomised subjects needed for different scenarios of the treatment effect, SD, discontinuation rate and power for HbA_{1c}. The highlighted scenario is the one which has been chosen for this sample size calculation.

Table 10-2 Different scenarios to check the robustness of the sample size calculation for HbA_{1c}

Treatment effect	Adjusted treatment effect	SD	Discontinuation rate	Power	Number of subjects randomised
0.8	CCI	1.1	35%	80%	112
0.8		1.2	35%	80%	132
0.8		1.3	35%	80%	156
0.8		1.2	35%	90%	176
0.7	0.52	1.2	35%	80%	172
0.9	0.66	1.2	35%	80%	106

10.2 Definition of analysis sets

The same definitions of analysis set as used for adults in the oral semaglutide phase 3a program will be used for the paediatric trial. The following analysis sets are defined in accordance with ICH E9³¹.

- The full analysis set (FAS) comprises all randomised subjects. Subjects contribute to a treatment group based on the trial product they were randomised to receive.
- The safety analysis set (SAS) comprises all randomised subjects who received at least one dose of trial product. Subjects contribute to a treatment group based on the trial product they actually received for the majority of the on-treatment observation period.

The FAS will primarily be used in the evaluation of the effect endpoints; the SAS will be used for the evaluation of the safety endpoints, exclusively.

Observation periods

For the efficacy and safety evaluations, five different observation periods will be defined:

- The **in-trial** observation period – the time period from when a subject is randomised up to and including the 5-week follow-up visit, including any period after initiation of rescue medication or premature discontinuation of trial product. This observation period includes the 52-week treatment period and the 5-week follow-up visit (week 0 – week 57).
- The **extended in-trial** observation period – the time period from when a subject is randomised until the final scheduled visit, including any period after initiation of rescue medication or premature discontinuation of trial product. This observation period includes the 52-week treatment period and the 12-week follow-up visit (week 0 – week 64).
- The **on-treatment** observation period – the time period when a subject is on treatment with trial product, including any period after initiation of rescue medication.
- The **on-treatment without rescue medication** observation period – the time period when a subject is on treatment with trial product, excluding any period after initiation of rescue medication.
- The **12-week follow-up** observation period – the time period from when a subject has completed the 52-week treatment period until the final scheduled visit.

The **in-trial** observation period begins at the date of randomisation and ends at the first of the following time points:

- the 5-week follow-up visit (visit 19)
- the last contact for subjects who premature discontinue trial product, or who withdraw from trial, are lost to follow-up or die prior to the 5-week follow-up visit.

The **extended in-trial** observation period begins at the date of randomisation and ends at the final scheduled visit, which can be one of the below:

- the end-of-trial (visit 20)
- the last contact for subjects who premature discontinue trial product, withdraw from trial, are lost to follow-up or die

The **on-treatment** observation period begins at the date of first dose of trial product; the end date depends on the assessment being evaluated:

- For all efficacy assessments and certain safety assessments (laboratory assessments, physical examination and vital signs), a plus-3-day window (i.e. the 3-day visit window) is used and the period ends at the first of the following time points:
 - last dose of trial product plus a 3-day window
 - end of the in-trial observation period
- For the remaining safety assessments (ECGs, eye examination categories, AEs, and hypoglycaemic episodes), a plus-38-day window (i.e. the 5-week follow-up period plus the 3-day visit window) is used and the period ends at the first of the following time points:
 - 5-week follow-up visit (visit 19)

- last dose of trial product plus 38 days
- end of the in-trial observation period.

The **on-treatment without rescue medication** observation period begins at the date of the first dose of trial product and ends at the first of the following time points:

- end of the on-treatment observation period
- initiation of rescue medication (if any)

The **12-week follow-up** observation period begins at the date of the end-of-treatment visit (visit 18) and ends at the last scheduled visit, which can be one of the below:

- the end-of-trial visit (visit 20)
- the last contact for subjects who withdraw from trial, are lost to follow-up or die

For the efficacy endpoints, the treatment policy estimand will be evaluated based on data from the in-trial observation period and the hypothetical estimand will be evaluated based on data from the on-treatment without rescue medication observation period. The safety evaluation will primarily be based on the on-treatment observation period, except for deaths and AE types with potentially long latency between onset and diagnosis, for which the in-trial observation period will be used. The observation period determines what data subjects contributes with to a specific analysis. Baseline values are by definition included in all observation periods; other data points collected outside the observation period used for an analysis will be considered missing.

10.3 Statistical analyses

10.3.1 Primary endpoint

The primary endpoint is change from baseline to week 26 in HbA_{1c} (%-point and mmol/mol).

Primary analysis for the primary estimand

The primary estimand will be estimated based on the FAS using week 26 measurements from the in-trial observation period. The primary statistical analysis will be a pattern mixture model using multiple imputations to impute missing week 26 data, assuming that such data were missing at random (MAR).

Wash-out multiple imputation approach (WO-MI): Missing values of HbA_{1c} at week 26 will be imputed using the Imputation, Analysis, Pooling framework.

Imputation: Defines an imputation step procedure utilising different imputation models depending on randomised treatment group and end of treatment status as described in the following steps:

1. For on-treatment participants in the treatment group, missing HbA_{1c} values for week 26 will be imputed based on observed data from the on-treatment participants. An analysis of covariance (ANCOVA) model with baseline HbA_{1c} will be used to impute 1000 values for each participant with missing data. This will result in 1000 complete data sets for on-treatment participants in the treatment groups.
2. For the participants in placebo, missing HbA_{1c} values for week 26 will be imputed based on all observed data at all time points in the placebo group and using a Mixed

Model for Repeated Measurements (MMRM) with study arm as factor and baseline HbA_{1c} as a covariate – both nested within visit. An unstructured covariance matrix for measurements within the same participant will be employed. If necessary for convergence, a toeplitz or compound symmetry structure will be assumed instead of the unstructured covariance matrix. Each missing value of HbA_{1c} at week 26 is imputed 1000 times by random sampling from normal distribution with the MMRM-predicted value at week 26 as mean and variance as a sum of prediction variance and residual variance.

3. For off-drug participants in the treatment group, missing HbA_{1c} values for week 26 will be imputed from the placebo group assuming that all drug effect will be washed out and gone before the landmark visit. The imputation procedure will be similar to jump to reference multiple imputation. An imputation model will be fitted to each of 1000 complete data sets resulting from MMRM imputation for the placebo in the previous step. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation model from each of 1000 fits will then be used to impute missing week 26 HbA_{1c} values once, ultimately resulting in 1000 complete data sets for off-drug participants in the treatment group.

Analysis model: For each of the 1000 (now complete) imputed datasets the change in HbA_{1c} from baseline to week 26 will be analysed using an ANCOVA with treatment, sex, age group and the interaction between sex and age group as categorical fixed effects and baseline HbA_{1c} as covariate.

Pooling: The results obtained from analysing the datasets will be combined using Rubin's rule to draw inference. Superiority in change in HbA_{1c} will be claimed if the upper limit of the 2-sided 95% confidence interval for the estimated treatment difference at week 26 obtained from the primary analysis is below 0%.

Primary analysis for the secondary estimand

The secondary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 26 from the on-treatment without rescue observation period. The primary analysis for the secondary estimand is based on a MMRM that accounts for the uncertainty pertaining to missing data. The MMRM approach assumes that data are MAR.

As dependent variables, the MMRM model will include all post baseline values collected at scheduled visits up to and including week 26. The independent effects will be trial product, sex, age group and the interaction between sex and age group as categorical fixed effects and the baseline value as a covariate, all nested within visit. An unstructured covariance matrix is employed for HbA_{1c} values of each subject, assuming that measurements from different subjects are independent. A restricted maximum likelihood will be used.

10.3.1.1 Sensitivity analyses

To investigate the sensitivity of the primary analysis results, sensitivity analyses will be performed for both estimands. In line with draft ICH E9 (R1) these analyses will primarily evaluate the sensitivity of the results due to the impact of missing data.

The estimation of the primary estimand will be repeated based on FAS using the in-trial observation period using the following sensitivity analyses:

- **Comparator multiple imputation analysis I:** Missing week 26 data will be imputed for 4 groups of subjects depending on the treatment arm and whether subjects at week 26 (i) have discontinued trial product or initiated rescue medication or (ii) are still on trial product and have not initiated rescue medication. For this imputation approach, it is assumed that the distribution of missing data for subjects in a specific treatment arm resembled the distribution of available data for other subjects in the same treatment arm with similar trial product and rescue medication statuses at week 26.

Missing values for each group will be imputed as follows: An ANCOVA with baseline HbA_{1c} measurement as a covariate will be fitted to observed values of the change from baseline in HbA_{1c} at week 26.

The estimated parameters for location and dispersion will be used to impute 1000 values for each subject with missing week 26 data based on baseline HbA_{1c}. Thus, 1000 complete data sets will be generated including observed and imputed values.

If data is too sparse to fit the described imputation model the groups will be collapsed in below order until the imputation model can be fitted:

- Subjects who have discontinued trial product or initiated rescue medication will be collapsed regardless of randomised treatment.

Subjects who have discontinued trial product or initiated rescue medication regardless of randomised treatment and subjects who are still on trial product, who have not initiated rescue medication and who are randomised to placebo will be collapsed.

- **Two-way tipping-point multiple imputation analysis:** Missing data will be imputed as for the primary analysis. Then, for each confirmed hypothesis, penalties which are required to turn the result of the primary analysis from statistically significant to non-significant will be added to the imputed week 26 values for both the oral semaglutide arm and for the placebo arm simultaneously.

The estimation of the secondary estimand will be repeated based on FAS using the on-treatment without rescue medication observation period and a two-way tipping-point analysis.

10.3.2 Secondary endpoints

10.3.2.1 Confirmatory secondary endpoints

- Change from baseline (week 0) to week 26 in FPG (mg/dL)

The change from baseline to week 26 in FPG will be analysed using same model approaches as for change from baseline to week 26 in HbA_{1c} with baseline FPG included in the model instead of baseline HbA_{1c}.

- Change from baseline (week 0) to week 26 in BMI SDS

The change from baseline to week 26 will be analysed using same model approaches as for change from baseline to week 26 in HbA_{1c} with baseline BMI SDS included in the model instead of baseline HbA_{1c}.

Hierarchical testing

The confirmatory secondary endpoints will be analysed in a hierarchical manner in the following order:

- Change from baseline (week 0) to week 26 in HbA_{1c} (primary efficacy endpoint)
- Change from baseline (week 0) to week 26 in FPG
- Change from baseline (week 0) to week 26 in BMI SDS

In order to confirm superiority for an endpoint in the hierarchical list above, the test for that endpoint and the tests for the endpoints higher up in the hierarchy must all be concluded significant with a difference favouring oral semaglutide.

10.3.2.2 Supportive secondary endpoints

Continuous efficacy endpoints

The continuous efficacy endpoints are change from baseline (week 0) to week 52 in:

- HbA_{1c} (%-point and mmol/mol)
- FPG (mg/dL)
- BMI SDS

and change from baseline (week 0) to week 26 and to week 52 in:

- Body weight (kg)
- Body weight (relative change, %)
- Waist circumference (cm)
- BMI percentile (age and gender adjusted) (%)
- BMI (kg/m²)
- BMI (Percent change, %)
- BMI percentage of the 95th percentile (% points)
- Systolic and diastolic blood pressure (mmHg)

The above continuous endpoints will be analysed separately using similar model approaches as for change from baseline to week 26 in HbA_{1c} with the associated baseline response as a covariate. The BMI SDS will be calculated using the LMS method³² using the WHO 2007^{28,33}.

For evaluation of the primary estimand the analysis will be performed separately for week 26 and 52. For evaluation of the secondary estimand the MMRM will include all scheduled post-baseline measurement up to and including week 52. From this model the estimated treatment differences (ratios) will be presented at week 26 and week 52 with 95% confidence intervals and two-sided p values for test of no difference. For endpoints where the first planned visit falls later than 8 weeks after randomisation, the baseline will not be carried forward.

Binary efficacy endpoints

The binary HbA_{1c} endpoints are:

- HbA_{1c} <7.0% (53 mmol/mol) at week 26 (yes/no), ADA target and ISPAD guidelines from 2018¹⁸
- HbA_{1c} ≤6.5% (48 mmol/mol) at week 26 (yes/no), AACE target
- HbA_{1c} <7.0% (53 mmol/mol) at week 52 (yes/no), ADA target and ISPAD guidelines from 2018¹⁸
- HbA_{1c} ≤6.5% (48 mmol/mol) at week 52 (yes/no), AACE target

Handling of missing data for binary endpoints

HbA_{1c}

Missing data for the above four binary endpoints will be accounted for using multiple imputation techniques. For the primary estimand the binary endpoints will be calculated as dichotomisations of the 1000 multiple imputations underlying the primary MI analysis. For the secondary estimand the model will be implemented using a sequential imputation approach assuming MAR. The imputation will be done as described below:

Intermittent missing values in the on-treatment without rescue observation period will be imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each treatment group separately and 1000 copies of the data set will be generated.

A sequential regression approach for imputing monotone missing values at planned visits will be implemented starting with the first visit after baseline and sequentially continuing to the planned end of treatment visit. For each treatment group an analysis of covariance model will be used to impute missing values at each planned visit. The model will include the baseline and post-baseline values prior to the visit in question as covariates.

The binary endpoints will be derived as dichotomisations of the 1000 multiple imputations from the sequential imputation.

For both estimands, each of the 1000 complete data sets will be analysed using a logistic regression model with treatment, sex, age group as categorical fixed effects and baseline HbA_{1c} as covariate. The results from this model will be used to predict the probability of achieving the efficacy endpoint for all participants had they (counterfactually) been assigned to each specific treatment. Average treatment difference in probability will be estimated by subtracting the average predicted probabilities and the corresponding standard errors will be calculated using the delta-method.

The results obtained from analysing the individual datasets will be combined using Rubin's rule to draw inference.

In addition to these endpoints the following will be explored:

- HbA_{1c} <7.0% (53 mmol/mol) without severe or BG confirmed symptomatic hypoglycaemia episodes at week 26 (yes/no)
- HbA_{1c} <7.0% (53 mmol/mol) without severe or BG confirmed symptomatic hypoglycaemia episodes at week 52 (yes/no)

Time to event:

- Time to additional anti-diabetic medication (to support the treatment policy estimand)
- Time to rescue medication (to support the hypothetical estimand)

Definition of additional anti-diabetic medication: New anti-diabetic medication and/or intensification of anti-diabetic medication initiated at or after randomisation and before (planned) end-of-treatment.

Definition of rescue medication: New anti-diabetic medication and/or intensification of anti-diabetic medication initiated at or after randomisation and before last date on trial product. This is a subset of the additional anti-diabetic medication.

The following rules will be applied based on the concomitant medication data reported by the investigator, to determine whether or not the recorded anti-diabetic medication is: 1) New anti-diabetic medication or 2) Intensification of anti-diabetic medication.

- **New anti-diabetic medication:** Anti-diabetic medication (4th-level ATC code) that is initiated at or after randomisation and is new compared to the anti-diabetic background medication used at randomisation (see above) and with a dosing duration of more than 21 days
- **Intensification of anti-diabetic medication:** A more than 20% increase in the dose of anti-diabetic medication at or after randomisation as compared to the anti-diabetic medication dose at randomisation (5th-level ATC code not changed) and with a dosing duration of more than 21 days.

More than 21 days is chosen as a minimum duration for the medication to be considered as 'anti diabetic medication'. This threshold is set to ensure that the short-term durations (i.e. ≤ 21 days) of anti-diabetic medication (e.g. in connection with concurrent illnesses) are not included because such intensifications are not likely to affect the efficacy endpoints.

Treatment policy estimand: Time to additional anti-diabetic medication

The treatment policy estimand is addressed for the FAS using the in-trial observation period and additional anti-diabetic medication will be considered an event regardless of whether or not subjects have discontinued treatment. Time from randomisation to additional anti-diabetic medication will be analysed using a Cox proportional hazards model with treatment and sex, age group and the interaction between sex and age group as categorical fixed effects as categorical fixed effects and baseline HbA_{1c} as a covariate. From this analysis the estimated Hazard ratios between each of the oral semaglutide dose levels and placebo together with associated two-sided 95% CIs and unadjusted two-sided p-values will be presented. The analysis aims to address the need of additional anti-diabetic medication regardless of whether this is due to lack of effect or tolerability. Switch to other anti-diabetic treatment is therefore also considered an event and withdrawn subjects or subject lost to follow-up will be considered as having an event on the day of withdrawal. Subjects will be censored on the day before planned end of treatment visit.

An additional analysis, censoring the subjects who withdraw or are lost to follow-up, will be performed. Details of this analysis will be specified in the SAP.

Hypothetical estimand: Time to rescue medication

The hypothetical estimand is addressed for the FAS using the on-treatment without rescue medication observation period. Time from first dose of trial product to initiation of rescue medication will be analysed using the same model as described above. The analysis aims to address lack of effect and only initiation of rescue medication as add-on to randomised treatment is considered an event. Switch to other anti-diabetic treatment is not considered an event and as a consequence subjects will be censored on the day before date of last trial product. Potential events occurring between randomisation and first date on trial product will be included in the analysis as events at day 0, in order to count all events of rescue medication.

Safety endpoints and assessments

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

- Adverse events
- Number of treatment-emergent AEs (TEAEs) during exposure to trial product, assessed up to approximately 57 weeks

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding. A treatment-emergent AE is defined as an AE with onset in the on-treatment observation period (see definition of observation periods in section [10.2](#)).

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

Furthermore, AEs with onset in the 12-week follow-up observation period will be summarised similarly (see definition of observation periods in section [10.2](#)).

Hypoglycaemic episodes

- Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes from randomisation to week 26
- Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks
- Treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episode from randomisation to week 26 (yes/no)
- Treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episode during exposure to trial product, assessed up to approximately 57 weeks (yes/no)

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

Analysis of severe or BG-confirmed symptomatic hypoglycaemic endpoints

The number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes will be evaluated for the on-treatment period using a negative binomial regression model with a log-link function and the logarithm of the duration of the subject's on-treatment observation period as offset. The model will include treatment and sex, age group and the interaction between sex and age group as categorical fixed effects and baseline HbA_{1c} as covariate. The binary endpoint showing whether a subject has at least one treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episode will be analysed using a logistic regression model with treatment, sex, age group as categorical fixed effects and baseline HbA_{1c} as covariate.

Other safety endpoints

Change from baseline (week 0) to week 26 and to week 52 in:

- Biochemistry
 - amylase (U/L)
 - lipase (U/L)
- Biomarkers
 - IGF-1 (ng/mL)
 - IGFBP 3 (ng/mL)
- Hormones
 - calcitonin (pmol/L)
 - estradiol (for girls) (pmol/L)
 - testosterone (for boys) (nmol/L)
 - prolactin (mIU/L)
 - TSH/thyrotropin (mIU/L)
 - FSH (mIU/mL)
 - LH (mIU/mL)
 - DHEAS (µmol/L)

The biomarker-, biochemistry and hormone-related safety endpoints will be evaluated using the primary analysis for the secondary estimand based on SAS using the on-treatment observation period. Endpoints will be analysed separately as described above for continuous efficacy endpoints. Results will be presented at week 26 and 52. Amylase and lipase endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

Anti-semaglutide antibodies endpoints

Anti-semaglutide antibodies endpoints during 57 weeks:

- Anti-semaglutide antibody status.
- Anti-semaglutide antibody titer.
- Anti-semaglutide antibodies with *in vitro* neutralising effect to semaglutide
- Anti-semaglutide antibodies cross reacting with endogenous GLP-1
- Cross reacting antibodies with *in vitro* neutralising effect to endogenous GLP-1)

The categorical antibodies endpoints will be summarised descriptively as counts and relative frequencies.

Other supportive safety endpoints

The following will be assessed at week 26 and 52:

- Height velocity (cm/year)

Height will be summarised descriptively by treatment arm and visit.

The height velocity will be calculated at week 26 and week 52. The week 26 velocity will be the difference in height at week 26 and baseline, divided by the actual time elapsed in that period. Similarly the height velocity at week 52 will be based on the heights at weeks 26 and 52. As some of the subjects will be at an age where they are no longer growing, the height velocity will be tabulated both for all subjects, and also only for subjects still growing (a height velocity <1.0 cm/year is defined as no longer growing).

Safety assessments

Change from baseline (week 0) to week 26 and to week 52 in:

- Height SDS
- Bone age assessment, X-ray (only at week 52) (years)
- Pubertal assessment (Tanner staging) (stage 1-5 where 5 is full sexual maturity)
- Pulse rate (beats/minute)

Change from pre-dose to post-dose (25 and 40 minutes) at week 12 and week 26 in:

- Lactate (mmol/L)

The safety assessments will be summarised descriptively by treatment arm and visit.

Supportive secondary pharmacokinetic endpoints

PK sampling of semaglutide from eight visits over the treatment period of 52 weeks with three samples performed during the dose escalation period will be included in a population PK analysis (for more details, see section [10.4](#)) comparing the following PK properties to historical adult data, at steady state:

- Apparent clearance (CL/F) (L/h)
- Average concentration (C_{avg}) (nmol/L)

SNAC PK samples collected in this trial will be evaluated using relevant summary statistics and compared to historical adult data:

- SNAC plasma concentrations (ng/mL)

10.3.3 Exploratory endpoints

Exploratory efficacy endpoints

Evaluated after intake of first tablet (week 0) and after 26 weeks:

- Swallowability of semaglutide tablet (questionnaire)

This will be evaluated using relevant summary statistics.

Change from baseline (week 0) to week 26 and to week 52 in:

- Glucose metabolism
- fasting insulin (pmol/L)
- fasting pro-insulin (pmol/L)
- pro-insulin to insulin ratio (%)
- fasting glucagon (pg/mL)
- fasting C peptide (pmol/L)
- homeostasis model assessment (HOMA-B and HOMA-IR) (ratio to baseline)
- Fasting lipid profile
- cholesterol, LDL, VLDL, HDL and triglycerides (mmol/L)

Glucose metabolism will be summarised descriptively by treatment arm and visit. In addition, glucose metabolism will be evaluated by use of basal insulin at randomisation (yes/no). Fasting lipids will be analysed separately using similar model approaches as for the primary endpoint with the associated baseline value as a covariate. Glucose metabolism and fasting lipids will be log-transformed, and for fasting lipids will be done prior to analysis with the associated log-transformed baseline value as a covariate.

Change from baseline (week 0) to week 26 and to week 52:

- Adiponectin
- total adiponectin (ng/mL)
- HMW (ng/mL)

Adiponectin related endpoints will be evaluated using both the treatment policy estimand and the hypothetical estimand. More details will be specified in the SAP. Furthermore, the endpoints will be explored using descriptive statistics based on FAS, including relevant summary statistics for total adiponectin, HMW adiponectin and HMW adiponectin –to–total adiponectin ratio.

OGTT-derived endpoints

The endpoints are change from baseline (week 0) to week 52 in:

- Incremental C-peptide ($iAUC_{cp,0-120\text{ min}}$) (nmol/L)
- Incremental insulin ($iAUC_{ins,0-120\text{ min}}$) (pmol/L)
- Incremental glucose ($iAUC_{g,0-120\text{ min}}$) (mmol/L)
- 2-hour glucose value (mmol/L)
- C-peptide index: Δ C-peptide from 0-30 minutes/ Δ glucose from 0-30 minutes [$\Delta C_{30}/\Delta G_{30}$] (nmol/mmol)
- Insulinogenic index: Δ insulin from 0-30 minutes/ Δ glucose from 0-30 minutes [$\Delta I_{30}/\Delta G_{30}$] (pmol/mmol)
- C-peptide derived oral disposition index (DIO; C-peptide index adjusted for insulin sensitivity [$\Delta C_{30}/\Delta G_{30}$] $\times$ 1/IF) (1/nM)
- Insulin derived oral disposition index (DIO; insulinogenic index adjusted for insulin sensitivity [$\Delta I_{30}/\Delta G_{30}$] $\times$ 1/IF) (1/nM)
- Incremental glucagon relative to glucose ($iAUC_{glucagon,0-120\text{ min}}$) (pg/mL)

- Early phase glucagon response relative to glucose after oral glucose ingestion (Δ glucagon from 0-30 minutes $\times$ Δ glucose from 0-30 minutes [Δ Glucagon₃₀ $\times$ Δ G₃₀]) (pg/mL $\times$ mmol)

The C-peptide index and the C-peptide derived oral disposition index endpoints will be evaluated using both the treatment policy estimand and the hypothetical estimand. More details will be specified in the SAP. All other OGTT related endpoints will be explored using relevant summary statistics

Exploratory endpoints related to the 12-week follow-up period

The following endpoints will be evaluated as change from baseline (week 0) to week 57 and to week 64:

- HbA_{1c} (%-point and mmol/mol)
- FPG (mg/dL)
- Body weight (kg)
- Body weight (relative change, %)
- Waist circumference (cm)
- BMI percentile (age and gender adjusted) (%)
- Glucose metabolism
- fasting insulin (pmol/L)
- fasting pro-insulin (pmol/L)
- pro-insulin to insulin ratio (%)
- fasting glucagon (pg/mL)
- fasting C peptide (pmol/L)
- homeostasis model assessment (HOMA-B and HOMA-IR) (ratio to baseline)

The above endpoints will be summarised descriptively by treatment arm and visit based on FAS. In addition, glucose metabolism related endpoints will be evaluated by use of basal insulin at randomisation (yes/no). Glucose metabolism related endpoints will be log-transformed.

Change from baseline (week 0) to week 64:

- Adiponectin
- total adiponectin (ng/mL)
- HMW (ng/mL)

Adiponectin related endpoints will be evaluated using similar estimands as for the primary endpoint. Details will be specified in the SAP. Furthermore, the endpoints will be explored using descriptive statistics based on FAS, including relevant summary statistics for total adiponectin, HMW adiponectin and HMW adiponectin-to-total adiponectin ratio.

OGTT-derived endpoints

The endpoints are change from baseline (week 0) to week 64 in:

- Incremental C-peptide (iAUC_{cp,0-120 min}) (nmol/L)
- Incremental insulin (iAUC_{ins,0-120 min}) (pmol/L)
- Incremental glucose (iAUC_{g,0-120 min}) (mmol/L)

- 2-hour glucose value (mmol/L)
- C-peptide index: Δ C-peptide from 0-30 minutes/ Δ glucose from 0-30 minutes [$\Delta C_{30}/\Delta G_{30}$] (nmol/mmol)
- Insulinogenic index: Δ insulin from 0-30 minutes/ Δ glucose from 0-30 minutes [$\Delta I_{30}/\Delta G_{30}$] (pmol/mmol)
- C-peptide derived oral disposition index (DIO; C-peptide index adjusted for insulin sensitivity [$\Delta C_{30}/\Delta G_{30}$] x 1/IF) (1/nM)
- Insulin derived oral disposition index (DIO; insulinogenic index adjusted for insulin sensitivity [$\Delta I_{30}/\Delta G_{30}$] x 1/IF) (1/nM)
- Incremental glucagon relative to glucose (iAUC_{glucagon,0-120 min}) (pg/mL)
- Early phase glucagon response to relative to glucose after oral glucose ingestion (Δ glucagon from 0-30 minutes x Δ glucose from 0-30 minutes [$\Delta \text{Glucagon}_{30} \times \Delta G_{30}$] (pg/mL x mmol)

The C-peptide index and the C-peptide derived oral disposition index endpoints will be evaluated using similar estimands as for the primary endpoint. Details will be specified in the SAP. All other OGTT-related endpoints will be explored using relevant summary statistics.

10.3.4 Interim analyses

No interim analyses will be performed.

10.3.5 Subgroup analyses

Subgroup analyses on the primary endpoint, based on race, sex, region, ethnicity and age group. Details will be provided in the SAP.

10.3.6 Sequential safety analysis and safety monitoring

Blinded and unblinded data evaluations during trial conduct will be performed by the DMC, as described in the DMC charter. Trial integrity will be ensured by using a statistician independent of trial conduct and external to Novo Nordisk to prepare the output for the DMC.

10.4 Pharmacokinetic and/or pharmacodynamic modelling

The population PK analysis for semaglutide 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.

Individual drug concentration data will be tabulated in the clinical trial report. The population PK analysis will be reported in a separate modelling analysis report included as an appendix to the clinical trial report. Selected results will be summarised in the clinical trial report.

The objective of this modelling analysis is to study the semaglutide steady-state exposure in children and adolescents with T2D after oral administration of semaglutide and to investigate the effects of pre-specified covariates on the semaglutide exposure. Semaglutide plasma 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. Data from other relevant trials in paediatric subjects can be included, if available at the time of analysis.

A previously developed population PK model for semaglutide will be used as a starting point in the analysis. The pre-specified analysis will explore the effects of covariates on semaglutide exposure.

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Exposure-response analysis

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

11 References

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12 Appendices

Appendix 1 Abbreviations and Trademarks

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis covariance
anti-GAD	anti-glutamic acid decarboxylase
BG	blood glucose
BMI	body mass index
Cavg	average concentration
CHMP	Committee for Medicinal Products for Human Use
CL/F	apparent clearance
CRF	case report form
CTR	clinical trial report
DHEAS	dehydroepiandrosterone sulphate
DMC	data monitoring committee
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	Food and Drug Administration Amendment Act
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1	glucagon-like-peptide-1
GLP-1 RA	glucagon-like-peptide-1 receptor agonist
HbA _{1c}	glycated haemoglobin
HDL	high density lipoprotein
HMW	high molecular weight
IA-2	Positive insulinoma associated-protein 2
IB	Investigator's Brochure
ICH	International Council for Harmonisation

ICMJ	International Committee of Medical Journal
IEC	independent ethics committee
IGF-1	insulin-like growth factor 1
IGFBP-3	insulin-like growth factor binding protein 3
IMD	international medical director
IMP	investigational medicinal product
IRB	institutional review board
ISPAD	International Society for Paediatric and Adolescent Diabetes
ITM	international trial manager
IWRS	interactive web response system
LAR	legally acceptable representative
LH	luteinizing hormone
LDL	low-density lipoprotein
LLoQ	lower limit of quantification
LSLV	last subject last visit
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MMRM	Mixed Model for Repeated Measurements
MODY	maturity onset diabetes of the young
NIMP	non-investigational medical product
OGTT	oral glucose tolerance test
PCD	primary completion date
PD	pharmacodynamic
PDCO	Paediatric Committee
PG	plasma glucose
PIONEER	Peptide InnOvationN for Early DiabEtes TRreatment
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SDS	standard deviation score
SMPG	self-measured plasma glucose
SNAC	sodium N-[8-(2-hydroxybenzoyl) amino] caprylate
T2D	type 2 diabetes
TSH	thyroid-stimulating hormone

TMM	trial materials manual
ULN	upper limit of normal
VLDL	very low density lipoprotein
WHO	World Health Organisation
WOCBP	woman of child bearing potential

Appendix 2 Clinical laboratory tests

- The laboratory tests detailed in [Table 12-1](#) and [Table 12-2](#) will be performed by the central laboratory. Information on central laboratory is found in [Attachment I](#).
- The laboratory tests detailed in [Table 12-3](#) will be performed by special laboratories in accordance with [Attachment I](#).
- For some of the analyses related to suspicion of acute pancreatitis and hypersensitivity reactions, a local laboratory must be used (see [Appendix 4](#) for assessments). In case of suspicion of trial drug induced severe acute (systemic) hypersensitivity, see [Table 12-3](#).
- 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 investigator must review all laboratory results for concomitant illnesses and AEs.
- Laboratory samples will be destroyed no later than at finalisation of the clinical trial report, except for anti-semaglutide antibody samples (see [Appendix 7](#)).
- For haematology samples (differential count) where the test result is not normal, then a part of the sample may be kept for up to one year or according to local regulations.
- 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.

Table 12-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• HbA_{1c} • Fasting glucagon • Fasting insulin • Fasting pro-insulin • Fasting plasma glucose (FPG)¹ • Fasting pro-insulin to insulin ratio • Fasting C-peptide • Random C-peptide (i.e. not fasting at visit 1) • Homeostasis model assessment (HOMA-B and HOMA-IR)
OGTT	• Plasma glucose, fasting and non-fasting • C-peptide, fasting and non-fasting • Insulin, fasting and non-fasting • Glucagon, fasting and non-fasting
Lipids (fasting)	• Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides • Very low density lipoprotein (VLDL) cholesterol
Hormones	• Adiponectin, total and high molecular weight (HMW)
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.	

Table 12-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	• Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Thrombocytes • Differential count: eosinophils, basophils, lymphocytes, monocytes, neutrophils
Biochemistry ¹	• Alanine Aminotransferase (ALT)² • Alkaline phosphatase (ALP) • Amylase • Aspartate Aminotransferase (AST) • Bilirubin (total)² • Creatine kinase • Creatinine² • Lipase • Potassium • Sodium • Urea (BUN) • Albumin • Calcium total • Calcium (albumin corrected) • Lactate
Biomarkers	• Insulin-like growth factor 1 (IGF-1) • Insulin-like growth factor binding protein 3 (IGFBP-3)
Insulin antibodies	• Anti-glutamic acid decarboxylase (anti-GAD) antibodies • Insulinoma associated-protein 2 (IA-2) antibodies
Hormones	• Calcitonin • Dehydroepiandrosterone sulphate (DHEAS) • Estradiol (for girls) • Follicle stimulating hormone (FSH) • Luteinizing hormone (LH) • Prolactin • Testosterone (for boys) • Thyroid stimulating hormone (TSH)
Pregnancy Testing	• Serum and urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential), see Appendix 5 and Appendix 12.
Urinalysis ³	• pH, glucose, protein, ketones, micro albumin, creatinine and the albumin:creatinine ratio (calculated)

NOTES:

¹Details 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](#).

²ALT, creatinine and bilirubin are the only biochemistry parameters to be measured at visit 1 to assess eligibility.

³For visits where urinalysis is required (please refer to the flowchart, section [2](#)) the subject should be asked to collect the first morning urine on the day of the visit and bring it to the site. The subjects should be provided with containers for urine collection and be trained in how to collect the urine sample and transport it to site. For information on collection, storage and shipment to the central laboratory please refer to the laboratory manual.

Table 12-3 Protocol-required special laboratory parameters

Laboratory assessments	Parameters
Antibodies	• Anti-semaglutide antibodies • Anti-semaglutide binding antibodies¹ • Anti-semaglutide antibody titer • Cross reactivity to native GLP-1 • <i>In vitro</i> neutralising effect of anti-semaglutide antibody positive samples² • Cross reacting antibodies with in vitro neutralising effect to endogenous GLP-1² • Anti-semaglutide IgE antibodies¹
PK	• Semaglutide PK • SNAC PK
NOTES: ¹ Anti-semaglutide IgE antibodies and anti-semaglutide binding antibodies are analysed in case of suspicion of trial drug induced severe acute (systemic) hypersensitivity, see Appendix 4 ² <i>In vitro</i> neutralising effect of anti-semaglutide antibody positive samples and cross-reacting antibodies with in vitro neutralising effect to endogenous GLP-1 will be analysed by Novo Nordisk Maaloev, refer to Attachment I.	

Laboratory/analyte results that could unblind the trial (i.e. PK and anti-semaglutide antibodies) will not be reported to the trial sites until after finalisation of the CTR and only upon request from the investigator.

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 Helsinki³⁵ and applicable ICH Good Clinical Practice (GCP) Guideline³⁶
- Applicable laws and regulations
- *Austria, Mexico and Russia only:* For country specific requirements, please see [Appendix 12](#).
- The protocol, informed consent form, investigator's brochure (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 clinical trial report 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 clinical trial report (CTR) synopsis to the IRB/IEC.

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/or the subject's LAR and answer all questions regarding the trial.
- The investigator must give the subject and the subject'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 a clinical trial.

- The investigator must ensure the subject and the subject's LAR ample time to come to a decision whether or not to participate in the trial.
- Subjects and their LAR must be informed that participation in the trial is voluntary.
- Subjects or their LAR will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines³⁶, Declaration of Helsinki³⁵ and the IRB/IEC or trial site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements.
- Subjects and/or their 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 assent form, the subject has to re-consent to the informed consent form for subject's reaching legal age.

4) Information to subjects during trial

The site will be offered a communication package for the subject'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 subject or the subject's LAR. The written information will be translated and adjusted to local requirements and distributed to the subject and the subject's LAR at the discretion of the investigator. The subject and the subject'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 subject's LAR may receive other written information during the trial.

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

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 subject's LAR must be informed that the subject's 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 subject's LAR must be informed that the subject's medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

6) Committee structure

Novo Nordisk safety committee

Novo Nordisk will constitute an internal NN9924 safety committee to perform ongoing safety surveillance. The NN9924 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.

After 6 months of the trial or after the first 10 subjects have been randomised to receive oral semaglutide and have reached maximum tolerated dose (whatever comes first) the DMC will review safety and tolerability of oral semaglutide and recommend to the Safety Committee if the trial can continue, be modified or stopped. After 12 months or after the first 18 subjects have been randomised to receive oral semaglutide and have reached maximum tolerated dose (whatever comes first) the evaluation will happen again. The DMC will also evaluate SNAC pharmacokinetic exposure. The DMC will continue to monitor safety and tolerability on a regular basis throughout the rest of the trial. Screening and randomisation can continue during DMC review.

Supportive panel

Global expert panel

A global expert panel (GEP) will consist of selected principal investigators, identified as national leaders and scientific experts, and of designated Novo Nordisk employees. The panel will discuss and advise on global and local operational issues related to trial conduct. The panel will operate under a charter agreed with Novo Nordisk.

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 clinical trial report for this trial.

One or two investigators will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators.

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 clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

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

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. 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 Editors³⁷.

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)³⁸, the Food and Drug Administration Amendment Act (FDAAA)³⁹, European Commission Requirements⁴⁰⁻⁴² 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) + 26 weeks corresponding to visit 12. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 12. 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:
 - Pregnancy forms
 - The following will be provided as paper CRFs to be used when access to the eCRF is revoked or the eCRF 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 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.
- 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 25 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. *Belgium*: For country-specific requirements, please refer to [Appendix 12](#).
- 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 sub-investigator 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 accepts liability in accordance with: please refer to [Appendix 12](#).

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 <u>meeting</u> the AE definition
• Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • A clinical 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. • Abuse: Persistent or sporadic, intentional excessive use of medicinal product, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm) • Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol or terms of the marketing authorization. • 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 <u>NOT</u> 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: 1. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. 2. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs. • Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experience of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Important medical event:**
 - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
 - The following adverse events must always be reported as SAEs using the important medical event criterion, if no other seriousness criteria are applicable:
 - suspicion of transmission of infectious agents via the trial product.
 - risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (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 need to be reported on specific event forms for evaluation of the safety of the trial product. The selection of these events is based on the non-clinical and clinical data of oral semaglutide, knowledge from the GLP-1 RA drug class as well as regulatory requirements.

Event type	Description
Acute gallstone disease	Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis)
Hepatic events	ALT or AST >5x UNL and total bilirubin ≤2x UNL, regardless of baseline level of ALT or AST* ALT or AST >3x UNL and total bilirubin >2x UNL, regardless of baseline level of ALT or AST** ALT or AST >2x baseline level if baseline was abnormal*** *Baseline level is considered to be the ALT/AST measurement at V2. **Please note that in case of a hepatic event defined as ALT or AST > 3 x UNL and total bilirubin > 2 x 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. ***Abnormal is defined as values >UNL.
Hypersensitivity reaction	All events of hypersensitivity reactions, where no clear alternative aetiology exists.
Neoplasm	All events of neoplasm
Pancreatitis	Diagnosis requires at least two of the following: 1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) 2) serum lipase (and/or amylase) at least three times greater than the upper limit of normal 3) characteristic findings of acute pancreatitis on imaging
Renal events	All renal events
Diabetic retinopathy and related complications	New onset or worsening of diabetic retinopathy
Medication error	A medication error is a 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 instead of trial product Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug. - Accidental administration of a lower or higher dose than intended. 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. Note: Intentional drug errors related to trial products are misuse/abuse and should be reported as AEs and not as medication errors
Lactic acidosis	Lactic acidosis is characterized by increased blood lactate level in association with metabolic acidosis
CK > 10x UNL	Events of CK > 10x UNL

Assessments in case of suspicion of hypersensitivity reactions:

In case of suspicion of a severe immediate systemic hypersensitivity reaction (e.g. anaphylaxis)⁴³ to the trial product, the subject must be discontinued from trial product but should remain in the trial (see protocol sections 8.1 and 7.8). If suspicion of such a hypersensitivity reaction occurs, the subjects should be instructed to contact the site staff as soon as possible for further guidance.

To assist in the diagnostic evaluation of a suspected severe immediate systemic hypersensitivity reaction to the trial product, it is recommended to draw a blood sample for measurement of tryptase and total IgE (total and/or mature tryptase, local assessment must be performed at a local laboratory) as soon as possible (0-3 hours) after the onset of the hypersensitivity reaction. Only if this sample is taken within 3 hours after onset, an additional follow-up sample should be drawn 2-4 weeks after the event in order to assess whether tryptase and total IgE levels were increased at the time of the hypersensitivity event. Tryptase and total IgE concentrations, if available, should be included in the specific event form when reporting the AE.

A blood sample for assessment of anti-semaglutide binding antibodies and anti-semaglutide IgE antibodies should also be drawn as soon as possible after the onset of the hypersensitivity reaction and again 2-4 weeks after the event and sent to central laboratory (see attachment I). The tryptase/total IgE, anti-semaglutide binding antibodies and anti-semaglutide IgE samples can be taken at the same sampling occasions. If it was not possible to obtain a tryptase/total IgE sample within 3 hours after onset of the reaction, the anti-semaglutide binding antibodies and anti-semaglutide IgE samples should be still taken (as soon as possible and again 2-4 weeks after the event). Analysis of anti-semaglutide binding antibodies and anti-semaglutide IgE from subjects treated with semaglutide will be performed at Novo Nordisk A/S or a Novo Nordisk A/S designated laboratory. These data will not be available to the investigator until the end of trial and cannot be used for medical decisions or diagnostic purposes.

In case of suspicion of immune complex disease ⁴³, the subject must be discontinued from trial product but should remain in the trial (see protocol sections 8.1 and 7.8). It is recommended to draw a blood sample for local assessment of complement levels (C3 and C4) to assist in the diagnostic evaluation. Complement level results should be included in the specific event form when reporting the AE.

Assessments in case of increased levels of aminotransferases:

In case of increased levels of aminotransferases according to thresholds in above table a prompt repeat testing (at the central laboratory) should be performed including ALT, AST, alkaline phosphatase (ALP) and total bilirubin, and discontinuation of trial product should be considered.

Thereafter, repeat testing (at the central laboratory) of ALT, AST, ALP and total bilirubin should be done regularly until the abnormalities return to normal or baseline state. Additional clinical information such as related symptoms, risk factors and contributing conditions (e.g. viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, hepatobiliary or pancreatic disorders) should be gathered to seek a possible cause of the observed laboratory test abnormalities.

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.
- 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 NIMP or concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as NIMP or 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 investigator’s brochure for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

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

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

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

Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
- **Recovering/resolving:** The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
- **Recovered/resolved with sequelae:** The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequelae meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the subject has not improved and the symptoms are unchanged or the outcome is not known.

- **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as “recovered/resolved”, “recovering/resolving”, “recovered/resolved with sequelae” or “not recovered/not resolved”. An AE with a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the subject is lost to follow-up.

Follow-up of AE and SAE

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

SAE reporting via electronic CRF

Relevant forms (AE and safety information 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 [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 their first menstrual period).

Definitions

Woman of Childbearing Potential (WOCBP)

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

Contraception guidance

Male subjects:

No contraception measures are required for male patients 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 below:

Table 12-4 Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent ^{a, b}
Failure rate of <1% per year when used consistently and correctly.
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 ^b
- 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
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 35 days after the last dose of trial product

Pregnancy testing

- WOCBP should only be included after a negative highly sensitive serum pregnancy test at visit 1 and a negative highly sensitive urine pregnancy test at visit 2.
- Serum and urine pregnancy testing should be performed throughout the trial in accordance with the flowchart, section [2](#). *Austria only*: For country specific requirements, please see [Appendix 12](#).
- If a subject prematurely discontinues treatment, a urine pregnancy test must be performed 5 weeks after end of treatment.
- If a girl becomes of childbearing potential during the trial, a urine pregnancy test must be performed for that subject as soon as possible or at the latest at the next site visit.
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Additional urine pregnancy testing should be performed during the treatment period, if required locally [Appendix 12](#). 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.

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.

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 eCRF within the timelines specified in [Figure 9-3](#).

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

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.

Appendix 7 Retention of human biosamples

Anti-semaglutide antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug, if required by health authorities or for safety reasons.

The samples will be stored at the special laboratory after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.

CCI

Only Novo Nordisk staff and biorepository personnel involved in the analyses will have access to the stored samples.

For all retained samples, 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 and a destruction certificate must be issued when the samples are destroyed.

In the event that the collected biosamples (anti-semaglutide antibody) will be used in the future, the investigator will become directly informed by Novo Nordisk about the results, if the findings are deemed clinically relevant and analytically valid and quantifiable. In such case, a written summary of the findings, including listings of subject specific values, will be provided once a firm conclusion from the results has been drawn by Novo Nordisk. Subjects can contact the investigator if they wish to be informed about results derived from stored biosamples obtained from their own body.

The subject may request the stored samples to be destroyed when withdrawing consent.

Appendix 8 Hypoglycaemic episodes

Novo Nordisk classification of hypoglycaemia in paediatrics

Hypoglycaemic episodes are classified according to ISPAD's definition of severe hypoglycaemia⁴⁴, as well as the Novo Nordisk classification of hypoglycaemia and the ADA classification of hypoglycaemia ([Figure 12-1](#)).

In normal physiology, symptoms of hypoglycaemia occur below a Plasma Glucose (PG) level of 3.1 mmol/L (56 mg/dL)⁴⁵. 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:

- Severe hypoglycaemia according to the ISPAD classification⁴⁴: Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?
- BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.

ADA/ISPAD classification of hypoglycaemia in paediatrics^{44, 45}

- Severe hypoglycaemia according to the ISPAD classification: 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).

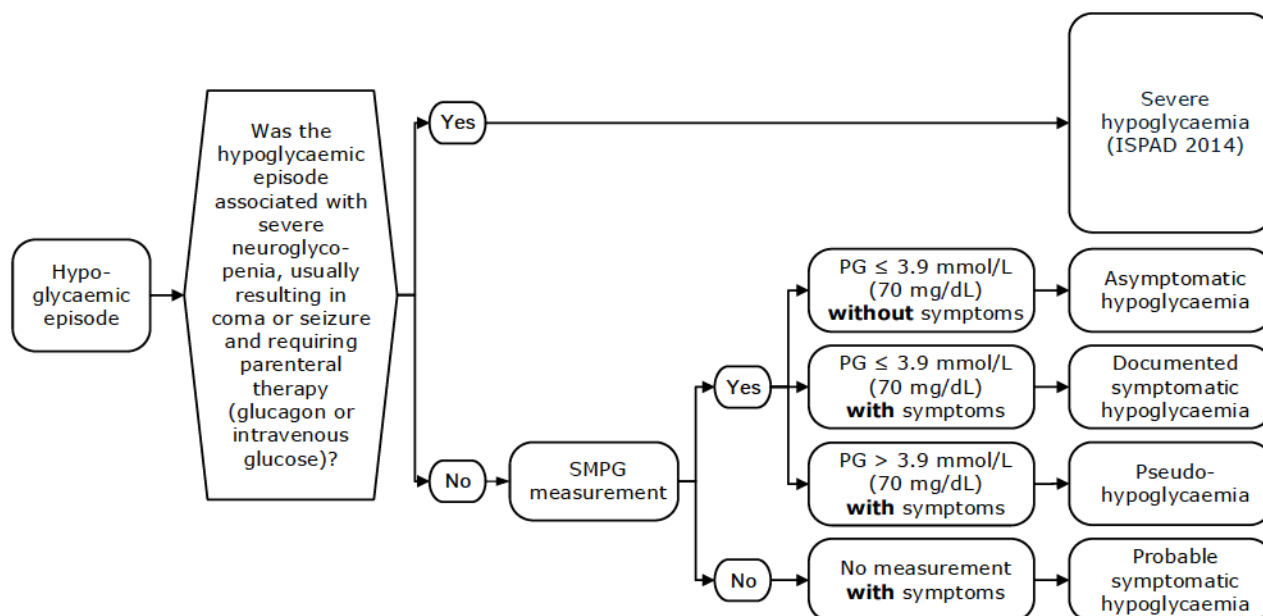
For hypoglycaemic episodes reported with missing information related to the classification, the following applies when classifying the episode according to the ADA/ISPAD classification:

- 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.

Figure 12-1 ADA/ISPAD classification of hypoglycaemia in paediatrics^{44, 45}



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

PG: plasma glucose SMPG: Self-measured plasma glucose

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 section [10.2](#)).

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

Hypoglycaemic episodes are classified according to ISPAD's definition of severe hypoglycaemia⁴⁴, as well as the Novo Nordisk classification of hypoglycaemia and the ADA classification of hypoglycaemia ([Figure 12-1](#)).

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 (section [2](#)) and instructions below. When a subject experience a hypoglycaemic episode, subject/investigator should record the general information in relation to the hypoglycaemia (timing, PG measurements, symptoms etc. as described in the diary/CRF). 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 in the eCRF.

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 guidelines⁴⁵.

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 "severe⁴⁴". The subject or parents/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 and/or the subject's parents/LAR 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^{28, 33, 46, 47}.

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

Appendix 9 Titration guideline

Basal insulin

It is important that other information, such as symptoms of hypoglycaemia and/or hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the subject's level of glycaemic control, is taken into consideration when decisions on dosing are made. The investigator should always use clinical judgement to avoid safety hazards. The investigator is responsible for the treatment of the subjects and can therefore overrule the guideline.

Table 12-5 Algorithm for up-titration of basal insulin dose

Mean fasting SMPG levels*	Increase in basal insulin dose
>10 mmol/L (>180 mg/dL)	+6 units
7.8 to 10 mmol/L (141–180 mg/dL)	+4 units
6.7 to <7.8 mmol/L (121–140 mg/dL)	+2 units
5.6 to <6.7 mmol/L (100–120 mg/dL)	+1 units

The table is adapted from the Texas Diabetes Council's Medical Professionals Advisory Subcommittee⁴⁸.

*The up-titration will be based on pre-visit mean fasting SMPG level values from week 10 and to week 15.

Table 12-6 Algorithm for down-titration of basal insulin dose

SMPG level	Reduction of basal insulin dose
One or more values < 3.1 mmol/L (56 mg/dL) without obvious explanation	Reduce insulin dose by 4 units (if dose >50 units, a dose reduction of 10% is suggested)
One or more values between 3.1–3.9 mmol/L (56–70 mg/dL) without obvious explanation	Reduce insulin dose by 2 units (if dose >50 units, a dose reduction of 5% is suggested).

Appendix 10 Blood pressure ranges for children and adolescents

According to exclusion criterion 12, section [6.2](#), subjects must be excluded from the trial in cases where they have uncontrolled treated or untreated hypertension >99th percentile for age and gender in children, in accordance with “The fourth report on the: Diagnosis, evaluation, and treatment of high blood pressure in children and adolescents”⁴⁹.

The hypertension percentiles used are based on age, gender and height percentile in accordance with CDC Growth Charts⁵⁰.

Determination of a subject’s hypertension > 99th percentile

In order to determine whether a subject is > the 99th percentile for age and gender, the investigator must define the subject’s height percentile according to [Figure 12-2](#) for girls and [Figure 12-3](#) for boys.

Based on the subject’s age and height percentile, it can be determined if the blood pressure is above the 99th percentile by using [Table 12-7](#) for girls and [Table 12-8](#) for boys.

Figure 12-2 Height for age percentiles in girls

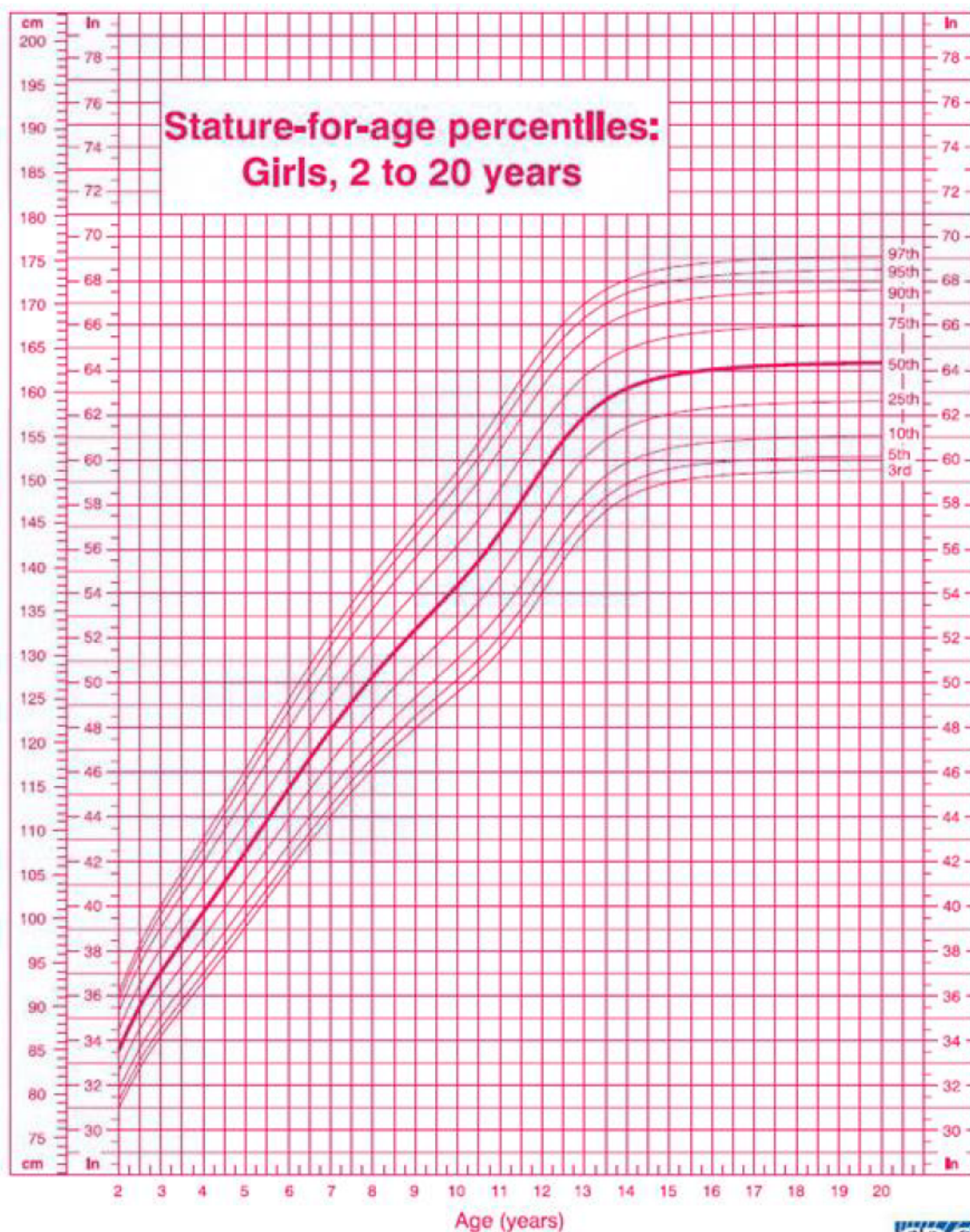


Figure 12-3 Height for age percentiles in boys

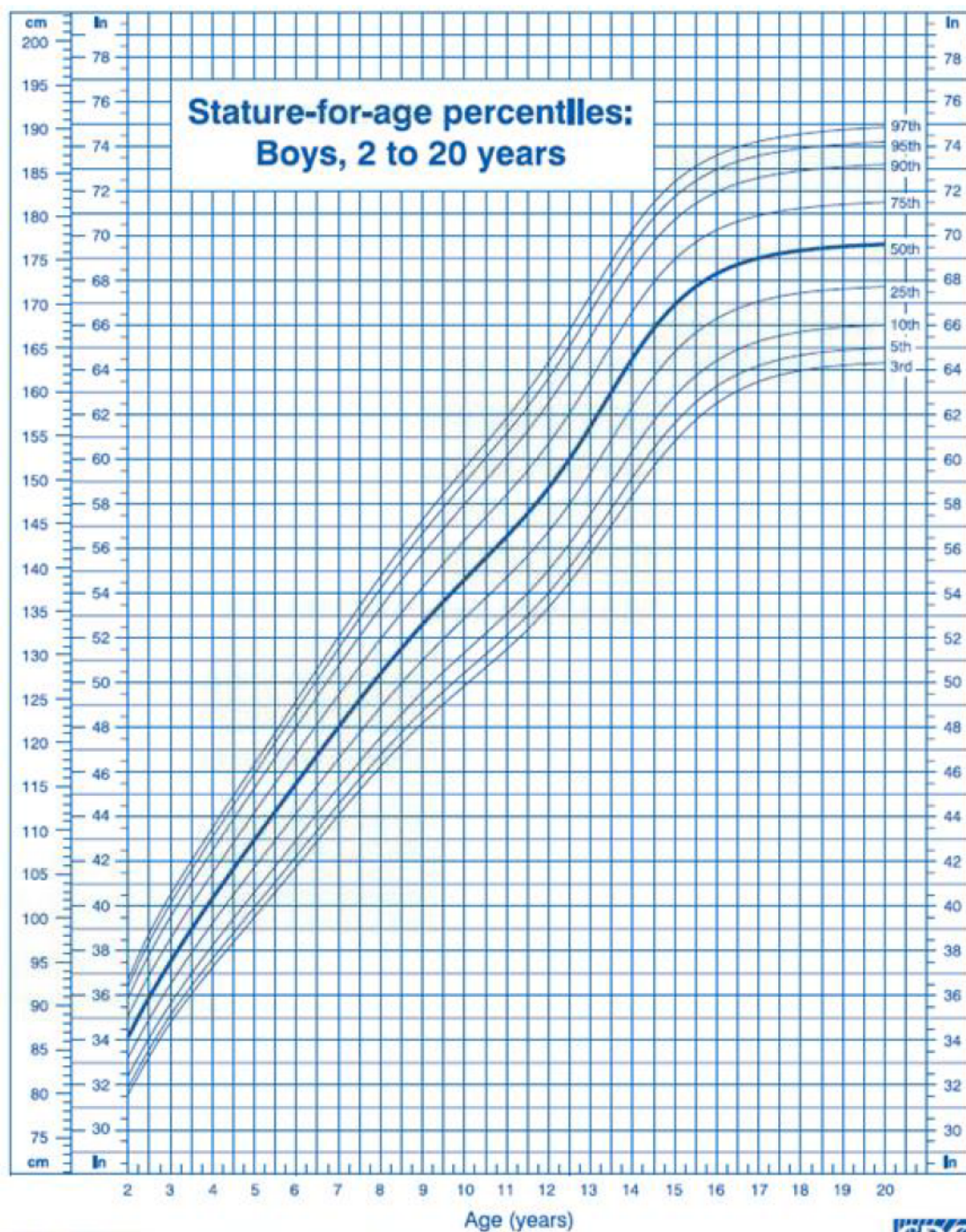


Table 12-7 Blood pressure levels for girls by age and height percentile

Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure

Table 12-8 Blood pressure levels for boys by age and height percentile

Blood Pressure Levels for Boys by Age and Height Percentile															
Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

Appendix 11 Calcitonin monitoring

Background

Non-clinical experiments conducted in rodents have demonstrated that semaglutide has the potential to stimulate growth and proliferation of thyroid C-cells. It is unknown whether semaglutide causes thyroid C-cell neoplasms, including medullary thyroid carcinoma (MTC) in humans, as human relevance could not be ruled out by clinical or nonclinical studies. However, based on the findings in rodents, monitoring of serum calcitonin (a sensitive biomarker for C-cell activation) is currently being performed in clinical trials with semaglutide.

While there is general agreement on the clinical interpretation of substantially elevated calcitonin levels (greater than 100 ng/L) as likely indicative of C-cell neoplasia⁵¹, the interpretation of values between the upper limit of normal and 100 ng/L can become problematic.

There is limited 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 adults⁵².

There are several known factors affecting calcitonin levels, namely renal dysfunction, smoking, and several drug classes (proton pump inhibitors, beta-blockers, insulin secretagogues). Physiology of C-cell activation in various clinical conditions and in different patient populations (i.e., with various co-morbidities) is poorly understood. There may be various clinical conditions not identified so far which mildly or moderately affect calcitonin secretion by C-cells.

Calcitonin and C-cell abnormalities - evaluation and follow-up

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 must be excluded from the trial.

Subjects who are screen failures and have a calcitonin level above the normal range should be referred to their primary care physician and consideration given to referring the subject to a paediatric endocrinologist or thyroid specialist for further evaluation.

A blood sample will be drawn at pre-specified trial visits for measurement of calcitonin. Calcitonin levels post randomisation will be reviewed monthly by the International Medical Director (IMD) for this project or the director's surrogate. Calcitonin levels above upper limit of normal will be flagged by the central laboratory on the laboratory report, and reported to the investigator, the Trial Manager (TM), and IMD. A calcitonin level post randomisation above the normal limit should be repeated within 4 weeks for confirmation. If the repeat calcitonin value is above the normal range, but less than 20 ng/L it will be at the discretion of the Investigator whether to conduct further evaluation during the trial.

If the repeat calcitonin level or a calcitonin level obtained at a visit is initially ≥ 20 ng/L, it is recommended that the investigator consider whether the subject should discontinue trial product. It is also recommended that consideration be given to referring the subject to a paediatric endocrinologist or thyroid specialist for further evaluation.

If calcitonin is ≥ 50 ng/L the trial product must be discontinued and the subject should immediately be referred to a thyroid specialist for further evaluation. The subject should remain in the trial; however, all medications suspected to relate to this condition must be discontinued until diagnosis has been established

Appendix 12 Country-specific requirements

Austria:

- A monthly pregnancy test is mandatory for female subjects of childbearing potential
- Indemnity statement: Arzneimittelgesetz (BGBl. Nr. 185/1983) last amended with BGBl. I Nr. 72/2023 [<https://ris.bka.gv.at/eli/bgbl/I/2023/72>]

Belgium:

- Law concerning experiments on the human person of 07 May 2004 - Article 29: §1. Even if without fault, the sponsor is liable for the damage which the subject and/or his rightful claimants sustain and which shows either a direct or an indirect connection with the trial.
- Use of concomitant medication and management of potential interactions should be performed in line with both the approved Rybelsus SmPC as well as the approved SmPCs for all non-investigational products (<http://bijsluiters.fagg-afmps.be/?localeValue=en>).
- Rescue treatment for T2D other than the options (metformin, basal and bolus insulins) described in Section [7.7.2](#) are prohibited.
- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 25 years after end of trial.

Mexico:

- 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.
- In reference to [Appendix 3](#) point 1) it will include the following responsibilities for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility:
 - a) Investigation follow-up;
 - b) Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the subject;
 - c) Timely compliance of the terms in which the authorisation 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.
- 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.
- 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.

- 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.

Russia:

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

United Kingdom:

- Section 6.2 Exclusion criterion # 15 amended: Past basal and squamous cell skin cancer and any carcinoma in-situ is only allowed if it has been treated and cured.
- Section 6.2 Exclusion criterion # 5 amended: Any disorder e.g. uncontrolled thyroid disease, which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol.
- Contraception must continue by women of childbearing potential for at least 2 months after discontinuing treatment.
- A monthly pregnancy test is mandatory for female subjects of childbearing potential.
- Use of concomitant medication and management of potential interactions should be performed in line with the approved Rybelsus SmPC section 4.5 (<https://www.medicines.org.uk/emc/product/11507/smpc#gref>).
- If clinically indicated, eye examination, ECG and any other safety monitoring assessment may be conducted during the treatment period at the discretion of the investigator.
- For clarification in section 9.2.6. If the hypoglycaemic episode fulfils the criteria of an SAE then the event will be recorded and reported as an SAE.

Portugal

- A monthly pregnancy test is mandatory for female subjects of childbearing potential. As this request may conflict with the planned onsite visits, home urine pregnancy test can be performed at home monthly and reported on the next on-site visit or in the following phone visit in the months were on site visits are not scheduled. Trial staff will be trained on this requirement at the Site Initiation Visits in order to instruct patients accordingly.

Appendix 13 Protocol amendment history

The Protocol amendment summary of changes table for the current protocol version is located directly before the table of contents.

Protocol version 8.0 (26 March 2025)

This amendment is considered to be non-substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014.¹

Overall rationale for preparing protocol, version 8.0

This version of the protocol was primarily prepared to include a standard text related to ADA assay maintenance.

Section # and name	Description of change	Brief rationale
Section 9.4.10	The text in the section has been updated to allow ADA assay maintenance.	To allow ADA assay maintenance
Appendix 4	Text has been revised to align with latest method of handling hypersensitivity and results.	For correctness

Protocol version 7.0 (08 October 2024)

This amendment is considered to be non-substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014.¹

Overall rationale for preparing protocol, version 7.0

This version of the protocol was primarily prepared to include aspiration in association with general anesthesia or deep sedation (important potential risk) and intestinal obstruction (important identified risk).

Section # and name	Description of change	Brief rationale
Section 3.3.2 Risks	The text in the section has been updated with aspiration in association with general anesthesia or deep sedation and intestinal obstruction.	The section has been updated to reflect that aspiration in association with general anesthesia or deep sedation has been endorsed as an important potential risk for semaglutide and intestinal obstruction has been endorsed as an important identified risk for semaglutide.
Appendix 2 Clinical laboratory tests	The laboratory parameters (urea and calcium) are presented in bullet format in Table 12-2 to improve clarity.	For clarity

Protocol version 6.0 (11 June 2024)

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014.¹

Overall rationale for preparing protocol, version 6.0

This version of the protocol was primarily prepared based on FDA request to consider FDA guideline on Adjusting for Covariates (May 2023) for the analysis on binary endpoints, and addition of Sponsor's name, legal address, IND number, Development stage, and updating EU CTR number on the cover page as per EU CTR requirements.

Section # and name	Description of change	Brief rationale
Cover page	Added the following details in the cover page: IND number: 114464 Sponsor Name: Novo Nordisk A/S Sponsor Legal Address: Novo Alle, 2880 Bagsvaerd, Denmark Development Stage: Post-market stage Updated 'EudraCT number: 2018-002952-34' to 'EU CT number: 2023-506923-27'	Updated the cover page as per EU CTR requirements.
Section 10.3.2.2 Supportive secondary endpoints	"For both estimands, each of the 1000 data sets will be analysed using a logistic regression model with treatment, sex, age group and the interaction between sex and age group as categorical fixed effects and baseline HbA1c as covariate. The results will be combined using Rubin's rule ³⁴ to draw inference." has been replaced by the following text added under binary efficacy endpoints: "For both estimands, each of the 1000 complete data sets will be analysed using a logistic regression model with treatment arm as factor and baseline HbA1c as covariate. The results from this model will be used to predict the probability of achieving the efficacy endpoint for all participants had they (counterfactually) been assigned to each specific treatment. Average treatment difference in probability will be estimated by subtracting the average predicted probabilities and the corresponding standard errors will be calculated using the delta-method."	The section has been updated based on FDA request to consider FDA guideline on Adjusting for Covariates (May 2023) for the analysis on binary endpoints.
Section 10.3.2.2 Supportive secondary endpoints	"The binary endpoint showing whether a subject has at least one treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episode will be analysed using a logistic regression model with treatment, sex, age group and the interaction between sex and age group as categorical fixed effects and baseline HbA1c as covariate." has been replaced by the following text added under Analysis of severe or BG-confirmed symptomatic hypoglycaemic endpoints:	The section has been updated based on FDA request to consider FDA guideline on Adjusting for Covariates (May 2023) for the analysis on binary endpoints.

Section # and name	Description of change	Brief rationale
	“The binary endpoint showing whether a subject has at least one treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episode will be analysed using a logistic regression model with treatment arm as factor and baseline HbA1c as covariate. “	
Appendix 12 Country-specific requirements	Updated ‘Arzneimittelgesetz (BGBl. Nr. 185/1983) last amended with BGBl. I Nr. 104/’ with ‘Indemnity statement: Arzneimittelgesetz (BGBl. Nr. 185/1983) last amended with BGBl. I Nr. 72/2023 [https://ris.bka.gv.at/eli/bgbl/I/2023/72]’ under Austria	Updated country specific requirements in relation to EU CTR.

Protocol version 5.0 (7 September 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014.¹

Overall rationale for preparing protocol, version 5.0

This version of the protocol was primarily prepared to clearly define exclusion criteria for subjects with elevated liver parameters, as well as for subjects with and without Gilbert’s syndrome, and to ensure that subjects enrolled in the study with elevated liver parameters do not have any liver disorder other than non-alcoholic fatty liver disease (NAFLD).

Section # and name	Description of change	Brief rationale
Section 6.2 Exclusion criteria	The following text has been removed from exclusion criteria no. 6: “<i>ALT ≥ 5 times the upper normal limit (UNL)</i>” <i>ALT ≥ 3 times the UNL and bilirubin ≥ 1.5 times the UNL</i>” The following text has been added to exclusion criteria no. 6: <i>For subjects without Gilbert’s Syndrome:</i> <i>ALT ≥ 5 times UNL</i> <i>For subjects with ALT ≥ 3- < 5 times UNL, aetiologies other than non-alcoholic fatty liver disease (NAFLD) must have been ruled out.</i> <i>Bilirubin > UNL</i> <i>For subjects with Gilbert’s Syndrome</i> <i>ALT ≥ 3 times UNL</i> <i>Bilirubin ≥ 1.5 times UNL</i>	To clearly define exclusion criteria for subjects with and without Gilbert’s Syndrome, while also taking into consideration bilirubin levels. Furthermore, to ensure that aetiologies other than NAFLD have been ruled out in subjects who are enrolled in the study with ALT levels ≥ 3 < 5 times UNL.
Section 6.4 Screen failures	The following updates have been made to the text in the rescreening section: However, there is no possibility for a newly screened subjects to be rescreened if the subject meets the updated exclusion criteria for c-peptide, ALT, or bilirubin.	To align with the current exclusion criteria.

Section # and name	Description of change	Brief rationale
Section 9.2.1.1, Table 9-2 AEs requiring additional data collection (via specific event form) Appendix 4 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting	The following italic text has been added: <i>ALT or AST >5x UNL and total bilirubin ≤2x UNL, regardless of baseline level of ALT or AST*</i> <i>ALT or AST >3x UNL and total bilirubin >2x UNL, regardless of baseline level of ALT or AST**</i> <i>ALT or AST >2x baseline level if baseline was abnormal***</i> <i>*Baseline level is considered to be the ALT/AST measurement at V2.</i> <i>*** Abnormal is defined as values >UNL.</i>	To ensure that the hepatic event criteria considers the difference between the participants with normal and abnormal baseline liver parameters.
Section 9.4.1 Concomitant illness and medical history	The following text has been added: <i>According to the updated exclusion criteria (Section 6.2), for subjects with ALT ≥3-<5 times the UNL, aetiologies other than NAFLD must have been ruled out as documented in medical records and a relevant concomitant illness should be reported.</i>	To align with the current exclusion criteria.

Protocol version 4.0 (22 May 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014.¹ Overall rationale for preparing protocol, Version 4.0: The overall rationale for the changes implemented in the amended protocol is to allow for a more representative population of patients with type 2 diabetes and therefore ensure the recruitment of sufficient number of subjects to be included in the study.

Section # and name	Description of change	Brief rationale
Section 2 Flowchart	The “X” under visit 2 for drug accountability has been removed.	Correction of typo.
Section 2 Flowchart	The section number for oral glucose tolerance test (OGTT) has been changed from “9.1.1” to “9.1.3”	Correction of typo.
Section 3.3.2 Risks	“Angioedema” has been added under Allergic reactions.	Updated to ensure that risk description of ‘Allergic reactions’ also covers the important potential risk of angioedema.
Section 4.2.3.2 Supportive secondary endpoints Section 10.3.2.2 Supportive secondary endpoints 9.4.10 Immunogenicity assessment (anti-semaglutide antibodies)	Text changed from: “Anti-semaglutide antibodies endpoints: • Anti-semaglutide antibodies endpoints during 57 weeks of study duration (yes/no): • Anti-semaglutide antibodies with in vitro neutralising effect (yes/no) • Anti-semaglutide antibodies cross reacting with endogenous GLP-1 (yes/no) • Cross reacting antibodies with in vitro neutralising effect to endogenous GLP-1 (yes/no) o Anti-semaglutide antibody level (% bound/total) during 57 weeks of study duration.” to	Update of description to align with current guidelines. This change has been implemented throughout the protocol.

Section # and name	Description of change	Brief rationale
	“Anti-semaglutide antibodies endpoints during 57 weeks: • Anti-semaglutide antibody status. • Anti-semaglutide antibody titer. • Anti-semaglutide antibodies with <i>in vitro</i> neutralising effect to semaglutide • Anti-semaglutide antibodies cross reacting with endogenous GLP-1 • Cross reacting antibodies with <i>in vitro</i> neutralising effect to endogenous GLP-1”	
Section 4.2.3.2 Supportive secondary endpoints Section 10.3.2.2 Supportive secondary endpoints	SNAC plasma concentration changed from “ng/L” to “ng/mL”	Correction of error.
Section 6.2 Exclusion criteria	Exclusion criteria no.6 has been changed from “ALT ≥ 2.5 times the upper normal limit (UNL)” to “ALT ≥ 5 times the upper normal limit (UNL)”	To allow for a more representative children and youth population of patients with type 2 diabetes. The ALT threshold of ALT ≥ 2.5 was conservative and was excluding patients who otherwise represent the target population.
Section 6.2 Exclusion criteria	Exclusion criteria no. 6 has been changed from “C-peptide <1.5 ng/mL” to “C-peptide <0.6 ng/mL”	To allow for a more representative children and youth population of patients with type 2 diabetes. The C-peptide <1.5 ng/mL was conservative and was excluding patients who otherwise represent the target population.
Section 6.2 Exclusion criteria Section 2 Flowchart Appendix 2 Clinical laboratory tests	The following text has been added to exclusion criteria no. 6 “ALT ≥ 3 times the UNL and bilirubin ≥ 1.5 times the UNL”.	As we have increased the ALT threshold to ≥ 5 times the upper normal limit, it is important that we also evaluate bilirubin at screening with the intent to exclude potential underlying liver disorder. This change has been implemented across the protocol.
Section 6.4 Screen failures	Text added: Subjects who have previously screen failed solely due to the previous exclusion criteria for ALT (≥ 2.5 times the upper limit) and/or C-peptide (<1.5 ng/mL), can be rescreened to assess if they are eligible according to the updated exclusion criterium 6 (see Section 6.2).	To describe the subjects who will be allowed to undergo re-screening in accordance with the amended exclusion criteria.

Section # and name	Description of change	Brief rationale
	However, there is no possibility for a newly screened subject to be rescreened if the subject meets the updated exclusion criteria for c-peptide, ALT or ALT and bilirubin combined..	
Section 7.1 Treatment administered	Text added: "For details regarding the trial products, please refer to the most recent version of European Medicines Agency (EMA) summary of product characteristics. ²⁷ "	Changed according to request from Belgium and United Kingdom health authorities.
Section 9 Trial assessments and procedures	Text in the footnote of Table 9-1 changed from "adiponectin (total and HMW)" to "HMW adiponectin".	As per the laboratory set-up, total adiponectin is to be analysed from the same tube as pro-insulin sample and do not require drawing of additional blood sample.
Section 9.4.5 Vital signs	Exclusion criteria mentioned in the text has been changed from "9" to "12"	Correction of typo.
Section 9.5 Pharmacokinetics	Text changed from "The investigator must record the exact time for sampling the blood in the eCRF." to "The investigator must record the exact time for sampling the blood in the laboratory requisition form."	To clarify the process for recording the time of blood sampling.
Section 9.6.2 Swallowability questionnaire	Text deleted: At visit 2, the subject will have an OGTT performed. The 2-hour OGTT should be done prior to trial product administration and the first dose of trial product should be administered per dosing instruction (see section 7.1).	To clarify when the trial product is to be administered at V2 and therefor avoid ambiguity and the OGTT being compromised.
Appendix 2 Clinical laboratory tests	"Adiponectin, total and high molecular weight (HMW)" has been removed from "Table 12-2 Protocol required safety laboratory assessments" and added to "Table 12-1 Protocol required efficacy laboratory assessments".	Correction of error.
Appendix 2 Clinical laboratory tests	The duration of keeping a part of the haematology samples, where the test results are not normal has been changed from "2" to "1" year.	To comply with the CRO's (ICON) retention requirements.
Appendix 2 Clinical laboratory tests Table 12-3 Protocol-required special laboratory parameters	Text added: Anti-semaglutide antibody titer Text added to second point in footnote: cross-reacting antibodies with in vitro neutralising effect to endogenous GLP-1	Correction of error.
Appendix 3 Trial governance considerations	The duration of retaining records and documents, pertaining to the conduct of the trial has been changed from "15 years" to "25 years"	Changed according to EU CTR requirement.
Appendix 4 Adverse events: definitions and procedures for recording, evaluate, follow-up, and reporting	Under assessment in case of suspicion of hypersensitivity reaction the following text has been changed from	Correction of error.

Section # and name	Description of change	Brief rationale
	“To assist in the diagnostic evaluation of a suspected severe immediate systemic hypersensitivity reaction (e.g. anaphylaxis), it is recommended to draw a blood sample for measurement of tryptase (total and/or mature tryptase, local assessment) within 3 hours of onset of the hypersensitivity reaction, and only if this is achieved, an additional follow-up tryptase sample should be drawn 2 weeks after the event in order to assess whether tryptase levels were increased at the time of the hypersensitivity event. A blood sample for assessment of anti-semaglutide IgE antibodies should also be drawn 2 weeks after the event and sent to central laboratory (see attachment I). Tryptase concentrations, if available, should be included in the specific event form when reporting the AE.” to “To assist in the diagnostic evaluation of a suspected severe immediate systemic hypersensitivity reaction to the trial product (e.g. anaphylaxis), it is recommended to draw a blood sample for measurement of tryptase (total and/or mature tryptase, local assessment must be performed at a local laboratory) as soon as possible (0-3 hours) after the onset of the hypersensitivity reaction. Only if this sample is taken within 3 hours after onset, an additional follow-up tryptase sample should be drawn 2-4 weeks after the event in order to assess whether tryptase levels were increased at the time of the hypersensitivity event. A blood sample for assessment of anti-semaglutide binding antibodies and anti-semaglutide IgE antibodies should also be drawn as soon as possible after the onset of the hypersensitivity reaction and again 2-4 weeks after the event and sent to central laboratory (see attachment I). The tryptase, anti-semaglutide binding antibodies and anti-semaglutide IgE samples can be taken at the same sampling occasions. If it was not possible to obtain a tryptase sample within 3 hours after onset of the reaction, the anti-semaglutide binding antibodies and anti-semaglutide IgE samples should be still taken (as soon as possible and again 2-4 weeks after the event). Tryptase concentrations, if available, should be included in the specific event form when reporting the AE.”	
Appendix 4 Adverse events: definitions and procedures for recording, evaluate, follow-up, and reporting	Text changed from “(e.g. severe hypersensitivity reactions)” to “(e.g. severe systemic hypersensitivity reactions)”.	For clarification
Appendix 12 Country specific requirements, Portugal	Text added: “Portugal A monthly pregnancy test is mandatory for female subjects of childbearing potential. As this request may conflict with the planned onsite visits, home urine pregnancy test can be performed at home monthly and reported on the next on-site visit or in the following phone visit in the months were on site visits are not scheduled. Trial staff will be trained on this requirement at the Site Initiation Visits in order to instruct patients accordingly.”	Changed according to requirements from Portuguese National Health Authorities.

Protocol version 3 (25 February 2021)

This amendment is considered to be non-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 Union¹, because it neither significantly impacts the safety nor physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for preparing protocol, Version 3:

The overall rationale for the changes implemented in the amended protocol is to address comments received from an independent Belgian Ethics Committee.

Section # and name	Description of change	Brief rationale
Appendix 12 Country-specific requirements, Belgium	Use of concomitant medication and rescue treatment has been clarified. Reference to Country-specific requirements (Appendix 12) have been added in the relevant protocol sections (Section 7.7 and Section 7.7.2).	See overall rationale
Appendix 12 Country-specific requirements, Belgium	It has been clarified that records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 25 years after end of trial. Reference to Country-specific requirements (Appendix 12) has been added in the relevant protocol section (Appendix 3).	See overall rationale

Protocol version 2, including version 1: (27 November 2020), United Kingdom

Overall rationale for preparing protocol, version 2:

The overall rationale for the changes implemented in the amended protocol is to address comments received from the Medicines & Healthcare products Regulatory Agency (MHRA).

Section # and name	Description of change	Brief rationale
Appendix 12 Country-specific requirements United Kingdom	Section 6.2 Exclusion criterion # 15 amended: Past basal and squamous cell skin cancer and any carcinoma in-situ is only allowed if it has been treated and cured.	See overall rationale
Appendix 12 Country-specific requirements United Kingdom	Section 6.2 Exclusion criterion # 5 amended: Any disorder e.g. uncontrolled thyroid disease, which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol.	See overall rationale
Appendix 12 Country-specific requirements United Kingdom	Contraception must continue by women of childbearing potential for at least 2 months after discontinuing treatment.	See overall rationale
Appendix 12 Country-specific requirements United Kingdom	A monthly pregnancy test is mandatory for female subjects of childbearing potential	See overall rationale
Appendix 12 Country-specific requirements United Kingdom	Use of concomitant medication and management of potential interactions should be performed in line with the approved Rybelsus SmPC section 4.5 (https://www.medicines.org.uk/emc/product/11507/smpc#gref)	See overall rationale
Appendix 12 Country-specific requirements United Kingdom	If clinically indicated, eye examination, ECG and any other safety monitoring assessment may be conducted during the treatment period at the discretion of the investigator.	See overall rationale
Appendix 12 Country-specific requirements United Kingdom	For clarification in section 9.2.6. If the hypoglycaemic episode fulfils the criteria of an SAE, then the event must be recorded and reported as an SAE.	See overall rationale