Cover Page for Protocol

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Protocol

Protocol Title:
Investigation of once-weekly semaglutide s.c. dose-response in patients with type 2 diabetes and overweight – a participant- and investigator-blinded and sponsor open-label study

Substance name: Semaglutide

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Protocol amendment summary of changes table

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Protocol version 3.0 (03 February 2023)

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 Union[1], because it neither significantly impacts the safety nor physical/mental integrity of subjects nor the scientific value of the study.

Overall rationale for preparing protocol, version 3.0:

The overall rationale for the changes implemented in the amended protocol is to include potential interim analyses in the study to get an early understanding of the safety, efficacy, and PK of higher doses of semaglutide s.c.

Section # and name	Description of change	Brief rationale
Section 4.3 Justification for dose	Nonclinical text related to drug, dose, and results is added	To explain why we disregard the monkey NOAEL related to cardiac safety for safety assessment
Section 6.1 Study intervention(s) administered	Footnote is added in Table 6-3 for NovoPen®4	To inform that NovoPen®4 is used outside approval
Section 8.4.1 Pharmacokinetics	Added word interim analyses	To align with section 9.4
Section 9.3.2.1 Primary estimand	Standard deviations is changed to standard errors	To correct typo error
Section 9.3.6 Other analyses	Added text related to interim analyses	To align with section 9.4
Section 9.4 Interim analysis	Added information on interim analysis with time points that may be conducted during the study	To include potential interim analyses in the study to get an early understanding of the safety, efficacy, and PK of higher doses of semaglutide s.c.
Section 10.2 Appendix 2: Clinical laboratory tests	Table 10-3 footnote text is updated to include interim analyses text	To align with section 9.4

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Protocol attachment I Global list of key staff and relevant departments and suppliers

Protocol attachment II Country list of key staff and relevant departments.

1 Protocol summary

1.1 Synopsis

This is an interventional, multi-centre, parallel-group, randomised, placebo-controlled, participant- and investigator-blinded within dose level, sponsor open-label, dose-response study of once-weekly subcutaneously administered semaglutide in patients with T2D and overweight as an add-on to a stable dose of metformin.

Rationale:

Data suggests that patients can achieve additional HbA_{1c} reduction and body weight loss of higher doses of once-weekly semaglutide s.c. without a significant impact on tolerability. This new information, and the accumulation of experience with semaglutide s.c., justifies characterisation of the dose-response curve, including higher doses than those previously investigated.

Consequently, this clinical study is designed to characterise the dose-response curve of once-weekly semaglutide s.c. up to 16 mg for change in HbA_{1c} from baseline to week 40 in patients with T2D and a BMI $\geq$ 27 kg/m^2 as an add-on to a stable dose of metformin.

Objectives, endpoints and estimand(s):

Objectives	**Endpoints**		
Primary	Title	Time frame	Unit
To characterise the dose-response curve of once-weekly semaglutide s.c. for change in HbA_{1c} from baseline to week 40 in patients with T2D and BMI $\geq$ 27 kg/m^2 as an add-on to a stable dose of metformin	Primary		
	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 40)	%-point
Secondary	Title	Time frame	Unit
To characterise the dose-response curve of once-weekly semaglutide s.c. for change in body weight from baseline to week 40 in patients with T2D and BMI $\geq$ 27 kg/m^2 as an add-on to a stable dose of metformin	Confirmatory		
	Change in body weight	From baseline (week 0) to end of treatment (week 40)	kg
To characterise the dose-response curve of once-weekly semaglutide s.c. for safety and tolerability from baseline to week 49 in patients with T2D and BMI $\geq$ 27 kg/m^2 as an add-on to a stable dose of metformin	Supportive		
	Number of treatment-emergent adverse events (TEAEs)	From baseline (week 0) to end of study (week 49)	Count of events
	Number of treatment-emergent severe hypoglycaemic episodes	From baseline (week 0) to end of study (week 49)	Count of events

Estimands:

For the primary objective, a primary estimand and an additional estimand are defined. Two intercurrent events were identified:

- Premature discontinuation of randomised treatment
- Initiation of rescue medication

The primary estimand addresses the main question of interest: What is the dose-response curve of once-weekly semaglutide s.c./pooled placebo for change in HbA_{1c} (%-point) from baseline to week 40 in patients with T2D and BMI $\geq$ 27 kg/m^2, as an add-on to a stable dose of metformin regardless of premature discontinuation of randomised treatment and initiation of recuse medication? Notably, in the treatment regimen evaluated, participants who cannot tolerate the received dose will have treatment discontinued.

The additional estimand addresses an additional question of interest: What is the dose-response curve of once-weekly semaglutide s.c./pooled placebo for change in HbA_{1c} (%-point) from baseline to week 40 in patients with T2D and BMI $\geq$ 27 kg/m^2, as an add-on to a stable dose of metformin, if all participants had remained on randomised treatment without initiation of rescue medication? Notably, in the treatment regimen evaluated, participants who cannot tolerate the received dose will have treatment discontinued.

Overall design:

The study consists of an up to 3-week screening period followed by a 40-week intervention period and a 9-week follow-up period. The intervention period includes 12-24 weeks dose escalation followed by 16-28 weeks on maintenance dose.

Study intervention groups and duration:

For each participant, the maximum intervention and study duration is 40 weeks and 52 weeks, respectively.

The following investigational medicinal products (IMP) are used in the study:

- Semaglutide [redacted] mg/mL
- Semaglutide [redacted] placebo

The IMPs will be administered subcutaneously with NovoPen®4 (medical device used outside approval).

Following the screening period, eligible participants will be randomised in a 3:1:3:1:3:1 ratio to receive semaglutide s.c. (2 mg, 8 mg, 16 mg) or matching placebo. Randomisation will be stratified according to HbA_{1c} at screening (<8.5%/≥8.5%).

Number of participants:

240 participants will be assigned to randomised treatment.

Participant characteristics:

Key inclusion criteria:

- Male or female.
- Aged 18-64 years (both inclusive) at the time of signing informed consent.
- Diagnosed with type 2 diabetes mellitus ≥ 180 days prior to the day of screening.
- HbA_{1c} of 7.0 – 10.5% (53 – 91 mmol/mol) (both inclusive).
- BMI ≥ 27.0 kg/m^2.
- Stable daily dose(s) ≥ 90 days prior to the day of screening of any metformin formulations.

Key exclusion criteria:

- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days before screening. However, short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed, as is prior insulin treatment for gestational diabetes.
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to day of screening or in the period between screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.
- Renal impairment measured as estimated glomerular filtration rate (eGFR) value of <30 mL/min/1.73 m^2 at screening.

Efficacy and safety data will be collected at regular intervals throughout the study.

Data monitoring committee: No

1.2 Flowchart

	Screening	Randomisation	Treatment period												End of treatment	Follow-up period	
																	End of study
Visit	V1	V2	V3	V4	V5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	P16	V17
Timing of Visit (Weeks)	-2	0	4	8	12	16	17	20	21	24	25	28	32	36	40	45	49
Visit Window (Days)	±7	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0/7	0/7
Informed Consent and Demography [a] (10.1.3)	X																
Childbearing Potential (10.4)	X																
Tobacco Use (5.3.2)	X																
Eligibility Criteria (5.1,5.2)	X	X															
Randomisation and Randomisation Criteria (5.5)		X															
Concomitant Medication 6.8)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Discontinuation Criteria (7.1)		X	X	X	X	X	X	X	X	X	X	X	X	X			
Medical History/Concomitant Illness (8.2)	X	X															
Pregnancy Test (8.2.7,8.3.5,10.4)	X	X													X		X
Body Weight (8.1.1)	X	X	X	X	X	X		X		X		X	X	X	X		
Height (8.2.1)	X																
Waist Circumference (8.1.2)	X	X													X		
Vital Signs (8.2.2)	X	X	X	X	X	X		X		X		X	X	X	X		X
Electrocardiogram (8.2.4)		X								X		X			X		
Eye Examination [b] (8.2.3)	X														X		
Physical Examination (8.2.1)	X														X		
Adverse Event (8.3,10.3)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic Episodes (10.8)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical Complaint (8.3.6,10.5)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Attend Visit Fasting (5.3.1)		X	X	X	X	X		X		X					X		X[c]

	Screening	Randomisation	Treatment period												End of treatment	Follow-up period	
																	End of study
Visit	V1	V2	V3	V4	V5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	P16	V17
Timing of Visit (Weeks)	-2	0	4	8	12	16	17	20	21	24	25	28	32	36	40	45	49
Visit Window (Days)	±7	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0/7	0/7
PK Sampling (8.4.1 10.2)			X	X		X		X		X		X		X	X		X
Laboratory Assessments (8.6, 10.2)	X	X	X	X	X	X		X		X		X	X	X	X		X
Antibody sampling (8.7, 10.2)		X	X	X		X				X					X		X
Biosamples for Future Analysis (10.2, 10.7)		X	X	X	X	X		X		X		X			X		
Spirometry [d] (8.1.3)		X													X		
Drug Dispensing (6.2)		X		X		X				X							
Training in Trial Product, Pen-handling (6.1)		X				X				X							
Collect, review and transcribe diaries			X	X	X	X		X		X		X	X	X	X		X

a: Demography consists of date of birth, sex, ethnicity and race (according to local regulation). Race and ethnicity must be self-reported by the participant.

b: Intra ocular pressure is part of the eye examination and can only be excluded if not feasible for the clinical site.

c: Fasting is defined as at least 2 hours prior to the visit without food or liquid, except for water (see Section 5.3.1).

d: Spirometry can only be excluded if the clinical site does not have the capability to perform the assessment.

2 Introduction

Semaglutide is a potent glucagon-like peptide-1 receptor agonist (GLP-1 RA) with a high degree of homology to human GLP-1. GLP-1 RAs are recommended for the treatment of patients with type 2 diabetes (T2D) with inadequate glycaemic control. Furthermore, patients on GLP-1 RAs can benefit from weight loss.[2] Guidelines have recently been updated to recommend GLP-1 RAs for patients with T2D and high cardiovascular (CV) risk, established CV disease, or chronic kidney disease (CKD).[2]

Semaglutide s.c. is approved globally (Ozempic® 0.5 mg and 1 mg, NN9535, based on the global clinical programme SUSTAIN) for once-weekly administration as an adjunct to diet and exercise to improve glycaemic control in adults with T2D. In addition, a higher maintenance dose of Ozempic® 2 mg is approved in US, EU, Canada and Switzerland based on a phase 3b study (SUSTAIN FORTE, NN9535-4506) comparing once-weekly semaglutide s.c. 2 mg and 1 mg in patients with T2D.

Semaglutide s.c. has also recently been approved in US, EU, and UK for once-weekly administration for chronic weight management (Wegovy® 2.4 mg, NN9536, based on the global clinical programme STEP) in people with obesity or overweight and with at least one weight-related comorbid condition (e.g. hypertension, T2D, or dyslipidaemia).

Furthermore, semaglutide is approved for once-daily oral administration (Rybelsus® 3, 7 and 14 mg, NN9924, based on the global clinical programme PIONEER) in multiple regions as an adjunct to diet and exercise to improve glycaemic control in adults with T2D.

2.1 Study rationale

Additional HbA_{1c} reduction and body weight loss have been demonstrated for semaglutide s.c. doses exceeding the highest once-weekly dose investigated in the original dose-finding study (NN9535-1821).[3] Furthermore, several phase 3 studies have demonstrated that implementing a prolonged dose escalation period can mitigate tolerability issues in doses up to 2 mg and 2.4 mg for the indication of T2D and chronic weight management, respectively.

In brief, available data (presented in section 2.2) suggests that patients can achieve additional efficacy of higher doses of once-weekly semaglutide s.c. without a significant impact on tolerability. This new information, and the accumulation of experience with semaglutide s.c., justifies characterisation of the dose-response curve, including higher doses than those previously investigated.

This clinical study is designed to characterise the dose-response curve of once-weekly semaglutide s.c. up to 16 mg for change in HbA_{1c} from baseline to week 40 in patients with T2D and a BMI ≥ 27 kg/m^2 as an add-on to a stable dose of metformin.

2.2 Background

Daily doses of semaglutide s.c. corresponding to weekly equivalents of 0.35 mg – 2.1 mg have demonstrated dose-dependent improvements in both glycaemic control and body weight loss for the indication of T2D.[4] The highest doses investigated were generally well-tolerated as reflected by the low proportion of participants (<5%) discontinuing treatment. Further, in SUSTAIN FORTE, a

phase 3b study, additional reduction of HbA_{1c} and body weight loss and similar safety profile were confirmed for semaglutide s.c. 2 mg as compared to semaglutide s.c. 1 mg.[5] Semaglutide s.c. 2 mg was comparable to 1 mg with respect to reported serious adverse events (SAE), and, in line with the safety and tolerability profile of the GLP-1 RA drug class.

In STEP 2, a phase 3a study of semaglutide s.c. for the indication of chronic weight management additional glycaemic control and body weight loss in adults with overweight or obesity, and T2D was demonstrated with semaglutide s.c. 2.4 mg compared to 1 mg. The reported rate of gastrointestinal adverse events was slightly higher in the semaglutide 2.4 mg group (4.2%) versus 1 mg group (3.5%), but discontinuations due to adverse events were low and similar in both groups.[6]

To ensure that both body weight management and intensified glycaemic control is indicated, the study population will consist of patients with inadequately controlled T2D on a stable dose of metformin and BMI ≥ 27 kg/m^2.

2.3 Benefit-risk assessment

The main benefits and risks related to participation in the study are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of semaglutide s.c. and NovoPen®4 may be found in the investigator's brochures[7, 8] (and any updates hereof), the Summary of Product Characteristics[9] and prescribing information[10] for Ozempic®.

2.3.1 Risk assessment

Table 2-1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention (semaglutide)		
Gastrointestinal disorders	Consistent with other GLP-1 RAs, the most frequent adverse events (AEs) with semaglutide are gastrointestinal (such as nausea, vomiting and diarrhoea). In general, these reactions are mild or moderate in severity, of short duration, and dose dependent. In participants treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating participants with impaired renal function as it may cause a deterioration of renal function.	Clinical studies have shown that a low starting dose and gradual dose escalation mitigates the risk of developing gastrointestinal symptoms. Participants with GI symptoms are recommended to drink plenty of fluids to avoid volume depletion.
Hypoglycemia	There is a low risk of hypoglycaemic episodes when semaglutide is used as monotherapy. Participants treated with semaglutide in combination with sulfonylurea or insulin may have an increased risk of hypoglycaemia.	The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin (if used as rescue medication) when initiating treatment with semaglutide.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Diabetic retinopathy complications	In a 2-year clinical study with s.c. semaglutide (NN9535-3744) involving 3,297 participants with T2D, high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose, EAC-confirmed events of diabetic retinopathy complications occurred in more participants treated with s.c. semaglutide (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among participants with a history of diabetic retinopathy at baseline. In the participants who did not have a documented history of diabetic retinopathy the number of events were similar for s.c. semaglutide and placebo. In the other clinical studies up to 1 year involving 4,807 participants with T2D, AEs related to diabetic retinopathy were reported in similar proportions of participants treated with s.c. semaglutide (1.7%) and comparators (2.0%).	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. These participants should be monitored closely and treated according to clinical guidelines.
Allergic reactions	As with all protein-based pharmaceuticals, treatment with semaglutide may evoke allergic reactions, including serious allergic reactions such as angioedema and anaphylactic reactions.	As a precaution, participants with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this study. In addition, participants will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the study product occurs.
Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 RAs. In the completed phase 3 studies with semaglutide s.c. and oral semaglutide, both the event rate and the proportion of participants experiencing confirmed pancreatitis were similar with semaglutide and comparator. Few events were confirmed; the events occurred throughout the study periods and the overall rates were similar to the rates reported in background populations.	Participants 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.
Neoplasms (malignant and non-malignant)	Patients with T2D, as well as patients with overweight or obesity, have an increased risk of certain types of cancer. There is no evidence from clinical studies that GLP-1-based therapies increase the risk of neoplasms. However, in the semaglutide s.c. as well as oral semaglutide phase 3a studies, the	Participants with presence or history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this study. Basal and squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer is allowed.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	proportion of participants with neoplasms (malignant and non-malignant) were slightly higher with semaglutide than with comparator. The number of participants exposed to semaglutide s.c. or oral semaglutide for a longer period is considered insufficient for a thorough assessment of the risk of neoplasms.	
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 studies or post-marketing data that GLP-1 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. There is no indication of an increased relative risk in the semaglutide treatment groups vs. comparator, including placebo. The rates of EAC-confirmed events of pancreatic cancer were consistently low across studies.	Participants with presence or history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this study.
Medullary thyroid cancer	Thyroid C-cell tumours were seen in mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 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 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 the clinical relevance of the findings is considered to be low.	To mitigate this risk, participants with a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 are excluded from clinical studies with semaglutide.
Study procedures		
Discomfort related to invasive study procedure	Discomfort may occur around the site of blood sampling.	Experienced and properly trained site personnel will ensure minimisation of discomfort caused by study procedures.
Risk of COVID-19 infection in relation to participation in the study	Participants may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the country at the time of study conduct.	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 minimise the risk as much as possible, the following measures have been taken:

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
		• Cautious participant recruitment planning ensures controlled participants 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. • On-site visits will be well-prepared and as short as possible. Physical contact between participants and site staff will be limited to the extent possible, and protective measures will be implemented (e.g. use of masks, sanitizers, no aerosol-generating procedures etc. according to the local practice). • Appendix 9 (Section 10.9) includes mitigations that can be implemented to ensure participant safety and data integrity in case a major emergency (COVID-19 outbreak) leads to lock-down of sites which affects the ability to perform study-related procedures.
Other		
Pregnancy and fertility	Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women.	Semaglutide should not be used during pregnancy. Women of childbearing potential are required to use highly effective contraceptive methods when participating in this study (Appendix 4, Table 10-6). If a participant wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued (please refer to Section 8.3.5 for further guidance). The effect of semaglutide on fertility in humans is unknown.

Risk assessment has been conducted for NovoPen®4 for semaglutide s.c. in accordance with ISO 14971:2019. A study-specific device risk assessment has been performed to ensure safe and accurate handling and dosing of semaglutide when using NovoPen®4 in patients with T2D and overweight.

No additional risks have been associated with using NovoPen®4 according to the clinical procedures specified in this protocol, compared with using NovoPen®4 within its approved intended use and indication for use.[8] The use of NovoPen®4 in this study is therefore considered to be of non-significant risk.

2.3.2 Benefit assessment

All participants will receive thorough medical attention and every randomised participant is expected to benefit from intensified glycaemic control as measured by HbA_{1c}, and in accordance with international guidelines on T2D management, semaglutide s.c. will be given as an add-on to metformin. Rescue medication will be prescribed for participants not achieving sufficient glycaemic control regardless of randomised treatment.

Investigational medicinal products (IMPs) and auxiliary supplies, including non-investigational medical device used outside approval, will be provided by Novo Nordisk A/S (please see Section 6.1 for more details).

2.3.3 Overall benefit-risk conclusion

Precautions have been implemented in the design and planned conduct of the study to minimise the risks and inconveniences of participation in the study. The safety profile for semaglutide generated from the clinical and non-clinical development programmes has not revealed any safety issues that would prohibit investigation of up to 16 mg semaglutide s.c. once-weekly.

In conclusion, the potential risks identified in association with semaglutide s.c. are considered acceptable in view of the anticipated benefits that may be afforded to patients with T2D.

3 Objectives, endpoints and estimands

3.1 Objectives and endpoints

The objectives and endpoints are presented in Table 3-1.

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	Title	Time frame	Unit
To characterise the dose-response curve of once-weekly semaglutide s.c. for change in HbA_{1c} from baseline to week 40 in patients with T2D and BMI $\geq$ 27 kg/m^2 as an add-on to a stable dose of metformin	Primary		
	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 40)	%-point
Secondary	Title	Time frame	Unit
To characterise the dose-response curve of once-weekly semaglutide s.c. for change in body weight from baseline to week 40 in patients with T2D and BMI $\geq$ 27 kg/m^2 as an add-on to a stable dose of metformin	Confirmatory		
	Change in body weight	From baseline (week 0) to end of treatment (week 40)	kg
To characterise the dose-response curve of once-weekly semaglutide s.c. for safety and tolerability from baseline to week 49 in patients with T2D and BMI $\geq$ 27 kg/m^2 as an add-on to a stable dose of metformin	Supportive		
	Number of treatment-emergent adverse events (TEAEs)	From baseline (week 0) to end of study (week 49)	Count of events
	Number of treatment-emergent severe hypoglycaemic episodes	From baseline (week 0) to end of study (week 49)	Count of events

3.2 Estimands

The estimands and their rationale are described in detail for each of the two primary and secondary objectives in Sections 3.2.1 and 3.2.2. Two intercurrent events were identified:

- Premature discontinuation of randomised treatment
- Initiation of rescue medication (see Section 6.8.1)

3.2.1 Addressing the primary objective

3.2.1.1 Primary estimand

The primary estimand addresses the main question of interest: What is the dose-response curve of once-weekly semaglutide s.c/pooled placebo for change in HbA_{1c} (%-point) from baseline to week 40 in patients with T2D and BMI $\geq$ 27 kg/m^2, as an add-on to a stable dose of metformin regardless of premature discontinuation of randomised treatment and initiation of recuse medication? Notably, in the treatment regimen evaluated, participants who cannot tolerate the received dose will have treatment discontinued.

The primary estimand is defined by the following five attributes:

- Population: Patients with T2D and BMI ≥ 27 kg/m^2.
- Endpoint: Change from baseline to week 40 in HbA_{1c} (%-point).
- Treatment condition: Randomised treatment as add-on to a stable dose of metformin, with or without premature discontinuation of treatment and initiation of rescue medication.
- Remaining intercurrent events: No further intercurrent events are identified. The two intercurrent events described as part of the treatment condition will all be handled by a treatment policy strategy.
- Population-level summary: Difference in mean changes from baseline.

Rationale for estimand: This estimand quantifies the difference in treatment effects between the different treatment regimens that can be expected in clinical practice. It reflects the clinical practice, under which the treatment regimens are to be applied.

3.2.1.2 Additional estimand

The additional estimand addresses an additional question of interest: What is the dose-response curve of once-weekly semaglutide s.c/pooled placebo for change in HbA_{1c} (%-point) from baseline to week 40 in patients with T2D and BMI ≥ 27 kg/m^2, as an add-on to a stable dose of metformin, if all participants had remained on randomised treatment without initiation of rescue medication? Notably, in the treatment regimen evaluated, participants who cannot tolerate the received dose will have treatment discontinued.

The estimand attributes: population, endpoint, and population-level summary are the same as for the primary estimand. The remaining attributes are:

- Treatment condition: Randomised treatment as add-on to a stable dose of metformin, without premature discontinuation of treatment and initiation of rescue medication.
- Remaining intercurrent events: No further intercurrent events are identified. The two intercurrent events described as part of the treatment condition will all be handled by a hypothetical strategy.

Rationale for estimand: This estimand quantifies the achievable difference in treatment effects between the different treatment regimens. It reflects the drug efficacy.

3.2.2 Addressing the secondary objective

The relevant endpoint is the secondary confirmatory endpoint “change from baseline to week 40 in body weight (kg)”.

Change in body weight - primary estimand

The main clinical question of interest for this secondary confirmatory objective is similar to the primary estimand for the primary objective.

The estimand attributes: population, treatment condition, remaining intercurrent events, and population-level summary are the same as for the primary estimand for the primary objective. The remaining estimand attribute is:

- Endpoint: Change from baseline to week 40 in body weight (kg).

Rationale for estimand: The rationale is the same as for the primary estimand for the primary objective.

Change in body weight – additional estimand

The additional clinical question of interest for this secondary confirmatory objective is similar to the additional estimand for the primary objective.

The estimand attributes: population, treatment condition, remaining intercurrent events, and population-level summary are the same as for the additional estimand for the primary objective. The remaining estimand attribute is:

- Endpoint: Change from baseline to week 40 in body weight (kg).

Rationale for estimand: The rationale is the same as for the additional estimand for the primary objective.

4 Study design

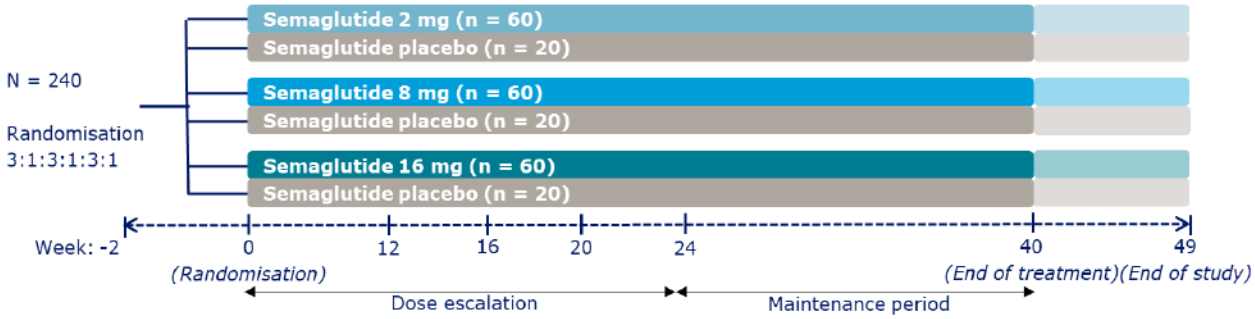
4.1 Overall design

This is an interventional, multi-centre, parallel-group, randomised, placebo-controlled, participant- and investigator-blinded within dose level, sponsor open-label, dose-response study of once-weekly subcutaneously administered semaglutide in patients with T2D and overweight with a baseline HbA_{1c} of 7.0–10.5% and as an add-on to a stable dose of metformin (Figure 4-1).

A total of 240 participants will be randomised in a 3:1:3:1:3:1 ratio to receive semaglutide s.c. (2 mg, 8 mg, 16 mg) or matching placebo. All participants are to escalate to the randomised target maintenance dose according to the dose escalation outlined in Table 6-2.

Randomisation will be stratified according to HbA_{1c} at screening (<8.5%/≥8.5%).

Figure 4-1 Study design



The study consists of:

- an up to 3-week screening period
- a dose escalation period of 12-24 weeks (see Table 6-2)
- a maintenance period of 16-28 weeks (see Table 6-2)
- a 9-week follow-up period

For each participant, the maximum intervention and study duration is 40 weeks and 52 weeks, respectively.

The number of injections, and injection volume, ranges from one injection of 210 µl to 3 injections of 560 µl between the target dose of the three dose levels (see Table 6-2). For each dose level, the active treatment arm and the corresponding volume-matched placebo arm will be blinded towards each other. To minimise the burden of study activity (by limiting the number of injections) double-blinding will be applied between placebo and semaglutide within each dose level, but not between the three dose levels.

In STEP 8[11] a differential change from baseline was observed for weight loss between placebo once daily and placebo once-weekly. However, there is no available data suggesting that once-weekly administration with a variable number of injections (i.e., 1 for placebo 2 mg, 2 for placebo 8 mg and 3 for placebo 16 mg) would drive a differentiated placebo response.

4.2 Scientific rationale for study design

This clinical study is designed to characterise the dose-response curve for once-weekly semaglutide s.c. including doses beyond what has previously been investigated. The 40-week study duration is considered sufficient to evaluate tolerability, safety, and enable differentiation between groups on efficacy measured by the primary endpoint, change in HbA_{1c}.

The sponsor open-label design permits access to ongoing comparative safety data to ensure continuous monitoring as an additional precaution. Participant- and investigator-blinding within dose level, in addition to randomisation and placebo-control, is implemented to minimise bias. This approach is considered justified striking the balance between participant safety and data integrity for the objective primary endpoint.

The unbalanced (3:1) randomisation ensures relative more observations on active treatment to inform the dose-response curve. The placebo group will enable differentiation of response related to semaglutide s.c. from response due to other factors such as study participation and intensified medical attention.

The dose of semaglutide s.c. (or volume-matched placebo within dose levels) will be doubled every fourth week in line with the approved posology for Ozempic® until the highest dose evaluated (16 mg) is initiated at week 24 (see Table 6-2).

The 9-week follow-up period (corresponding to roughly 9 times $t_{1/2}$[10]) is implemented to allow wash-out of 16 mg semaglutide before post-treatment safety evaluation and to avoid drug interference in the anti-drug antibody assays.

4.3 Justification for dose

The starting dose in this study will be 0.29 mg as this is the dose closest to the approved starting dose of semaglutide s.c. for the indication of T2D of 0.25 mg which can be injected using the NovoPen®4 for administration of semaglutide [redacted] mg/mL (see Table 6-2). Although the approved starting dose of semaglutide s.c. is 0.25 mg, a single dose of 0.5 mg has been administrated in previous clinical studies with acceptable tolerability.

The semaglutide s.c. doses of 2 mg, 8 mg, and 16 mg is chosen to allow differentiation of efficacy and safety including tolerability between doses. Using an established pharmacokinetic (PK) model for semaglutide s.c. and assuming dose-proportionality, the predicted C_{avg} for 8 mg and 16 mg are 217 nmol/L (90% range: 157 – 293 nmol/L) and 434 nmol/L (90% range: 313 – 587 nmol/L), respectively.

The predicted plasma exposure at 16 mg/week is approximately 2-fold lower than exposures at the no observed adverse effect levels (NOAEL) in chronic toxicity study in rats (C_{avg}: 754 nmol/L). In monkeys, the NOAEL in the chronic toxicity study was determined by an ECG abnormality of the heart (left bundle branch block like recording; LBBB) observed at the highest dose (0.36 mg/kg twice weekly; C_{avg}: 760 nmol/L) in one out of eight female monkeys. Cardiac histopathology was normal in the animal. Overall, based on the nonclinical data and the large amount of available clinical safety data for semaglutide, including thorough evaluations in the cardiovascular outcomes study (SUSTAIN 6, NN9535-3744), the LBBB observation in one monkey is not considered to

affect the safety profile of semaglutide and has therefore been disregarded in the present safety assessment. Accordingly, the relevant animal to human exposure ratio at 16 mg/week is 754 nmol/L/434 nmol/L = 1.7; i.e., the predicted human exposure at 16 mg is approximately 2-fold lower than the nonclinical exposures.

In a PK study of different formulations of oral semaglutide (NN9924-4633), 49 participants achieved exposure levels higher than the 217 nmol/L predicted C_{avg} for the 8 mg semaglutide s.c. dose and 8 participants achieved exposure levels higher than the 434 nmol/L predicted C_{avg} for the 16 mg semaglutide s.c. dose. The AE profile of the 57 participants was similar to the expected safety profile for GLP-1 RAs, and there was no correlation between exposure levels and AE reporting (data on file). The proportion of participants discontinuing trial product due to AEs was approximately 17%. In this current study, dose escalation duration is doubled to mitigate GI AEs.

In brief, non-clinical and clinical data suggests that investigation of up to 16 mg semaglutide s.c. is both tolerable and safe and may provide additional benefit for patients with T2D and overweight.

4.4 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit.

The primary endpoint is evaluated at visit 15 (week 40). The primary completion date (PCD) is defined as the date of visit 15 (week 40) on which the last participant in the clinical study has an assessment for the primary endpoint. If the last participant is withdrawn early, the PCD is considered the date when the last participant would have completed visit 15.

5 Study population

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

Pre-screening is defined as review of the patient medical records, including handing out participant information, as well as database review. Any pre-screening activities must be documented on site by the investigator.

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Male or female.
3. Aged 18-64 years (both inclusive) at the time of signing informed consent.
4. Diagnosed with type 2 diabetes mellitus ≥ 180 days prior to the day of screening.
5. HbA_{1c} of 7.0 – 10.5% (53 – 91 mmol/mol) (both inclusive).
6. BMI ≥ 27.0 kg/m^2.
7. Stable daily dose(s) ≥ 90 days prior to the day of screening of any metformin formulations.

Hungary: Please see Appendix 10 (Section 10.10) for country-specific requirements.

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

1. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days before screening. However, short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed, as is prior insulin treatment for gestational diabetes.
2. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).
3. Use of any medication with unknown or unspecified content within 90 days before screening.
4. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to day of screening or in the period between screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.
5. Renal impairment measured as estimated glomerular filtration rate (eGFR) value of <30 mL/min/1.73 m^2 at screening.
6. Myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within 180 days before screening.
7. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.
8. Planned coronary, carotid or peripheral artery revascularisation.
9. Presence or history of pancreatitis (acute or chronic).

10. Presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in situ prostate cancer) within 5 years before screening.
11. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma*.
12. Known or suspected hypersensitivity to study intervention(s) or related products.
13. Previous participation in this study. Participation is defined as signed informed consent.
14. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using highly effective contraceptive method, as defined in Appendix 4 (Section 10.4).
15. Participation (i.e., signed informed consent) in any interventional, clinical study within 90 days before screening.
16. Receipt of an approved COVID-19 vaccine within 14 days prior to screening or planned COVID-19 vaccination between screening and randomisation.
17. Any disorder, unwillingness or inability, which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.
18. Anticipated change in lifestyle (e.g., eating, exercise or sleeping pattern) during the study.

*As declared by the participant or in the medical records.

5.3 Lifestyle considerations

5.3.1 Meals and dietary restrictions

To ensure alignment regarding performance of assessments across participants and study sites, the below restrictions apply.

Participants must attend visits fasting according to the flowchart (Section 1.2).

- Fasting is defined as no food or liquid, except for water, for at least 6 hours prior to the visit.
- For the end of study visit (visit 17) fasting is defined as at least 2 hours prior to the visit without food or liquid, except for water.
- Any medication which should be taken with or after a meal should be withheld on the day of the visit until blood samples have been obtained.
- Assessments requiring participants to fast are listed in Appendix 2 (Section 10.2)

If a participant is not fasting as required, the participant should be called in for a new visit within the visit window to have the fasting procedures performed.

5.3.2 Caffeine, alcohol and tobacco

Participants should avoid caffeine and tobacco use for at least 30 minutes prior to measurement of vital signs (Section 8.2.2).

Tobacco use is defined as smoking at least one cigarette or equivalent daily.

5.3.3 Activity

Participants should avoid physical activity for at least 30 minutes prior to measurement of vital signs (Section 8.2.2).

5.4 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently eligible for participation according to the inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, and eligibility criteria.

A screen failure must be made in the system (Randomisation and Trial Supplies Management system (RTSM)/Interactive Web Response System (IWRS).

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

5.5 Randomisation criteria

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

1. No receipt of an approved COVID-19 vaccine between screening and randomisation.

6 Study intervention(s) and concomitant therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Trial product comprise investigational medicinal products (IMPs), including placebo and comparators, non-investigational medicinal products (NIMPs) and/or investigational medical devices.

6.1 Study intervention(s) administered

Table 6-1 provides an overview of the IMPs in the study. The doses and injection volumes of the IMPs to be administered in each study arm during dose escalation steps and the maintenance period are presented in Table 6-2.

Table 6-1 Investigational medicinal products

Intervention arm	Semaglutide	Semaglutide placebo
Intervention name	Semaglutide [redacted]	Semaglutide [redacted] placebo
Intervention type	IMP, test product	IMP, reference therapy
Pharmaceutical form	Solution for injection	Solution for injection
Route of administration	Subcutaneous	Subcutaneous
Medical device	The trial product will be administered with NovoPen®4 (medical device used outside approval[1]). Participants will be provided with DFU verbally and in writing.	The trial product will be administered with NovoPen®4 (medical device used outside approval[1]). Participants will be provided with DFU verbally and in writing.
Trial product strength	[redacted] mg/mL	Not applicable
Dose and dose frequency	Once-weekly For doses refer to Table 6-2	Once-weekly For doses refer to Table 6-2
Dosing instructions and administration	Dose to be administered with the NovoPen®4 in accordance with the DFU.	Dose to be administered with the NovoPen®4 in accordance with the DFU.
Sourcing	Manufactured and supplied by Novo Nordisk A/S	Manufactured and supplied by Novo Nordisk A/S
Packaging and labelling	• Labelled and packaged by Novo Nordisk A/S • Labelled in accordance with Annex 13,[12] local regulations and study requirements • Trial product will be provided in 3 mL cartridge	• Labelled and packaged by Novo Nordisk A/S • Labelled in accordance with Annex 13,[12] local regulations and study requirements • Trial product will be provided in 3 mL cartridge

Abbreviations: IMP = Investigational Medicinal Product, DFU = Directions for use.

[1]The medical device NovoPen®4 is used outside its approved intended use and/or indication for use but is not being assessed for device approval procedure (according to Article 82 of EU MDR2). Safety data collection and safety reporting are required for the medical device. Please see Section 8.3 for details on adverse events and other safety reporting, and Section 2.3.1 for information on study-specific device risk assessment.

Investigational medicinal products (IMP)

The IMPs are listed in Table 6-1.

Directions for use

The investigator must document that directions for use was given to the participant verbally and in writing as a directions for use (DFU) document at the first dispensing visit, and as specified in the flowchart (Section 1.2). The investigator should hand out dose reminder cards to the participants at all clinic visits as applicable per treatment arm.

Dosing instructions

Participants will be instructed to administer semaglutide/semaglutide placebo by subcutaneous injection in the abdomen, upper arm, or thigh once-weekly on the same day of the week throughout the study at a time that is convenient for the participant. If the dosing day coincides with a clinic visit the dose must be administered after blood samples have been obtained – this is not required for V5 and V13.

Administration of 2 mg, 8 mg and 16 mg semaglutide/semaglutide placebo doses requires 1, 2 and 3 injections, respectively. The 2nd and 3rd injection should be administered immediately after the 1st injection using a different site of injection, either within the same or a new body region, but at least 5 cm from the first injection site.

The required dose volume (corresponding to a number of increments on the pen as outlined in Table 6-2) for doses up to 4 mg must be administered from one cartridge and cannot be split across cartridges. It is only allowed to split the 8 mg and 16 mg doses across cartridges, as these two doses require more than one injection. Each injection, of 42 and 56 increments for the 8 mg and 16 mg dose, respectively, must be administered from the same cartridge. If the required increments cannot be administered with a partly used cartridge, a new and unused cartridge must be used for administration.

Dose escalation

Dose escalation of semaglutide should take place during the first 12, 20 and 24 weeks after randomisation for semaglutide s.c. 2 mg, 8 mg, and 16 mg, respectively as illustrated in Table 6-2.

Dose modification is not allowed. Participants should reach the randomised target maintenance dose following the specified dose-escalation. If the participant cannot tolerate the received dose (e.g. persistent severe nausea, vomiting or diarrhoea events) they will be discontinued from randomised treatment.

Table 6-2 Overview of dose escalation and maintenance dose

Randomised treatment		Dose escalation/maintenance						Maintenance
		4 weeks	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks	16 weeks
Semaglutide 2 mg	Dose	0.29 mg	0.58 mg	1.06 mg	2.02 mg			
	Increments on pen	3	6	11	21			
Semaglutide 8 mg	Dose	0.29 mg	0.58 mg	1.06 mg	2.02 mg	4.03 mg	8.06 mg	
	Increments on pen	3	6	11	21	42	2x 42	
Semaglutide 16 mg	Dose	0.29 mg	0.58 mg	1.06 mg	2.02 mg	4.03 mg	8.06 mg	16.13 mg
	Increments on pen	3	6	11	21	42	2x 42	3x 56

Each increment on the NovoPen®4 corresponds to 10 µl, e.g., 3 increments are 30 µl. With the concentration of the IMP and injection volumes that can be delivered with the NovoPen®4 for semaglutide [redacted] mg/mL, the target doses administered are 2.02 mg, 8.06 mg and 16.13 mg; however, the dose arms are referred to as 2 mg, 8 mg and 16 mg throughout the protocol.

Missed doses

If a single dose of randomised treatment is missed, it should be administered as soon as noticed, if the time until the next scheduled dose is at least 2 days (48 hours). If a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the participant should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week.

Non-investigational medicinal products (NIMP)

Anti-diabetic background medication (metformin) and rescue medication are considered NIMPs and will not be supplied by Novo Nordisk.

Auxiliary supplies including non-investigational medical device

The auxiliary supplies outlined in Table 6-3 will be provided by Novo Nordisk.

Table 6-3 Auxiliary supplies including non-investigational medical device

Item	Details
Directions for use (DFU)	DFU for NovoPen®4 will be handed out separately.
Blood glucose (BG) meter and related auxiliaries	A Precision Xtra BG meter will be handed out at the randomisation visit (V2). Participants will be instructed in how to use the BG meter and the instructions will be repeated during the study as needed.
NovoPen®4[a]	NovoPen®4 for s.c. administration of semaglutide and semaglutide placebo. NovoPen®4 has been packed and labelled specifically for the present study.
Needles	Needles for NovoPen®4. Details will be provided in the Trial Materials Manual (TMM). Only needles provided by Novo Nordisk and with a maximum length of 6 mm must be used for administration of IMP.

[a] NovoPen®4 is used outside approval.

6.2 Preparation, handling, storage and accountability

Only participants enrolled in the study may use IMP and only delegated site staff may supply IMP.

Each site will be supplied with sufficient IMP for the study on an ongoing basis according to recruitment and randomisation.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMP received, and that any discrepancies are reported and resolved before use of the IMP.

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 delegated site staff.

The investigator must inform Novo Nordisk immediately if any IMP has been stored outside specified conditions. The IMP must not be dispensed to any participant before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the Trial Materials Manual (TMM).

The investigator or designee is responsible for IMP accountability and record maintenance (i.e., receipt, accountability and final disposition records). Accountability must be performed at visit V4, V6, V10 and V15 at cartridge level returned either as used/partly used, unused or lost and recorded in the RTSM/IWRS. The medical device must be returned at the end of treatment visit (V15)

The investigator or designee must instruct the participant in what to return at next visit.

The investigator or designee must instruct the participant on how to manage the in-use time of the dispensed IMPs.

Destruction of IMP 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, if not otherwise agreed at the site selection.

All returned (used or un-used), expired or damaged IMPs and medical device (for technical complaint samples, see Appendix 5 [Section 10.5]) must be stored separately from non-allocated IMPs and medical devices. No temperature monitoring is required.

Non-allocated IMPs, including expired or damaged products, must be accounted for by the site and/or reconciled by the monitor, at the latest at closure of the site.

6.3 Measures to minimise bias: Randomisation and blinding

All participants will be screened and centrally randomised using RTSM/IWRS and assigned to the next available treatment according to the randomisation schedule. Randomised treatment will be allocated by the RTSM/IWRS and dispensed by the investigator at the study visits summarised in the flowchart.

At screening, each participant will be assigned a unique 6-digit Subject ID which will remain the same throughout the study. Each site will be assigned a 3-digit number and all Subject ID will start with the site number.

Eligible participants will be randomised in a 3:1:3:1:3:1 ratio to receive semaglutide s.c. (2 mg, 8 mg, 16 mg) or matching placebo.

Randomisation will be stratified according to HbA_{1c} at screening (<8.5%/≥8.5%).

The study is open to sponsor and blinded within dose level to participant and investigator. Participants and investigators are blinded to allocation of randomised treatment. Novo Nordisk personnel will have access to the allocation of randomised treatment throughout the study.

The RTSM/IWRS is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's randomised treatment is warranted. Participant safety must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Novo Nordisk prior to unblinding a participant's randomised treatment unless this could delay emergency treatment of the participant.

If a participant's randomised treatment is unblinded, Novo Nordisk (Global Safety department) must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation. The person breaking the blind must print the blind break confirmation notification generated by the RTSM/IWRS, sign and date the document. If RTSM/IWRS is not accessible at the time of blind break, the RTSM/IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

Participant will continue randomised treatment after unblinding, if there are no safety concerns as judged by the investigator.

The laboratory responsible for PK and antibody analysis will have access to the allocation of randomised treatment.

6.4 Study intervention compliance

Drug treatment compliance

Throughout the study, the investigator will remind the participants to follow the study procedures and requirements to encourage participant compliance.

When participants self-administer randomised treatment at home, compliance with administration of randomised treatment will be assessed, and the assessment documented in source documents at each visit where information is available. If any suspicion of non-compliance arises, the site must enter into a dialogue with the participant, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Accountability information; counting returned IMP
- Review of dosing diaries
- Collection of information for administration of randomised treatment:
    - Date of dose
    - Time of dose
    - Actual dose (increment value shown in dose counter)
    - Injection site

Start and stop dates for randomised treatment will be recorded in the eCRF.

6.5 Dose modification

Dose modification is not allowed. Please refer to Section 6.1 for description of dose escalation and missed doses.

6.6 Continued access to study intervention after end of study

When discontinuing study intervention, the participant should be transferred to a suitable marketed product at the discretion of the investigator.

The long half-life of semaglutide must be taken into consideration when selecting anti-diabetic treatment after discontinuation of randomised treatment.

6.7 Treatment of overdose

There is no specific antidote to semaglutide in the event of an overdose.

Any dose of semaglutide greater than the planned dose according to Table 6-2 and which deviate from the intended dose to an extent where clinical consequences for the study participants are likely to happen, as judged by the investigator, will be considered an overdose.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.3 and Appendix 3 (Section 10.3) for further details.

In the event of an overdose, the investigator should closely monitor the participant for overdose-related AEs/SAEs and laboratory abnormalities. Appropriate treatment should be initiated according to the participants' clinical signs and symptoms. A prolonged period of observation and/or treatment for symptoms may be necessary, considering the long half-life of semaglutide of approximately one week.

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the participant.

For more information on overdose, also consult the current version of the NN9535 investigator's brochure (IB).

6.8 Concomitant therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of the first visit (V1) or receives until the end of study must be recorded along with:

- Trade name or generic name
- Primary indication
- Dates of administration including start and stop dates
- Dose (only applicable for anti-diabetic medication)
- Frequency (only applicable for anti-diabetic medication)

Approved COVID-19 vaccines that the participant received within 6 months prior to screening should be recorded in the eCRF at the screening visit (V1).

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 8.3.

After signing the informed consent, participants must continue their anti-diabetic background medication (metformin) throughout the entire study and the background medication dose should remain at the same dose level and with the same frequency during the entire study intervention period unless glycaemic rescue medication is needed (as described in Section 6.8.1) or a safety concern related to the use of anti-diabetic background medication arises.

6.8.1 Rescue medicine

Glycaemic rescue medication, i.e. intensification of anti-diabetic background medication and/or initiation of new anti-diabetic treatment, should be implemented at the discretion of the investigator in case of persistent hyperglycaemia. Please see Section 7.1.2 for rescue criteria.

Rescue medication should be selected according to ADA/EASD guideline[2] (excluding GLP-1 RAs, dipeptidyl peptidase-4 (DPP-4) inhibitors and amylin analogues).

Participants that are started on rescue medication should continue to follow the protocol-specified visit schedule and stay on randomised treatment unless the investigator judges that it will jeopardise participant's safety.

Rescue medication should be documented in medical records and reported on the concomitant medication form in the eCRF.

Rescue medication will not be supplied by Novo Nordisk but reimbursed, if required according to local regulations, as long as the participant is in the study.

7 Discontinuation of study intervention and participant discontinuation/withdrawal

Discontinuation of specific sites or of the study as a whole is detailed in Appendix 1 (Section 10.1.11).

7.1 Discontinuation of study intervention

Randomised treatment may be discontinued at any time during the study at the discretion of the participant or at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

The randomised treatment must be discontinued, if any of the following applies for the participant:
1. Pregnancy
2. Intention of becoming pregnant
3. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study
4. Safety concern as judged by the investigator
5. Confirmation of acute pancreatitis

The participants should continue with the remaining scheduled visits and assessments until the time of the originally scheduled end of treatment visit (V15) and follow-up visit (V17).

Efforts must be made to have participants attend and complete all scheduled visit procedures to collect the required data for the analysis of the primary and confirmatory secondary endpoints. Only participants who withdraw consent will be considered as withdrawn from the study. Participants must be informed about the continued scientific importance of their data, even if they discontinue randomised treatment.

The primary reason for discontinuation of randomised treatment must be specified in the eCRF, and final IMP accountability must be performed. Discontinuation of randomised treatment must be made in the RTSM/IWRS.

7.1.1 Temporary discontinuation of study intervention

In case of suspicion of acute pancreatitis, the randomised treatment should promptly be interrupted (discontinuation of randomised treatment should not be made in RTSM/IWRS before diagnosis of acute pancreatitis is confirmed). Appropriate actions should be initiated, including local measurement of amylase and lipase (see Appendix 3, Section 10.3 for reporting of AE). If acute pancreatitis is confirmed, randomised treatment should not be restarted, and discontinuation of randomised treatment must be made in RTSM/IWRS. If the Atlanta criteria[13] are not fulfilled and thus, the suspicion of acute pancreatitis is not confirmed, randomised treatment may be resumed.

If a participant has discontinued randomised treatment due to temporary safety concern not related to the randomised treatment, randomised treatment can be resumed. Similarly, a participant who discontinues randomised treatment on their own initiative should be encouraged to resume randomised treatment.

If a participant has missed a single dose, the missed dose guidance in Section 6.1 must be followed. If more than one dose is missed, the investigator should consult Novo Nordisk global medical experts for guidance regarding continuation of randomised treatment.

7.1.2 Rescue criteria

Participants with persistent and unacceptable hyperglycaemia should be offered treatment intensification at the discretion of the investigator and in accordance with the ADA/EASD guidelines excluding GLP-1RAs, DPP-4 inhibitors and amylin analogues.

To allow time for dose escalation and to observe the expected effect of randomised treatment on glycaemic parameters, rescue criteria will be applied from week 12 and onwards. If any of the HbA_{1c} values exceeds the limit outlined below and no intercurrent cause of the hyperglycaemia can be identified, a confirmatory HbA_{1c} in the central laboratory should be obtained within 30 days. If the confirmatory HbA_{1c} exceeds the value described below then the participant should be offered treatment intensification (rescue medication) at the discretion of the investigator, and in accordance with the guidelines in Section 6.8.1.

Rescue medication should be offered from week 12 (V5) to week 40 (V15) to:

- Participants with persistent HbA_{1c} value above 8.5% (69 mmol/mol) that is confirmed within 30 days by the central laboratory and considered unacceptably high according to investigator's assessment.

7.2 Participant discontinuation/withdrawal from the study

A participant may withdraw consent at any time at his/her own request.

If a participant withdraws consent or is withdrawn by the investigator prior to randomisation, the participant will not be asked to have any follow-up assessments performed. The following data must be collected: Demography, eligibility criteria, date of informed consent, date of screening and the date when participant's participation ended. The end of study form must be completed.

If a participant withdraws consent after randomisation, the investigator must ask the participant if he/she is willing, as soon as possible, to have assessments performed according to visit 15. See the flowchart for data to be collected.

Final IMP accountability must be performed even if the participant is not able to come to the site. Discontinuation of randomised treatment must be made in the RTSM/IWRS.

If the participant withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent for the purpose of the study or scientific research.

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

Although a participant 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 participant's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the eCRF.

7.2.1 Replacement of participants

If a participant discontinues randomised treatment, withdraws consent or is withdrawn by the investigator, he/she will not be replaced.

7.3 Lost to follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, at least three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's source document.
- Should the participant continue to be unreachable by the end of study, he/she will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.

8 Study assessments and procedures

The following sections describe the assessments and procedures, while their timing is summarised in the flowchart (Section 1.2).

Informed consent must be obtained before any study-related activity, see Appendix 1 (Section 10.1.3).

All screening evaluations must be completed and reviewed to confirm that potential participants meet all inclusion criteria and none of the exclusion criteria.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reason for screen failure, as applicable.

At screening, participants will be provided with a card stating that they are participating in a study and giving contact details of relevant site staff that can be contacted in case of emergency.

Adherence to the study design requirements, including those specified in the flowchart, is essential and required for study conduct.

The investigator must ensure to keep regular contact with each participant throughout the entire study, and always have updated contact information. Even if a visit is missed and it is not possible to reschedule, every effort must be made to have all participants followed for the primary endpoint and AEs.

It is the responsibility of the investigator to schedule the visits and phone contacts as per the protocol flowchart (Section 1.2) and to ensure they take place. See section 6.4 for study intervention compliance.

Suggested order of assessments:
- ECG and vital signs
- Blood samples
- Other assessments

Diaries will include the following in relation to the visit they support:
- Instruction on how to use the diary
- Reminders:
    - to attend visit fasting (see Section 5.3 and flowchart in Section 1.2)
    - to return IMP at visit V4, V6, V10 and V15
    - to return diary at next site visit
- Information to be collected:
    - detailed dosing information (see Section 6.4) for all doses administered
    - hypoglycaemic events (according to Appendix 8 (Section 10.8))
    - health issues (AEs, SAEs, concomitant medication)

Visit-specific diaries must be handed out at the randomisation visit (V2) and at all following site visits. Participants must be instructed in how to use the diary.

Information from the diaries must be transcribed by the investigator or designee to the appropriate sections of the eCRF after a medical review of the data by the investigator to ensure that AEs and SAEs, including any overall change in health and concomitant medication are reported. If applicable, addition of missing information after interviewing the participant should be recorded in the source documents and transferred to the eCRF as relevant.

Review of diaries, ECG, laboratory reports, etc., must be documented in the source documents or the participant's medical record. If clarification of entries or discrepancies in the diary is needed, the participant must be questioned, and a conclusion made in the participant's source documents. Care must be taken not to bias the participant.

Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 (Section 10.2) for further details on laboratory samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart (Section 1.2).

8.1.1 Body weight

Body weight should be measured and recorded as specified in the flowchart (Section 1.2). Body weight should be measured on a digital scale, preferably using the same scale throughout the study. The scale must be calibrated yearly as a minimum, unless the manufacturer or local requirements certifies that calibration of the scale is valid for the duration of the study.

Measurement must be performed without shoes and only wearing light clothing and recorded in the eCRF in kilogram [kg] or pound [lb] with a precision of 1/10 unit (e.g. 80.3 kg / 177.0 lb).

BMI will be calculated in the eCRF based on body weight and height measurements at screening.

8.1.2 Waist circumference

Waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest and will be measured using a non-stretchable measuring tape at visits outlined in the flowchart (Section 1.2). The measurement of waist circumference should be performed and recorded in the eCRF to the nearest ½ cm or ¼ inch.

The waist circumference should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The participant should be standing with arms down their side and feet together. The measuring tape should touch the skin but not compress soft tissue. The participant should be asked to breathe normally, and the measurement should be taken when the participant is breathing out gently.

8.1.3 Spirometry

At clinical sites with capability, spirometry should be performed as outlined in the flowchart (Section 1.2).

The test procedure for spirometers that measure inspiration and expiration includes 1) maximal inspiration, 2) a 'blast' of expiration, 3) continued complete expiration for a maximum of 15 seconds, and 4) inspiration at maximal flow back to maximum lung volume.

The procedure should be performed according to the international guidelines[14]:

1. Have participant assume the correct posture with head slightly elevated
2. Attach nose clip, place mouthpiece in mouth, and close lips around the mouthpiece
3. Breathe normally
4. Inspire completely and rapidly with a pause of ≤2 s at total lung capacity
5. Expire with maximal effort until no more air can be expelled while maintaining an upright posture
6. Inspire with maximal effort until completely full
7. Repeat instructions as necessary, coaching vigorously
8. Repeat for a minimum of three manoeuvres, (usually no more than eight)
9. Check the forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) repeatability and perform more manoeuvres as necessary

For expiration-only devices, inspiration through the mouthpiece does not apply.

The FEV_1 and FVC measurement of the most representative manoeuvre, as per investigator's discretion, must be recorded in the eCRF in the unit litres.

8.1.4 Clinical efficacy laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the flowchart and the laboratory manual.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the flowchart (Section 1.2).

Medical history is a medical event that the participant experienced prior to the time point from which AEs are collected. Only relevant medical history including COVID-19, as judged by the investigator, should be reported in the eCRF. Findings of specific medical history listed below should de described in designated forms:

- Diabetes
- Eye disease
- Kidney disease
- Neuropathy
- Cardiovascular disease
- Pancreatic disease
- Gallbladder disease
- Dyslipidaemia
- Other

A **concomitant illness** is any illness that is already present at the time point from which AEs are collected or found as a result of a screening procedure or other study procedures performed before exposure to study intervention under clinical investigation.

In case of an abnormal and clinically significant finding fulfilling the definition of medical history or concomitant illness, the investigator must record the finding on the medical history/concomitant illness form.

8.2.1 Physical examinations

A physical examination will include assessments of:

- general appearance
- skin
- thyroid gland
- respiratory system
- cardiovascular system
- gastrointestinal system including mouth
- central and peripheral nervous system

Any abnormal, clinically significant findings before first administration of randomised treatment must be recorded as concomitant illness. Any new abnormal, clinically significant findings or clinically significant worsening from time of first administration of randomised treatment must be reported as an AE (Section 8.3 and Appendix 3 (Section 10.3)).

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

Height must be measured at screening and recorded in the eCRF. Measurement must be performed without shoes and recorded to nearest ½ cm or ¼ inch.

8.2.2 Vital signs

Pulse rate, systolic and diastolic blood pressure will be assessed at visits outlined in the flowchart (Section 1.2). Please see sections 5.3.2 and 5.3.3 for restrictions prior to vital signs assessment.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., no use of television, cell phones).

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

Blood pressure will consist of 3 systolic and diastolic blood pressure measurements with intervals of at least 1-2 minutes. An additional fourth blood pressure measurement must be performed if the first two readings on systolic or diastolic blood pressure differ by >10 mmHg. No more than four measurements should be performed.

- The last 2 systolic and last 2 diastolic blood pressure measurements should be recorded in the eCRF. The eCRF will calculate the mean of the last 2 measurements.

Pulse rate will be measured in connection to the blood pressure measurements.

- The pulse rate for the last 2 measurements should be recorded in the eCRF. The eCRF will calculate the mean of the last 2 measurements.

8.2.3 Eye examination

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

Results of an eye examination performed by an ophthalmologist or another suitably qualified health care provider (e.g., optometrist) must be available and evaluated by the investigator before randomisation to assess eligibility. The eye examination must be performed as a fundus photography (e.g., 2-field 60 degree or better, colour or red-free) or by slit-lamp biomicroscopy examination (e.g., using a pre-corneal or corneal contact lens examination). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

If the participant 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 participant has experienced worsening of visual function since the last examination. If the applicable eye examination was performed before the participant signed the informed consent form, it must be documented that the reason for performing the examination was not related to this study.

After randomisation an eye examination must be performed according to above as per protocol flowchart (Section 1.2). Results must be available at V15 (end of treatment visit). An eye examination performed within 3 weeks prior to V15 is acceptable, provided no clinical symptoms suggestive of eye disease have occurred in the meantime.

The eye examination should include measurement of intra ocular pressure (IOP) of both eyes. The IOP should be recorded in the eCRF in the unit mmHg. If the measure is available, the IOP should be captured in the eCRF when a previous eye examination is used for screening. In case IOP cannot be collected, or information is not available from previous eye examination then this measure can be omitted, and a new eye examination is not required.

The investigator should indicate the outcome of each eye examination. Relevant findings prior to randomisation must be recorded as concomitant illness/medical history. Relevant findings occurring after randomisation should be reported as an AE (please refer to Section 8.3).

8.2.4 Electrocardiograms

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

The investigator must perform review of the ECG for clinically significant abnormal findings.

ECG must be performed according to the manual from the supplier.

8.2.5 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the protocol flowchart.

8.2.6 Plasma glucose measurements

Plasma glucose (PG) should always be measured using a BG meter and recorded in the diary and eCRF when a hypoglycaemic episode is suspected. See Appendix 8 (Section 10.8) for more information on reporting of hypoglycaemic episodes.

When using BG meters, the measurement is performed with capillary blood calibrated to plasma equivalent glucose values, i.e., the measurement is performed on blood while the value is reported as plasma; therefore 'PG' is the term to use as descriptor for the value.

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 (see auxiliary supplies in Section 6.1).

Participants should be instructed in how to record the results of the PG values in the diaries. The record of each PG 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 values stored in the memory of the BG meter and correct reporting of these in the diary is advised to ensure adequacy of the data reported in the study database.

8.2.7 Pregnancy testing

Woman of childbearing potential (WOCBP) should only be included after a negative, highly sensitive urine pregnancy test (refer to Appendix 2, Section 10.2).

Pregnancy testing should be performed according to the flowchart (Section 1.2) and whenever a menstruation is missed or when pregnancy is otherwise suspected. Pregnancy testing is advised 9 weeks after premature discontinuation of randomised treatment.

Additional pregnancy testing should be performed during the treatment period, if required locally, refer to Appendix 10 (Section 10.10).

8.3 Adverse events and other safety reporting

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

The definition of AEs and SAEs can be found in Appendix 3 (Section 10.3), along with a description of AEs requiring additional data collection.

The definitions of AEs, SAEs, adverse device effects (ADEs), serious adverse device effects (SADEs), unanticipated serious adverse device effects (USADEs) and device deficiencies pertaining to the medical device used outside approval can be found in Appendix 6 (Section 10.6). Technical complaints are covered in section 8.3.6.

Some AEs require additional data collection on a specific event form. The relevant event(s) are listed below in Table 8-1, together with other events requiring collection of additional information.

Table 8-1 AEs requiring additional data collection, and other events requiring additional data collection

Event type	AE requiring additional data collection	Other event requiring collection of additional information
Acute kidney injury	X	
Diabetic retinopathy	X	
Gallbladder disease	X	
Hepatic event	X	
Hypersensitivity reaction	X	
Neoplasms (malignant and non-malignant)	X	
Acute pancreatitis	X	
Medication error	X	
Misuse and abuse	X	
Hypoglycaemic episodes		X

Definitions and reporting timelines for the events mentioned in the above table can be found in Appendix 3 (Section 10.3) and Appendix 8 (Section 10.8) for hypoglycaemic episodes.

8.3.1 Time period and frequency for collecting AE information

All AEs and SAEs must be collected from first administration of IMP under clinical investigation and until the end of study visit in accordance with the flowchart (Section 1.2) or whenever, within the above time period, the site becomes aware of an AE or SAE.

Conditions present prior to the timepoint from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or during other study-related procedures performed before exposure to IMP under clinical investigation, will be recorded as medical history/concomitant illness.

AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3) and Appendix 6 (Section 10.6). All SAEs must be recorded and reported to Novo Nordisk within 24 hours, and 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 study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discontinued from/completed the study, and the investigator considers the event to be related to the IMP and/or medical device used outside approval or related to study participation, the investigator must promptly notify Novo Nordisk.

8.3.2 Method of detecting AEs

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 3 (Section 10.3) and Appendix 6 (Section 10.6).

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

8.3.3 Follow-up of AEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs should be followed until final outcome of the event or until the participant is lost to follow-up as described in Section 7.3. Further information on follow-up and final outcome of events is given in Appendix 3 (Section 10.3) and Appendix 6 (Section 10.6).

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 study intervention under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR) and unanticipated serious adverse device effect (USADE).

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

8.3.5 Pregnancy

Details of pregnancies in female participants will be collected after first exposure to IMP and until Visit 17. For details regarding collection and reporting of pregnancy information, please refer to Appendix 4 (Section 10.4).

8.3.6 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form.

Instructions for reporting technical complaints can be found in Appendix 5 (Section 10.5).

In order for Novo Nordisk to perform a complete investigation of reported SAEs, Novo Nordisk might ask the investigator to complete a technical complaint form.

8.4 Pharmacokinetics and pharmacodynamics

8.4.1 Pharmacokinetics

Plasma samples will be used to evaluate the pharmacokinetics of semaglutide and will be collected according to the flowchart (Section 1.2) and Table 10-3 in Appendix 2 (Section 10.2). All samples must be drawn prior to administration of randomised treatment if administration is planned on the sampling day – please see dosing instructions in Section 6.1.

Procedures for sampling, handling, labelling, storage, and shipment must be performed in accordance with the laboratory manual.

Residual PK samples may be used for exploratory metabolite analysis. Potential metabolite analysis will be reported separately from the CSR.

Genetic analyses will not be performed on these plasma samples.

Bioanalysis of the plasma samples for semaglutide will be performed at a special laboratory using a validated assay. The PK bioanalysis is outlined in the Special laboratory study plan. Assay descriptions will be provided in a bioanalytical report prepared by the laboratories, and the bioanalytical report will be provided before finalisation of the CSR. Quality controlled data must be available for review by Non Clinical and Clinical Assay Sciences, Novo Nordisk, prior to interim analyses or database lock. After final reporting, study samples will be destroyed (upon approval by Novo Nordisk), and confirmation of destruction must be sent to Novo Nordisk.

Bioanalysis will be performed on samples from participants randomised to the three active treatment arms. Samples from participants receiving placebo will not be analysed.

8.4.2 Pharmacodynamics

Not applicable for this study.

8.5 Genetics

Not applicable for this study.

8.6 Biomarkers

Collection of samples for biomarker research is part of this study. Blood samples will be collected from all participants according to Table 10-5 in Appendix 2 (Section 10.2). The purpose of the biomarker research is to further develop the understanding of the biology following semaglutide treatment which may benefit future development programmes and ultimately the patients receiving treatment. The biomarker research will include the following exploratory biomarkers:

- Brain natriuretic peptide (BNP)
- C-terminal crosslinked telopeptide type I collagen (CTXI)
- Glucose-dependent insulinotropic polypeptide (GIP)
- Procollagen-1 N-terminal peptide (P1NP)
- Leptin
- Soluble leptin receptor

These predefined biomarkers will be analysed prior to DBL and reported in the CSR

In addition, serum biosamples are collected for future research on biomarkers, proteomes and metabolites among others. Refer to Section 8.8 for further details and Appendix 7 (Section 10.7(for retention.

8.7 Immunogenicity assessments

8.7.1 Anti-semaglutide antibodies

Antibody blood samples will be collected according to the flowchart (Section 1.2) and Table 10-4 in Appendix 2 (Section 10.2). All samples must be drawn prior to administration of randomised treatment if administration is planned on the sampling day – please see dosing instructions in Section 6.1. Please see Section 5.3.1 regarding fasting requirements prior to antibody sampling.

Procedures for sampling, handling, storage, labelling and shipment of samples must be performed in accordance with the laboratory manual.

Samples from participants randomised to semaglutide will be analysed for anti-semaglutide antibodies following a tiered approach. Samples positive for anti-semaglutide antibodies will be titrated. In addition, confirmed antibody-positive samples will be further characterised for cross-reactivity in native GLP-1. Confirmed antibody positive follow up samples (Visit 17) will be analysed for *in vitro* neutralising effect towards semaglutide. Follow-up samples (Visit 17) confirmed positive for cross-reactivity will be analysed for *in vitro* neutralising effect towards native GLP-1.

Anti-semaglutide antibody analysis including cross-reactivity to native GLP-1 will be performed by a specialised lab appointed by Novo Nordisk. The *in vitro* neutralising antibody analysis towards semaglutide and native GLP-1 will be performed by Novo Nordisk.

The investigator will not be able to review the results of antibody measurements in relation to AEs as the data will unblind the investigator and as antibody samples may not be analysed until after last participant last visit.

Refer to Appendix 7 (Section 10.7) for details on retention of antibody samples.

8.7.2 Hypersensitivity

If suspicion of a hypersensitivity reaction occurs the participants should be instructed to contact the site staff as soon as possible for further guidance.

Hypersensitivity reactions must be reported as AEs according to Section 8.3 and additional data collection will be performed for these events.

In the event of a **systemic** hypersensitivity reaction, judged by the investigator as possibly or probably related to randomised treatment, additional blood sampling should be performed. If possible, a blood sample should be taken as soon as possible and no later than 1-2 weeks after the reaction. A second sample should be taken 3-4 weeks after the reaction.

The additional blood samples will be analysed for the following parameters:

- Tryptase (only if retrieved within 0.5 – 2 hours post the hypersensitivity reaction)
- Anti-semaglutide IgE antibodies
- Anti-semaglutide binding antibodies

In addition, the baseline antibody sample from the same participant will also be assessed on the above-mentioned assays to compare antibody levels and allergy markers on samples drawn prior to first administration of randomised treatment. Data obtained in these cases will not be available for the investigators until after the end of the study and cannot be used for any diagnostic purposes.

The analyses will be performed by Novo Nordisk.

8.8 Human biosamples for future research

Collection of biosamples for future analysis is a component of this study. The samples will be stored in a biobank and allow for future analyses when new knowledge or improved testing technologies may have become available during or after the study. Participation is optional, and participants must sign a separate informed consent to indicate their participation in the biobank component(s) of the study. Participants who do not wish to participate in the biobank component(s) may still participate in the study.

Blood samples will be collected at visits described in Appendix 2 (Table 10-2) and according Appendix 7 (Section 10.7) and stored for future use.

Analyses of circulating biomarkers will measure hormones, metabolites or other non-genetic serum entity with the purpose of understanding and predicting response to semaglutide s.c. as well as understanding type 2 diabetes, overweight or other related conditions.

The samples may be analysed as part of a multi-study assessment. Results will not be reported to the investigator for assessments of AEs nor will they be part of the clinical study report. The primary objective of the analysis is to investigate on a population level and results are very unlikely to have clinical utility on an individual level. Furthermore, the analyses will be done on pseudonymised data. Therefore, any outcome of the analyses will not be reported directly to participants or sites. The result may be reported in publications, at scientific conferences or to authorities.

The human biosamples for future research will be stored for up to 15 years after end of study at a central laboratory or appropriate storage facility (see Appendix 7 [Section 10.7]).

8.9 Health economics

Not applicable for this study.

9 Statistical considerations

The statistical analysis plan (SAP) will be finalised prior to first patient first visit (FPFV), and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary confirmatory estimands.

9.1 Statistical hypotheses

Not applicable

9.1.1 Multiplicity adjustment

Not applicable

9.2 Analysis sets

Two participant analysis sets are defined:

Participant analysis set	Description
Full analysis set	All randomised participants. Participants will be included in the analyses according to the planned randomised treatment.
Safety analysis set	All participants who are exposed to randomised treatment. Participants will be included in the analyses according to the treatment they actually received.

Four data points sets are defined:

Data points set (DPS)	Description
DPS1 – in-study	All observed data points from randomisation until the first date of: • end of study visit (V17) • death • withdrawal of informed consent • last contact as defined by investigator for participants that are lost to follow up
DPS2 – on-treatment	All observed data points from first drug date until the first date of: • end of DPS1 • last administration of randomised treatment +63 days
DPS2 - modified	All observed data points with acute onset (laboratory assessments, and physical examination) from first drug date until the first date of: • end of DPS1 • last administration of randomised treatment +7 days
DPS3 – on-treatment without rescue	All observed data points from first drug date until the first date of: • initiation of rescue medication • last administration of randomised treatment +7 days

The full analysis set (FAS) will be used when analysing efficacy endpoints and assessments, and the safety analysis set (SAS) will be used when analysing safety endpoints and assessments.

The FAS and DPS1 are used to estimate the primary estimand for the primary endpoint and the secondary estimand for the confirmatory secondary endpoint.

The FAS and DPS3 are used to estimate the additional estimands for the primary and confirmatory secondary endpoint.

The SAS and DPS2 are used as the primary data points set to evaluate safety data (AEs, eye examination, vital signs and hypoglycaemic episodes). The primary evaluation of antibodies will be based on the safety analysis set and DPS2.

The SAS and a modified DPS2 are used to present safety data with an acute onset (laboratory assessments, and physical examination).

9.3 Statistical analyses

Dose-response modelling

To characterise the dose-response relationship for change in HbA_{1c} (%-point) and change in body weight (kg) at week 40 for the primary and additional estimand, the following dose-response candidate models in Table 9-1 will be fit separately. The variable d is the nominal dose level, and the other variables are model parameters to be estimated.

Table 9-1 Dose-response candidate models

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

E_0: the expected effect on HbA_{1c} /Body weight when treated with semaglutide s.c./pooled placebo, ED_{50}: The dose, which produces half of E_{max}, E_{max}: Maximum effect attributable to the drug.

The candidate models will be fit to the mean estimated endpoint changes at week 40 for the evaluated semaglutide s.c. doses and pooled placebo derived from the analyses models described above according to the estimand evaluated. When fitting the models, the mean estimated endpoint change will be weighted by their inverse estimated variances.

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

9.3.1 General considerations

From the statistical analyses the point estimate, two-sided 95% CIs, and the associated two-sided p-values will be presented for the following comparison:

- Semaglutide 2 mg vs pooled placebo
- Semaglutide 8 mg vs pooled placebo
- Semaglutide 16 mg vs pooled placebo
- Semaglutide 8 mg vs Semaglutide 2 mg
- Semaglutide 16 mg vs Semaglutide 8 mg
- Semaglutide 16 mg vs Semaglutide 2 mg

For all analyses and reporting, the three placebo arms will be pooled into one placebo group. Furthermore, to investigate the pooling of placebo descriptive statistics will be provided of change in HbA_{1c} at week 40 and change in body weight (kg) at week 40 will be done without pooling the placebo.

If an assessment has been made both at screening and randomisation, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing, and the assessment was made at screening, the screening value will be used as the baseline value. The participants with missing baseline values will not contribute to any analysis that adjust for the given baseline.

The stratification factor in the statistical analysis will be based on observed baseline value of $HbA_{1c} \geq 8.5\%$ (Y/N).

9.3.2 Primary endpoint analysis

The primary endpoint is change from baseline to week 40 in HbA_{1c} (%-point).

9.3.2.1 Primary estimand

The primary estimand, presented in Section 3.2.1.1, will be estimated based on the FAS using the in-study data points set (DPS1).

The primary analysis for this estimand is an analysis of covariance (ANCOVA) with randomised treatment and stratification factor as fixed effects and baseline HbA_{1c} as a covariate.

Handling of missing data

Jump to reference: Missing week 40 data will be imputed using multiple imputation assuming that missing data are missing not at random. The imputation will be performed by sampling among all available assessments at week 40 in the pooled placebo group. A pattern mixture model approach is applied where withdrawn participants without a follow-up visit are assumed to respond as if treated with placebo for the entire study. This approach is also known as “jump to reference” and makes the

assumption that participants instantly after discontinuation lose any effect of randomised treatment beyond what can be expected from the pooled placebo group.

Multiple copies (500 copies) of the full dataset will be generated by imputing missing values based on estimated parameters for the pooled placebo group. This will be done as follows:

- 500 copies of the dataset will be generated.
- An enriched ANCOVA model with stratification factor and sex as fixed effects and baseline HbA_{1c} as covariate will be fitted to the change from baseline to week 40 in HbA_{1c} for the completers in the pooled placebo group only.
- For each of the 500 copies of the dataset, the estimated parameters and their variances from this model will be used to impute missing week 40 values for participants in all treatment arms, based on their factor level and the values of the covariate.
- For each of the 500 complete datasets, the change from baseline to week 40 in HbA_{1c} will be analysed repeating the ANCOVA described above. The estimates and standard errors (SEs) for the 500 data sets are pooled to one estimate and associated SE using Rubin's rule.[15]

9.3.2.2 Supplementary analysis

Additional estimand analysis

The additional estimand, presented in Section 3.2.1.2, will be estimated based on the FAS using post-baseline data collected up to and including week 40 from the 'on-treatment without rescue' observation period (DPS3).

Imputation of missing data will be handled by MI assuming that missing data are MAR. The imputation will be performed separately within each treatment group defined by randomised treatment. First, intermittent missing values are imputed using a Markov Chain Monte Carlo method to obtain a monotone missing data pattern, generating 500 complete data sets. Secondly, a sequential conditional linear regression approach for imputing monotone missing values will be implemented starting with the first visit after baseline and sequentially continuing to the last planned visit at week 40. The model used for imputation will include stratification factor and sex as fixed effects and baseline and post-baseline HbA_{1c} values observed prior to the visit in question as covariates.

The 500 complete datasets will be analysed using an ANCOVA with stratification factor and randomised treatment as fixed effects and baseline HbA_{1c} as a covariate. Rubin's rule will be applied to combine the estimates and draw inference.

9.3.3 Secondary endpoints analysis

9.3.3.1 Primary estimand

For the endpoint "change from baseline to week 40 in body weight (kg)" a similar analysis as described in Section 9.3.2.1 will be performed, but with values of body weight instead of HbA_{1c}.

9.3.3.2 Supplementary analysis

Additional estimand

A similar analysis as described in Section 9.3.2.2 will be performed, but with values of body weight instead of HbA_{1c}.

9.3.3.3 Supportive

For details on analyses of supportive secondary endpoints, please refer to the SAP.

9.3.4 Exploratory endpoints analysis

Not applicable, as there are no exploratory endpoints in the study.

9.3.5 Safety analyses

All safety analyses will be made on the safety analysis set. The standard safety assessments (AEs, laboratory parameters, vital signs, etc.) will be reported descriptively based on the DPS2 and modified DPS2; including any notable changes of clinical interest in laboratory parameters. The primary evaluation of antibodies will be based on the safety analysis set and DPS2.

9.3.6 Other analyses

Population pharmacokinetic (PK) and exposure-response analyses is described below. For other analyses, please refer to the SAP.

Pharmacokinetic and/or pharmacodynamic modelling

Population PK and exposure-response analyses will be used to characterize the exposure-response curve of semaglutide s.c., and to support selection of a dose for potential future investigation in patients with T2D.

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

9.4 Interim analysis

A maximum of two interim analyses may be conducted to make treatment group comparisons during the study to support internal decisions and planning. The first may, at the earliest, occur when at least one third of the participants from the active 8 mg arm have completed visit 12, and the second may, at the earliest, occur when at least one third of the participants from the active 16 mg arm have completed visit 13, corresponding to eight weeks on maintenance dose, respectively in each arm. These interim analyses will include available safety, efficacy, and PK data.

A minimum group of Novo Nordisk staff, i.e., the interim charter group, would perform the interim analyses. The members of the interim charter group will be specified in an interim charter. No change in the study design and conduct can occur based on the interim analyses. Detailed information on the interim analyses will be specified in an interim charter. It is not considered a protocol deviation if no interim analysis is performed.

9.5 Sample size determination

Three doses of semaglutide s.c. (2 mg, 8 mg, and 16 mg) are considered adequate to characterise the shape of the curve for the dose-response relationship. The sample size for each dose is determined to achieve a sufficient precision on the dose-response relationship. Furthermore, sample size calculation is done for analyses addressing the primary estimand with primary and confirmatory secondary endpoint.

Historical data considered for lower doses of semaglutide s.c. in the sample size calculation are as outlined in Table 9-2 and Table 9-3.

Table 9-2 Historical data for change in HbA_{1c} from baseline to target week

	STEP 2	SUSTAIN FORTE	SUSTAIN 2
N	404	433	344
Semaglutide s.c. dose	2.4 mg	2 mg	1 mg
Treatment period	In-study	On-treatment	On-treatment
Target week	Week 44	Week 40	Week 40
Mean	-1.8%-points	-2.2%-points	-1.72%-points
Standard deviation	1.1%-points	1.0%-points	1.02%-points

STEP 2: NN9536-4374; SUSTAIN FORTE: NN9535-4506; SUSTAIN 2: NN9535-3626.

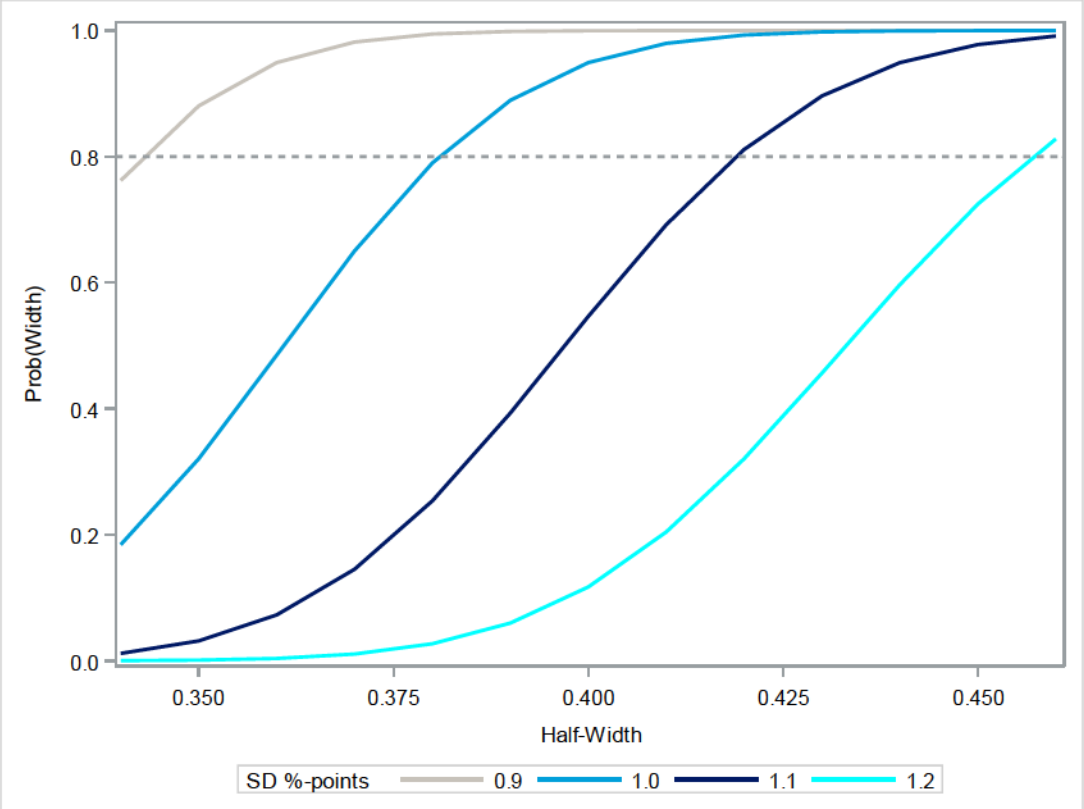
Table 9-3 Historical data for change in Body weight from baseline to target week

	STEP 2	SUSTAIN FORTE	SUSTAIN 2
N	383, 381	434	346
Semaglutide s.c. dose	2.4 mg	2.0 mg	1.0 mg
Treatment period	In-study	On-treatment	On-treatment
Target week	Week 36, Week 44	Week 40	Week 40
Mean	-9.3kg, -9.7kg	-7.0kg	-5.94kg
Standard deviation	7.3 kg average of week 36, 44	5.8kg	5.13kg

STEP 2: NN9536-4374; SUSTAIN FORTE: NN9535-4506; SUSTAIN 2: NN9535-3626.

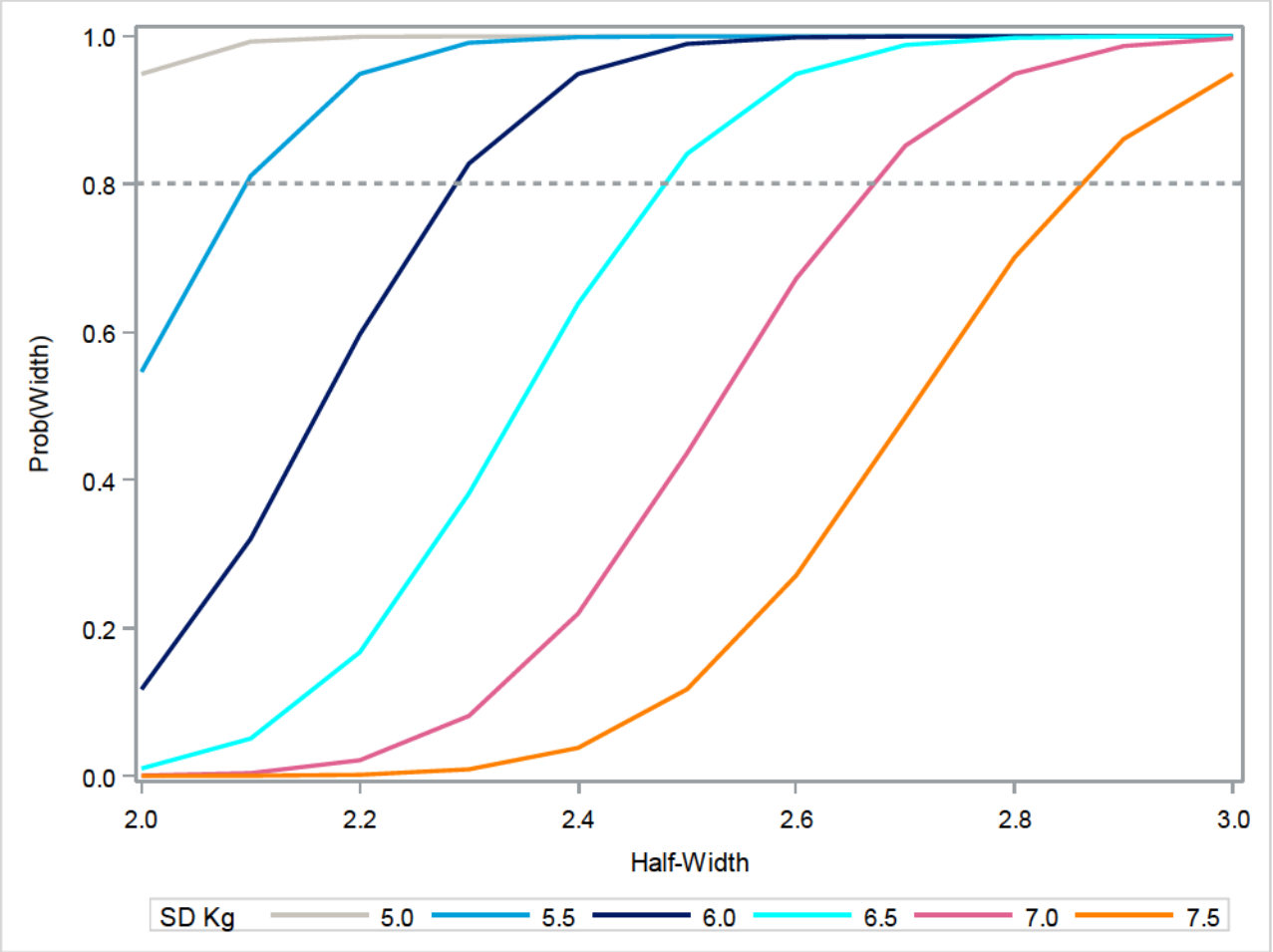
Since there are no available historical data for the higher doses of semaglutide s.c., a range of per-group SDs has been investigated in Figure 9-1 for HbA_{1c} (%) and Figure 9-2 for Body weight (kg) under the assumption of 60 participants in each active treatment/pooled placebo group.

Figure 9-1 Sensitivity of precision (95% CI half-width) for various SDs – HbA_{1c}(%-point)



With 60 participants in each active treatment/pooled placebo group and for various SDs between 0.9 and 1.2%-points, there is at least 80% probability that the 95% CI will be contained within ±0.34 and ±0.46%-points of the estimate. This is considered a sufficient range of precision to characterise the dose-response relationship of semaglutide s.c.

Figure 9-2 Sensitivity of precision (95% CI half-width) for various SDs – Body weight (kg)



With 60 participants in each active treatment/pooled placebo group and for various SDs between 5.0 and 7.5 kg, there is at least 80% probability that the 95% CI will be contained within ±2.0 and ±3.0 kg of the estimate. This is considered a sufficient range of precision to characterise the dose-response relationship of semaglutide s.c.

Under the assumption of 60 participants in each active treatment/pooled placebo group, the same range of SDs and their corresponding mean differences providing a power of 80% have been evaluated in Figure 9-3 for HbA_{1c} (%) and Figure 9-4 for Body weight (kg). Treatment differences between 0.46 and 0.62%-points and 2.6 and 3.9kg have 80% power when making any pairwise comparison of HbA_{1c} and Body weight change from baseline to week 40 between groups in this study.

In conclusion, the total sample size will be 240 participants.

Figure 9-3 Treatment differences with 80% power for various SDs – HbA_{1c}(%)

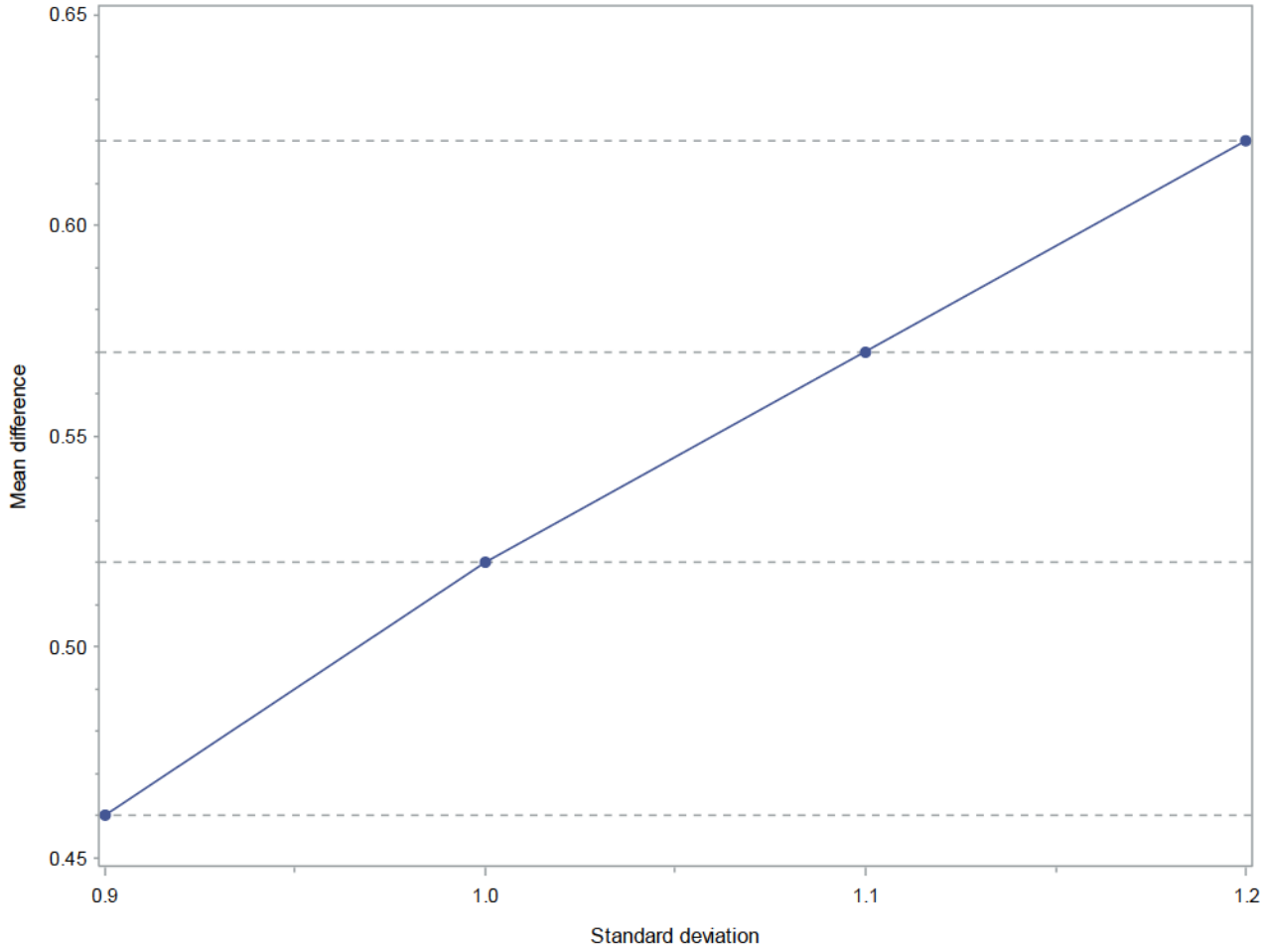
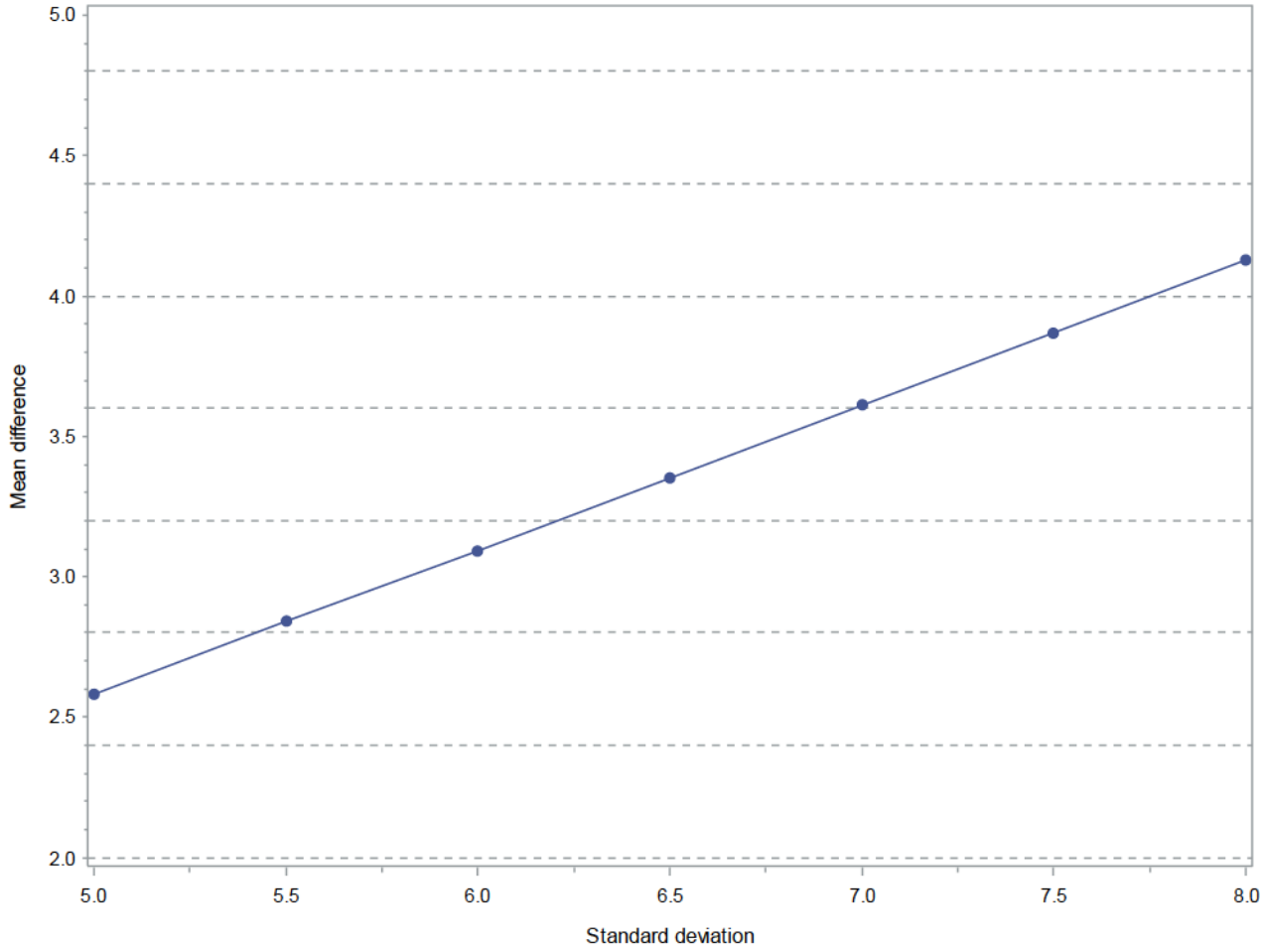


Figure 9-4 Treatment difference with 80% power for various SDs – Body weight (kg)



10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[16] and applicable ICH Good Clinical Practice (GCP) Guideline[17]
- Applicable laws and regulations

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 study is initiated.

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

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate safety hazard to study participants.

Before a site is allowed to start screening participants, written notification from Novo Nordisk must be received.

The investigator will be responsible for:

- providing written summaries of the status of the study 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 study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- ensuring submission of the CSR synopsis to the IRB/IEC
- reporting any potential serious breaches to the sponsor immediately after discovery

United states: Please see Appendix 10 (Section 10.10) for country-specific requirements.

10.1.2 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 study and one year after completion of the study.
For US sites: Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

10.1.3 Informed consent process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. This includes the use of an impartial witness where required according to local requirements.

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

Participants must be informed that their participation is voluntary. Participants will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH GCP[17] guidelines, Declaration of Helsinki,[16] privacy and data protection requirements, where applicable, and the IRB/IEC or site.

The medical record must include a statement that written informed consent was obtained before any study-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 study-related activity.

The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.

Participants must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

A copy of the informed consent form(s) must be provided to the participant.

A separate informed consent form intended for collection of additional blood samples for future research is available for this study (see Section 8.8).

A separate informed consent form intended for a male partner of a female participant in case of an abnormal pregnancy or child born with health problem is available for this study (Appendix 4, Section 10.4).

10.1.4 Information to participants during the study

The site will be offered a communication package for the participant during the conduct of the study. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the participants. The written information will be translated and adjusted to local requirements and distributed to the participant at the discretion of the investigator. The participant may receive a "thank you for your participation letter" after completion of the study. Further, the participant may receive other written information during the study.

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

10.1.5 Data protection

Participants will be assigned a 6-digit unique identifier, a subject ID. Any participant records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the participant are transferred to Novo Nordisk.

The participant and any biological material obtained from the participant will be identified by subject ID, visit number and study ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of participants as required by local, regional and national requirements.

The participant must be informed about his/her privacy rights, including that his/her personal study-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 participant.

The participant must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Personal data may be collected from participants due to process requirements from Novo Nordisk's suppliers. This data is needed to ensure that the relevant data analysis for the study can be performed, but will not be part of the data transferred to Novo Nordisk, the assessment of the study endpoints or the clinical study report. A list of any such data values must be kept as part of the study documentation along with an explanation of why it was required.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee.

10.1.7 Dissemination of clinical study data

Study information will be disclosed at clinicaltrials.gov and novonordisk-trials.com and, if applicable, also on other national or regional study registries. It will be disclosed according to applicable requirements, relevant recommendations or regulations, such as the Declaration of Helsinki,[16] the International Committee of Medical Journal Editors (ICMJE),[18] the Food and Drug Administration Amendment Act (FDAAA),[19] European Commission Requirements,[1, 20, 21] EU MDR[22] and in accordance with Novo Nordisk commitment to clinical transparency. If a participant requests to be included in the study via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the participant. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

Novo Nordisk or designee is responsible for the data management of this study including quality checking of the data.

To demonstrate his/her oversight of the collected data, the investigator should sign the CRF on a regular basis during the conduct of the study as well as at the end of the study, as described in the CRF completion guideline.

All participant data relating to the study will be recorded on 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 eCRF.

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 on study intervention not yet allocated to a participant)
- Device deficiency that could have led to an SAE form

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.

10.1.8.2 Monitoring

The investigator must permit study-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 study. If the electronic source data does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone).

Study monitors will perform ongoing source data verification of critical data points to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents. Study monitors will perform ongoing source data review to ensure that the study

is being conducted in accordance with the current approved protocol and any other study agreements, ICH GCP[17], and all applicable regulatory requirements, evaluating the adequacy of critical processes at site for the execution of the protocol, collection of study data, to ensure that the safety and rights of participants are being protected.

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 sites.

Quality tolerance limits (QTLs) will be predefined in the relevant monitoring plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.

10.1.8.3 Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without delay and the implications of the deviation must be reviewed and discussed.

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

10.1.9 Source documents

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

If source data is entered directly in a paper CRF, each data entry or clear series of data entries must be signed and dated separately by the study staff making the entry.

The original of the completed diaries must not be removed from the site, unless they form part of the eCRF and a copy is kept at the site.

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the site. Any source data generated by investigator's subcontractors must be archived and accessible by the site.

Data that is transcribed into the eCRF 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 participant's medical history in source documents, such as participant'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 site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical study documentation

Records and documents, including signed informed consent forms, pertaining to the conduct of this study must be retained by the investigator for 25 years after end of study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.

The investigator must be able to access his/her study documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other participant data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by Novo Nordisk. Site-specific CRFs and other participant data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.

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

10.1.11 Study and site closure

Novo Nordisk reserves the right to close the site or terminate the study at any time for any reason at the sole discretion of Novo Nordisk. If the study is suspended or terminated, the investigator must inform the participants 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.

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

The investigator may initiate 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 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 participants by the investigator
- discontinuation of further study intervention development.

10.1.12 Responsibilities

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

A qualified physician, who is an investigator or a sub investigator for the study, must be responsible for all study-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 study and the quality of the data produced) in the investigator trial master file. The documents, including the participant identification code list must be kept in a secure locked facility so that no unauthorised 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. This also includes ensuring that no indirect sharing of user credentials for IT systems used in this study takes place (e.g., by not sharing IT equipment with others in a way where user credentials have the possibility of being shared). 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 participants to a specific qualified physician who will be readily available to participants 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).

10.1.13 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 studies 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 study or by persons for whom the said site or investigator are responsible.

Novo Nordisk carries liability in accordance with country-specific requirements of Poland. Please refer to Appendix 10 (Section 10.10).

10.1.14 Publication policy

The information obtained during the conduct of this study 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 study intervention. All information supplied by Novo Nordisk in connection with this study 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 study.

The information obtained during this study may be made available to other investigators who are conducting other clinical studies with the study intervention, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this study to researchers who require access for research projects studying the same or related diseases and/or study intervention studied in this study.

Novo Nordisk may publish on its clinical studies website a redacted CSR for this study.

One investigator will be appointed by Novo Nordisk to review and sign the CSR (signatory investigator) on behalf of all participating investigators.

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of studies 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 study 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 CSR 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 study.

At the end of the study, 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 study 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.

10.1.14.2 Authorship

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

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[23]

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 site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

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

For a multicentre clinical study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or participants, 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 study.

10.1.14.4 Investigator access to data and review of results

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

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

10.2 Appendix 2: Clinical laboratory tests

The tests detailed in Table 10-1 to Table 10-5 will be performed by the central laboratory unless otherwise noted.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g., to follow up on AEs, this must be done at a local laboratory.

The central lab will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their laboratory SOPs. These data will not be transferred to the study database. The investigator should review such values for AEs and report these according to this protocol.

The investigator must review all laboratory results for concomitant illnesses and AEs.

The investigator must keep an overview, e.g. a log, of laboratory samples not handled according to the laboratory manual. In addition, the investigator must keep an overview, e.g. a log, of laboratory samples stored at site.

Laboratory samples will be destroyed no later than at end of study or no later than at finalisation of the CSR.

Human biosamples for future research and residual antibody samples will be stored as described in Appendix 7 (Section 10.7).

US: For country-specific requirements; please see Appendix 10 (Section 10.10).

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters	Visits
Glucose metabolism	• HbA_{1c}	V1, V2, V3, V4, V5, V6, V8, V10, V12, V13, V14, V15
	• Fasting plasma glucose[a, b]	V2, V3, V4, V5, V6, V8, V10, V15
	• Fasting insulin[b]	
	• Fasting glucagon[b]	
	• Fasting C-peptide[b]	
	• HOMA B	
	• HOMA IR	
	• Beta-hydroxybutyrate	

Notes:

[a] An FPG result <3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as an AE at the discretion of the investigator (Appendix 3, Section 10.3).

[b] Assessment to be done in fasting state (see Section 5.3.1).

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters	Visits
Haematology	• Basophils • Eosinophils • Erythrocytes • Haemoglobin • Leucocytes • Lymphocytes • Mean corpuscular volume • Monocytes • Neutrophils • Thrombocytes	V1, V10, V15
Biochemistry[a]	• Alanine Aminotransferase (ALT) • Alkaline phosphatase • Amylase • Aspartate Aminotransferase (AST) • Bilirubin • Calcium • Creatinine • Lipase • Phosphate • Potassium • Sodium	V1, V6, V8, V10, V12, V15
Lipids[b]	• Free fatty acids • High density lipoprotein cholesterol • Low density lipoprotein cholesterol • Total cholesterol • Triglycerides • Very low density lipoprotein cholesterol	V2, V3, V4, V5, V6, V8, V10, V15
Pregnancy Testing[c]	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test	V1, V2, V15, V17
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation	V1, V6, V8, V10, V12, V15
	• Uric acid	V2, V3, V4, V5, V6, V8, V10, V15
	• hs-CRP	V2, V3, V4, V5, V6, V8, V10, V15
	• Biosamples for future research	V2, V3, V4, V5, V6, V8, V10, V12, V15

Notes:

[a] Details of required actions and follow-up assessments for increased liver parameters are given in Appendix 3 (Section 10.3) (Hy's Law).

[b] Assessment to be done in fasting state (see Section 5.3.1).

[c] For women of childbearing potential, as needed, local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC, see Appendix 4 (Section 10.4).

Table 10-3 Protocol-required PK assessments

Laboratory assessments	Parameters	Visits
Pharmacokinetics[a, b]	• Semaglutide plasma concentration	V3, V4, V6, V8, V10, V12, V14, V15, V17

Notes:
[a] Analysis will be performed by a special laboratory contracted by Novo Nordisk.
[b] Results will not be provided to the investigator. These results will not be used for any clinical evaluation during the study unless it is decided to conduct interim analyses.

Table 10-4 Protocol-required antibody assessments

Laboratory assessments	Parameters	Visits
Antibodies[a, b]	• Anti-Semaglutide Antibody Confirmation (Positive/Negative) • Anti-semaglutide Antibodies level (Titer) • Antibodies cross reacting with native GLP-1 (Positive/Negative)	V2, V3, V4, V6, V10, V15, V17
	• Semaglutide AB (neutralising effect) (Positive/Negative)	V17
	• Antibodies neutralising native GLP-1 (Positive/Negative)	V17

Notes:
[a] Analyses will be performed by a special laboratory contracted by Novo Nordisk, with the exception of neutralising antibodies assessment, which will be performed by Novo Nordisk laboratory.
[b] Results will not be provided to the investigator, as these results will not be used for any clinical evaluation during the study.

Table 10-5 Protocol-required biomarkers

Laboratory assessments	Parameters	Visits
Biomarkers[a]	• BNP	V2, V15
	• CTXI[b]	V2, V15
	• GIP	V2, V3, V4, V5, V6, V8, V10, V15
	• P1NP[b]	V2, V15
	• Leptin[b, c]	V2, V10, V15
	• Soluble leptin receptor[b, c]	V2, V10, V15

Notes:
[a] Results will not be provided to the investigator, as these results will not be used for any clinical evaluation during the study.
[b] Assessment to be done in fasting state (see Section 5.3.1).
[c] Analysis will be performed by a special laboratory contracted by Novo Nordisk.

10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and procedures for recording, evaluating, follow-up, and reporting

For definitions and procedure for recording, evaluation, follow-up and reporting concerning the medical device used outside approval, please also refer to Appendix 6 (Section 10.6).

10.3.1 Definition of AE

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

Events to be reported as AEs:

- Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected
- Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected
- Exacerbation/worsening of a chronic or intermittent 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 IMP regardless of intent

A 'lack of efficacy' or 'failure of expected pharmacological action' per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.

Events NOT to be reported as AEs:

- Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions. This includes those conditions identified during screening or identified during other study procedures performed before exposure to IMP.
  Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.
- Medical or surgical procedures (e.g., endoscopy, appendectomy). The condition that leads to the procedure is the AE.
- Medical or surgical procedures not preceded by an AE or worsening of a known condition.

10.3.2 Definition of an SAE

An SAE is any untoward medical occurrence that fulfils at least one of the following criteria:

- **Results in death**
- **Is life-threatening**
- The term 'life-threatening' refers to an event in which the participant 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 participant has been admitted 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 seriousness 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 (e.g., elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE.

  Note: Hospitalisations for administrative, study-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for medical or surgical procedures, planned before study 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), that 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 by the investigator 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 participant 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 must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:
  - Suspicion of transmission of infectious agents via IMP
  - Risk of liver injury defined as alanine aminotransferase (ALT) or asparate aminotransferase (AST) >3x UNL and total bilirubin >2x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of AEs requiring additional data collection and other events requiring collection of additional information

Adverse events requiring additional data collection

An AE requiring additional data collection is an AE where Novo Nordisk has evaluated that additional data is needed in the evaluation of safety.

Acute kidney injury

Events of an abrupt or rapid decline in renal filtration function. This condition is usually marked by a rise in serum creatinine concentration or by azotemia (a rise in blood urea nitrogen [BUN] concentration).

Diabetic retinopathy

New onset or worsening of diabetic retinopathy.

Gallbladder disease

Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis).

Hepatic event

Hepatic event defined as:

- Disorders of the liver including cholestatic conditions and liver related signs and symptoms
- ALT or AST > 3x UNL and total bilirubin > 2x UNL*
- ALT or AST > 3x UNL with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

*Please note that in case of a hepatic event defined as ALT or AST > 3x UNL and total bilirubin > 2x UNL, where no alternative aetiology exists (Hy's law), this must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable.

Hypersensitivity reactions

All events of hypersensitivity reactions (possibly caused by allergic reactions, immune complex disease and anti-semaglutide antibody formation).

Neoplasms (malignant and non-malignant)

All events of neoplasms.

Acute pancreatitis

The diagnosis of acute pancreatitis requires two of the following three features:

- abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
- serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal
- characteristic findings of acute pancreatitis on imaging

Medication error:

A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the participant, such as:

- administration of wrong drug and/or use of wrong device
  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- wrong route of administration, such as intramuscular instead of subcutaneous
- accidental administration of a higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the study participant were likely to happen as judged by the investigator, although they did not necessarily occur.

Misuse and abuse:

- Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g., overdose to maximise effect)
- Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g., overdose with the intention to cause harm)

Note: Medication error, misuse and abuse must always be reported on an AE form and a specific event form must be completed. The AE diagnosis on the AE form must reflect what occurred (e.g., accidental overdose, intentional overdose or other). If the medication error and/or misuse and abuse resulted in a clinical consequence, this must be reported on an additional AE form.

Other events requiring collection of additional information

Hypoglycaemic episodes:
All hypoglycaemic episodes must be recorded on a hypoglycaemic episode form. If the hypoglycaemic episode fulfills the criteria for an SAE, then in addition to the hypoglycaemic episode form, an AE form and a safety information form must be filled in. One AE form and safety information form can cover several hypoglycaemic episode forms, if the participant has not recovered between the episodes.

10.3.4 Recording and follow-up of AE and/or SAE

10.3.4.1 AE and SAE recording

The investigator will record all relevant AE/SAE information in the eCRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event.

There may be instances when copies of source documents (e.g., medical records) for certain cases are requested by Novo Nordisk. In such cases, all participant identifiers, with the exception of the subject ID, must be redacted on the copies of the source documents before submission to Novo Nordisk.

For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the study at the latest. For sign-off of SAE-related forms, refer to "AE and SAE reporting via paper CRF" later in this section.

Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the study, 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.

10.3.4.2 Assessment of severity

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

- **Mild**: An event that is easily tolerated by the participant, 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: An AE that is assessed as severe should not be confused with an SAE. Both AEs and SAEs can be assessed as severe.

10.3.4.3 Assessment of causality

The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

Relationship between an AE/SAE and the relevant IMP 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 IMP.

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

The investigator should use the investigator's brochure and/or product information, for marketed products, 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 update the causality assessment in the eCRF.

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

10.3.4.4 Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved**: The participant has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented
- **Recovering/resolving**: The condition is improving, and the participant is expected to recover from the event. This term may also be applicable for AEs ongoing at the time of death (where death was due to another AE).

Note: For SAEs, this term is only applicable if the participant has completed the follow-up period and is expected to recover.

- **Recovered/resolved with sequelae**: The participant has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved**: The condition of the participant has not improved, and the symptoms are unchanged, or the outcome is not known. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal**: This term is only applicable if the participant died from a condition related to the reported AE. Outcomes of other reported AEs in a participant 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 participant is lost to follow-up

10.3.4.5 Follow-up of AE and SAE

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

If a participant dies during participation in the study or during a recognised follow-up period, the investigator should, upon request, provide Novo Nordisk with a copy of the autopsy report including histopathology, if available.

New or updated information should be recorded in the eCRF.

10.3.5 Reporting of SAEs

AE and SAE reporting via CRF

Relevant forms must be completed in the eCRF.

For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information forms within the designated reporting timelines (see Figure 10-1):

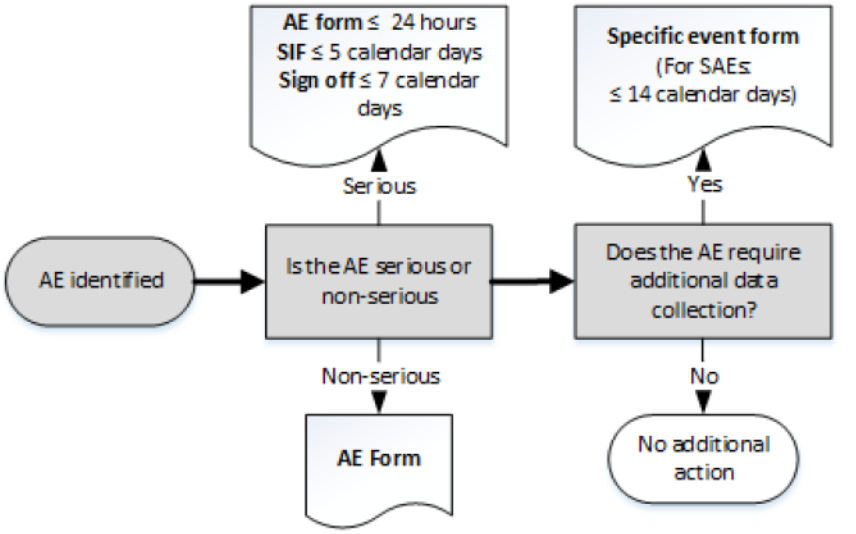
- AE form within 24 hours
- Safety information form within 5 calendar days
- Both forms must be signed within 7 calendar days after first knowledge by the investigator.
- Specific event form within 14 calendar days.

If the eCRF is unavailable for more than 24 hours, then the sites will use the paper AE form, and if the eCRF is unavailable for more than 5 calendar days, then the site will use the paper safety information form. The site should enter the SAE data in the eCRF as soon as it becomes available.

The relevant CRF forms (AE and safety information forms) must be forwarded to Novo Nordisk in accordance with Section 10.1.5.

After the study is completed, the study database will be locked, and the eCRF 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 participant or receives updated information on a previously reported SAE after eCRF decommission, the site can report this information on a paper AE and safety information form (see below) or to Novo Nordisk by telephone.

Figure 10-1 Decision tree for determining the event type and the respective forms to complete with associated timelines



- **Timelines** are from the awareness of an AE.
- **Hypoglycaemic episodes** should be reported on the hypoglycaemic episodes form. If the hypoglycaemic episode fulfils the criteria for an SAE, then an AE form and a safety information form must also be filled in.
- **Queries and follow-up** requests to be resolved ≤ 14 calendar days.
- In general data must be recorded in the CRF as soon as possible, preferably within 5 working days (see Appendix 1)

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

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

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.
If fertility is unclear (e.g., amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Females in the following categories are not considered WOCBP

1. Premenarcheal
2. Females with one or more of the following:
   - Documented total hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For females with permanent infertility due to an alternate medical cause other than the above (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining study enrolment.
3. Postmenopausal female:

- A postmenopausal state is defined as amenorrhoea for at least 12 months without an alternative medical cause in a female > 45 years of age. Alternative medical causes for amenorrhoea include, but are not limited to, hormonal contraception or hormonal replacement therapy.
- Females ≥ 60 years of age can be considered postmenopausal.

Females on HRT and whose menopausal status is in doubt are considered of childbearing potential and will be required to use one of the highly effective contraception methods.

Note: Documentation regarding categories 1-3 can come from the site staff's review of participant's medical records, medical examination or medical history interview.

10.4.2 Contraceptive guidance

Male participants

No contraception measures are needed for male participants, as the risk of teratogenicity/fetotoxicity caused by transfer of semaglutide s.c. in seminal fluid is unlikely.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly. Table 10-6 lists the highly effective methods of contraception allowed. Local regulations may apply, see Appendix 10 (Section 10.10).

Highly effective contraception should be utilised for a least 63 days after last dose of IMP (corresponding to time during treatment and until the end of relevant systemic exposure).

Table 10-6 Highly effective contraceptive methods allowed[24]

Highly effective methods[a] (Failure rate of <1% per year when used consistently and correctly):
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  • oral
  • intravaginal
  • transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation
  • oral
  • injectable
  • implantable
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner
Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
• 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 study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

NOTES a. Contraceptive use by men or women should comply with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

The following methods are not acceptable methods of contraception: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM).

Greece: Please see Appendix 10 (Section 10.10) for country-specific requirements.

10.4.3 Collection of pregnancy information

Female participants who become pregnant

Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.

Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a participant's pregnancy (see Figure 10-2).

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate which will be forwarded to Novo Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.

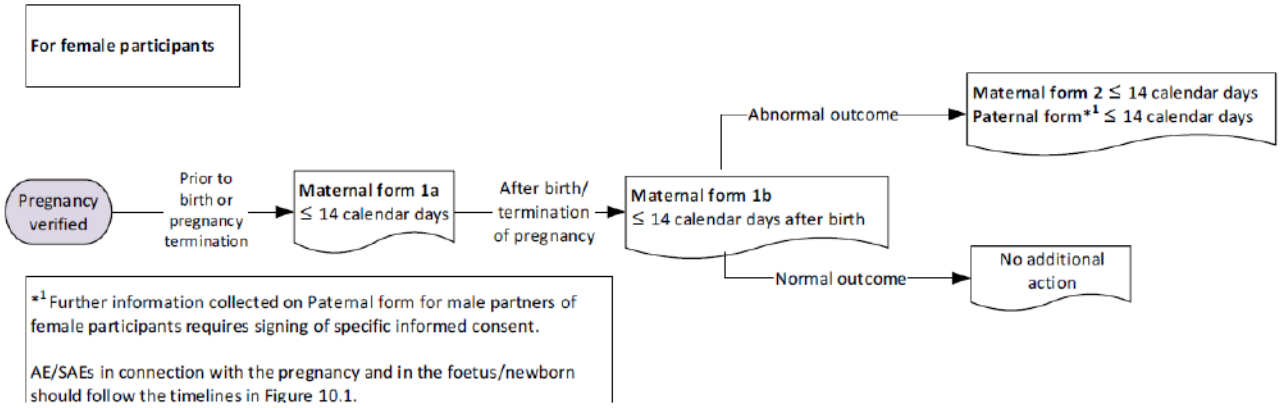
Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding 'gestational', 'pregnancy-related' or a similar term when reporting the AE/SAE.

Pregnancy outcome should be documented in the participant's medical record. Abnormal pregnancy outcome (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE. In case of abnormal pregnancy outcome, paternal information should be recorded in the appropriate form after obtaining the necessary signed paternal informed consent.

If the investigator learns of an SAE occurring as a result of a post-study pregnancy which is considered related to the IMP by the investigator, the SAE should be reported to Novo Nordisk as described in Appendix 3 (Section 10.3).

Figure 10-2 Decision tree for determining the forms to complete for collection of pregnancy information and timelines for reporting – For female participants



Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 Appendix 5: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

10.5.1 Definition of technical complaint

A technical complaint is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself. Technical complaints include the definition of device deficiency, please refer to Appendix 6 (Section 10.6).

Examples of technical complaints:

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

Time period for detecting technical complaints

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

10.5.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk

For contact details for Customer Complaint Center, please refer to Attachment I.

Technical complaints on products allocated to a participant must be reported on a separate technical complaint form:

1. For products with DUN: One technical complaint form must be completed for each affected DUN.
2. For products without DUN: One technical complaint form must be completed for each batch, code or lot number.

For medical device used outside approval, evaluate on the technical complaint form if the technical complaint could have led to an SAE.

If the technical complaint on a medical device used outside approval could have led to an SAE, a device deficiency that could have led to SAE form must be completed as described in Appendix 6 (Section 10.6).

Timelines for reporting technical complaints to Novo Nordisk

The investigator must complete the technical complaint form in the eCRF within:

- 24 hours if could have led to an SAE
- 24 hours if related to an SAE
- 5 calendar days for all other technical complaints

If the eCRF is unavailable, or when reporting a technical complaint on a product that is not yet allocated to a participant, the information must be provided on a paper form 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 and notify the monitor within 5 calendar days of obtaining the sample at 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 study intervention.

10.5.3 Reporting of technical complaints for products not included in the technical complaint form

Technical complaints on products not included in the technical complaint form should be reported to manufacturing holder.

10.6 Appendix 6: AEs, ADEs, SAEs, SADEs, USADEs and device deficiencies: Definitions and procedures for recording, evaluating, follow-up, and reporting in Medical device studies

10.6.1 Definition of AE and adverse device effects

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the medical device used outside approval and whether anticipated or unanticipated. This definition includes events related to the medical device used outside approval or comparator and events related to the procedures involved. For users or other persons, this definition is restricted to events related to the medical device used outside approval or comparators.

An adverse device effect (ADE) is an AE related to the use of a medical device used outside approval. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device used outside approval as well as any event resulting from use error or from intentional misuse of the medical device used outside approval or comparator if the comparator is a medical device. See the IB for the medical device used outside approval for the anticipated ADEs

10.6.2 Definition of SAE, serious adverse device effect and unanticipated serious adverse device effect

An SAE is an AE that fulfils at least one of the following criteria:

1. Results in death
2. Leads to serious deterioration in the health of the participant, user or other person that either results in:
   a) A life-threatening illness or injury. The term 'life-threatening' refers to an event in which the participant 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.
   b) Persistent or significant disability/incapacity: A permanent impairment of a body structure or a body function including chronic diseases.
   c) In-patient or prolonged hospitalisation. Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
   d) Important medical event: Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
3. Congenital anomaly/birth defect: Results in foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

Serious adverse device effect

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

Unanticipated serious adverse device effect

An unanticipated serious adverse device effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment analysis report (see Section 2.3).

Anticipated serious adverse device effect is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment

10.6.3 Definition of serious health threat

A serious health threat is a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in study participants, users or other persons, and that requires prompt remedial action for other participants, users or other persons. This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

10.6.4 Definition of device deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. Device deficiencies include malfunctions, use errors, and the inadequacy of the information supplied by the manufacturer, including labelling. This definition includes device deficiencies related to the medical device used outside approval.

Device deficiency is part of technical complaint definition, please refer to Appendix 5 (Section 10.5).

10.6.5 Definition of use error

A use error is a user action or lack of user action while using the medical device that lead to a different result than that intended by the manufacturer or expected by the user.

Use error includes the inability of the user to complete a task.

Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment.

Users might be aware or unaware that a use error has occurred.

Note: An unexpected physiological response of the participant is not by itself considered a use error.

Note: A malfunction of a medical device that causes an unexpected result is not considered a use error.

10.6.6 Recording and follow-up of AE and/or SAE and device deficiencies

10.6.6.1 AE, SAE and device deficiency recording

When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information.

There may be instances when copies of source documents (e.g., medical records) for certain cases are requested by Novo Nordisk. In such cases, all participant identifiers, with the exception of the subject ID, will be redacted on the copies of the source documents before submission to Novo Nordisk.

For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the study at the latest. For sign-off of SAE-related forms, refer to Section 10.6.2.

The investigator will record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF.

For device deficiencies, it is very important that the investigator describes any corrective actions taken to prevent recurrence of the event.

10.6.6.2 Assessment of severity

The investigator will make an assessment of severity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the participant, 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: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the criteria described in the definition of an SAE, NOT when it is rated as severe.

10.6.6.3 Assessment of causality

The investigator is obligated to assess the relationship between the medical device used outside approval, the procedure and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine relationship.

Relationship between an AE/SAE and the medical device used outside approval and the procedure should be assessed as:

- Causal: when relationship is beyond any doubt
- Probable: when relationship seems relevant and/or the event cannot be explained by another cause
- Possible: when relationship is weak but cannot be ruled out
- Not related: when relationship can be excluded

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the use of the medical device under investigation, will be considered and investigated.

The investigator will also consult the investigator's brochure in his/her 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 for AE or SAE.

There may be situations in which an AE/SAE has occurred, and the investigator has minimal information to include in the initial report to Novo Nordisk. However, it is very 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 an AE/SAE follow-up report with the updated causality assessment.

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

10.6.6.4 Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved**: The participant has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented.
- **Recovering/resolving**: The condition is improving, and the participant is expected to recover from the event. This term may be applicable in case of chronic conditions, cancer of AEs ongoing at time of death (where death is due to another AE).
  Note: for SAEs, this term is only applicable if the participant has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae**: the participant has recovered from the condition but with lasting effect due to disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved**: the condition of the participant has not improved, and the symptoms are unchanged, or the outcome is no known.
  Note: this term may be applicable in case of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal**: This term is only applicable if the participant died from a condition related to the reported AE. Outcome of other reported AEs in a participant 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 participant is lost to follow-up.

10.6.6.5 Follow-up of AE/SAE/device deficiency

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/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to Novo Nordisk within 24 hours of receipt of the information.

10.6.7 Reporting of SAEs, Serious Device Deficiency that could have led to an SAE and serious health threats

Relevant CRF forms (AE and safety information forms, device deficiency that could have led to an SAE form) must be forwarded to Novo Nordisk in accordance with Section 10.1.9.

Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE, device deficiency that could have led to and SAE and safety information form within the designated reporting time frames:

- AE and device deficiency that could have led to an SAE form within 24 hours
- Safety information form within 5 calendar days
- All forms must be signed within 7 calendar days after first knowledge by the investigator.

A suspicion of a serious health threat must be indicated in the SAE form or in the device deficiency that could have led to an SAE form.

For device deficiency that could have led to an SAE, a technical complaint form must also be completed, refer to Appendix 5 (Section 10.5).

10.7 Appendix 7: Retention of human biosamples

In countries where applicable, the study will involve collection of human biosamples for future research to be stored in a central laboratory facility.

Human biosamples (also in some cases known as human biospecimen or human biological materials) are samples that have been taken from the human body during life or after death. It includes:

- Primary cells, tissues, organs or cell containing fluids of human origin (for example, whole blood, urine, saliva, synovial fluid)
- Cell free fluids of primary human origin (for example, serum and plasma)
- Extracts or derivatives of the above, when derived by purification (for example, DNA, RNA, proteins, membranes, microsomes and other cellular substructures).

Serum samples will be collected according to the flowchart (Section 1.2) and Table 10-2 in Appendix 2 (Section 10.2). One serum sample will be collected per timepoint and divided in two aliquots for storage.

The biosamples will be stored at a central laboratory, at a central storage facility or an analysing laboratory contracted by Novo Nordisk for up to 15 years after end of study. Only relevant Novo Nordisk, consultants, auditors, research organisations or laboratories working for or collaborating with Novo Nordisk as well as storage facility employees will be able to access the stored biosamples and associated data. The biosamples may be transferred to other countries for analysis and will be destroyed at the latest 15 years after end of study.

The analyses of the biosamples for future research are not intended to identify participant-specific findings, but to understand and predict response to semaglutide as well as understanding T2D and related conditions on a population level.

Analysis will be done on the biosamples and associated data (data relating to the test results or results from the main study).

Novo Nordisk will ensure that third party collaborators live up the regulations on data protection, see Appendix 1 (Section 10.1.5).

The participant may request the stored biosamples for future research to be destroyed by withdrawing the designated informed consent at any timepoint during and after the study. For samples that have already been analysed, the results can still be used for scientific research and will not be removed from the datafile.

Residual antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug, if required by health authorities or for safety reasons. The samples will be stored at Novo Nordisk, or a specialised lab assigned by Novo Nordisk, after end of study and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of study after which they will be destroyed.

10.8 Appendix 8: Hypoglycaemic episodes

Table 10-7 Classification of hypoglycaemia

Classification of hypoglycaemia		
Level	Glycaemic criteria	Description
Hypoglycaemia alert value (level 1)	< 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (level 2)	< 3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (level 3)[1]	No specific glucose threshold	[1]Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery
Notes: The Novo Nordisk terms are adapted from IHSG,[25] ADA,[26] ISPAD,[27] type 1 diabetes outcomes program,[28] ATTD.[29] Severe hypoglycaemia as defined by Seaquist[30] and ISPAD.[27]		

Severe hypoglycaemia

[1]Severe hypoglycaemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[30]

Nocturnal hypoglycaemia

Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.

Reporting of hypoglycaemic episodes

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

Reporting of hypoglycaemic episodes by BG meters:
Plasma glucose (PG) should always be recorded in the diary/eCRF when a hypoglycaemic episode is suspected.

When a participant experiences a hypoglycaemic episode, the participant should record the general information in relation to the hypoglycaemia (timing, PG measurements, symptoms, etc.) as described in the diary. The investigator should ensure correct reporting of the hypoglycaemic episode and report the hypoglycaemic episode to the eCRF. In case a participant is not able to fill in the diary (e.g., in case of hospitalisation), the investigator should still report the hypoglycaemic episode on the hypoglycaemic episodes form.

Upon onset of a hypoglycaemic episode the participant is recommended to measure PG every 15 minutes until the PG value is ≥3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines.[30]

Repeated PG measurements and/or symptoms will by default be considered as one hypoglycaemic episode until a succeeding PG value is ≥ 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved and should be reported as only one hypoglycaemic episode. In case of several low PG values within the hypoglycaemic episode, the lowest value is the one that will be reported as the PG value for the hypoglycaemic episode, but the start time of the episode will remain as the time for the first low PG value and/or symptom. The remaining values will be kept as source data.

If the severity of a hypoglycaemic episode changes, only one hypoglycaemic episode will be reported, reflecting the most severe degree of hypoglycaemia.

Regarding the question: "To feel better, did you need help to get a sugary drink, food, or medicine?" the investigator must instruct the participants to answer "Yes", if the episode was an event that required assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.[30]

Additional information (e.g., description of symptoms, alleviation of symptoms, seizure or coma) in relation to severe hypoglycaemic episodes must be recorded in the hypoglycaemic episode (e)CRF.

Diary review

At each contact the investigator must review the diary data for correct reporting of PG values and hypoglycaemic episodes. In case of incomplete or incorrect data in the diary, the participant must be questioned whether there have been any severe hypoglycaemic episodes since the last visit and report accordingly.

For low PG values for hypoglycaemic episodes with incomplete reporting information:

1. If a hypoglycaemic episode form in the diary is not completed by the participant within 7 calendar days of the PG measurement, the episode should be described in the source documents and reported by the investigator on a hypoglycaemic episode (e)CRF with as much information as possible. If the participant did not need help to get a sugary drink, food, or medicine, Novo Nordisk will only ask for start date due to recall bias.[31, 32]

Re-training of participants

The participant must be re-trained in how to report hypoglycaemic episodes if the investigator identifies low PG values not reported as hypoglycaemic episodes. The training should be documented by the investigator in source documents.

10.9 Appendix 9: Mitigations to ensure participant safety and data integrity during an emergency situation

10.9.1 Definition and scope of appendix

A major emergency is defined as a situation that causes substantial restrictions to study site access for participants and/or sponsor representatives.

In case local restrictions due to COVID-19 outbreak lead to lock-down of a site, the site must contact Novo Nordisk to allow for implementation of mitigations mentioned in this appendix based on mutual agreement.

According to local regulation, health authorities and independent ethics committees should be notified in case elements of the emergency appendix are activated.

Sites should always try to follow the assessments outlined in the original flowchart (Section 1.2) to the extent possible. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.

Sites should comply with local regulations, requirements and/or guidelines if they are issued.

10.9.2 Visits

Screening (Visit 1) and randomisation (Visit 2) should always be performed as on-site visits. If a site is unable to perform these visits on-site, screening and randomisation of new participants at that site should be on hold until on-site visits are possible.

Visits 1, 2, 10 and 15 should be performed as on-site visits, if in any way possible. If not, assessments can be conducted remotely (video, phone or similar) or as off-site visits.

On-site visits (Visits 3-6, 8, and 12-14) can be converted to remote visits (video, phone or similar) or off-site visits.

If the end of treatment visit cannot be performed on-site, using remote (video, phone or similar) or off-site visits within the given visit window, the visit window for the assessment can be extended for up to 1 week.

If the end of study visit cannot be performed on-site, using remote (video, phone or similar) or off-site visits within the given visit window, the visit window for the assessment can be extended for up to 1 month.

At each visit, the investigator must indicate in the eCRF how the visit was performed and specify the reason for the preferred assessment method.

10.9.3 Assessments

Assessments used for safety or the confirmatory endpoints (i.e., HbA_{1c}, body weight and AEs) should be prioritised. The preferred order for the method of assessment is: on-site, off-site video, phone. Specifications regarding how to perform these assessments using remote visits or as off-site visits will be provided by Novo Nordisk and will be based on options and requirements at country

level and if permitted by local regulations. Specifications will include training for raters performing remote assessments and adoption of modifications for equivalent administration of assessments using remote visits (video, phone or similar).

Local laboratories or diagnostic facilities can be used for haematology, biochemistry and ECG at the investigator's discretion if on-site visits are not possible or in case of temporary lockdown of the central laboratory. Only findings meeting the definition for an AE (refer to Appendix 3 [Section 10.3]) should be reported in the eCRF.

If the HbA_{1c}, body weight and AE assessments cannot be performed as on-site visits, remote visits or be analysed at a local laboratory or diagnostic facility, they should be performed at the first possible timepoint following the originally scheduled visit in agreement with Novo Nordisk.

10.9.4 Study intervention

Alternative dispensing methods of IMP may be implemented, and details will be communicated and documented. The dispensing options will be provided by Novo Nordisk A/S and will be based on options and requirements at country level and if permitted by local regulations.

10.10 Appendix 10: Country-specific requirements

Greece

- Appendix 4, Section 10.4: Contraceptive guidance and collection of pregnancy information:
  Contraception and pregnancy testing should be in accordance with the current EU recommendations: Clinical Trials Facilitation and Coordination Group CTFG, Recommendations related to contraception and pregnancy testing in clinical trials.

Hungary

- Section 5.1: Inclusion criteria:
  Participant's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth.

Poland

- Appendix 1 (Section 10.1.13): Indemnity statement:
  Novo Nordisk carries liability insurance for the Trial - Terms and Conditions compliant with the Ordinance of Ministry of Finance from 18 May 2005 amending the Ordinance of Ministry of Finance from 30 April 2004 on Compulsory Liability Insurance of Researcher and Sponsor.

United States

- Appendix 1, Section 10.1.1: Regulatory and ethical considerations:
  FDA form 1572:
  For US sites:
    - Intended for US sites
    - Conducted under the IND
    - All US investigators, as described above, will sign FDA Form 1572

  For sites outside the US:
    - Intended for participating sites outside of the US
    - Not conducted under the IND
    - All investigators outside of the US will not sign FDA form 1572

  Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the study.
- Appendix 2, Section 10.2: Clinical laboratory tests:
  For haematology samples (differential count) where the test result is not normal, a part of the sample may be kept for up to two years or according to local regulations.

10.11 Appendix 11: Abbreviations

ADA	American Diabetes Association
ADE	adverse device effect
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATTD	Advanced Technologies & Treatments for Diabetes
BG	blood glucose
BMI	body mass index
BNP	brain natriuretic peptide
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Corona virus disease 2019
CRF	case report form
CSR	clinical study report
CTFG	clinical trial facilitation group
CTXI	C-terminal crosslinked telopeptide type I collagen
CV	cardiovascular
DBL	database lock
DFU	directions for use
DPP-4	dipeptidyl peptidase-4
DPS	data points set
DUN	dispensing unit number
EAC	event adjudication
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FEV_1	forced expiratory volume

FPFV	first participant first visit
FPG	fasting plasma glucose
FVC	Forced vital capacity
GCP	Good Clinical Practice
GI	gastrointestinal
GIP	Glucose-dependent insulinotropic peptide
GLP-1 RA	glucagon-like peptide-1 receptor agonist (
$HbA1_c$	glycated haemoglobin
HOMA B	homeostatic model assessment of beta-cell function
HOMA IR	homeostatic model assessment insulin resistance
HRT	hormone replacement therapy
hs-CRP	highly sensitive C-Reactive Protein
IB	investigator's brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IHSG	The International Hypoglycaemia Study Group
IMP	investigational medicinal product
IND	investigational new drug
IOP	intraocular pressure
IRB	institutional review board
ISO	International Organization for Harmonization
ISPAD	International Society for Pediatric and Adolescent Diabetes
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	interactive web response system
LAM	lactational amenorrhoea method
LBBB	left bundle branch block like recording
LPLT	last participant last treatment
LPLV	last participant last visit
MDR	Medical Device Regulation
NIMP	non-investigational medicinal product
NOAEL	no observed adverse effect levels
NYHA	New York Heart Association
P1NP	Procollagen 1 N-Terminal Propeptide
PCD	primary completion date
PG	plasma glucose

PK	pharmacokinetic
QTL	quality tolerance limits
RTSM	Randomisation and Trial Supplies Management
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	safety analysis set
SD	standard deviation
SE	Standard error
SIF	Safety information form
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TEAE	treatment emergent adverse event
TMM	Trial Materials Manual
UNL	upper normal limit
USADE	Unanticipated serious adverse device effect
WOCBP	woman of childbearing potential

10.12 Appendix 12: 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 2.0: (16 June 2022), global

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 Union[1], because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall rationale for preparing protocol version 2.0

Section # and name	Description of change	Brief rationale
Section 5.1 Inclusion criteria	Correction of unit for HbA_{1c}	To state the right unit
Section 6.1 Study intervention(s) administered	Correction of an error in the footnote of Table 6-2	To align the footnote with Table 6-2
Section 10.2 Appendix 2 Clinical laboratory tests	Addition of footnote to Table 10-5	To make it clear in the protocol that analysis of leptin and soluble leptin receptor will be performed by a special laboratory contracted by Novo Nordisk

11 References

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