Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05478252
Sponsor trial ID:	NN9535-4820
Official title of study:	Investigation of Clinical Comparability of Semaglutide Drug Products Based on the Proposed and the Approved Drug Substance Manufacturing Processes in Participants with Type 2 Diabetes
Document date*	20 February 2023

*Document date refers to the date on which the document was most recently updated.
Note: The date in the header of Page 2, 93 is the date of compilation of the documents and not of an update to content.

9.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

Protocol Title: Investigation of Clinical Comparability of Semaglutide Drug Products Based on the Proposed and the Approved Drug Substance Manufacturing Processes in Participants with Type 2 Diabetes

Substance: Semaglutide

Universal Trial Number: U1111-1266-2391

EudraCT Number: 2021-001501-69

Study phase: 3b

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

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	**Date**	**Applicable in countries and/or sites**
Protocol version 4.0	20 February 2023	Global
Protocol version 3.0	05 October 2022	Global
Protocol version 2.0	08 April 2022	Global
Original protocol version 1.0	31 January 2022	Global

Protocol version 4.0 (20 February 2023)

This amendment is considered 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]

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis Section 3.1.1 Primary estimand Section 4.2 Scientific rationale for study design Section 9.1 Statistical hypothesis Section 9.5 Sample size determination	Non-inferiority margin changed from -0.3 to 0.3 and the statistical hypothesis has been corrected to reflect the actual test for non-inferiority of semaglutide J against semaglutide B	This has been done to correct wrong specification
Section 1.1 Synopsis Section 3.1 Objectives and endpoints Section 9.2 Analysis sets	The additional estimand has been changed to be the primary estimand and vice versa. Moreover, the primary estimand has changed to follow a treatment policy strategy, while the additional estimand has changed to follow a mix of the hypothetical strategy and the treatment policy estimand	This has been done in accordance with feedback received from health authority
Section 9.3.2 Primary endpoint analysis Section 9.3.3 Secondary endpoint analysis - is implicitly affected due to direct referencing to Section 9.3.2	The strategies for handling missing data have been updated	This has been done in accordance with the change of the estimands
Section 9.3.2.2 Additional estimand	The imputation strategy for the new primary estimand that follows the treatment policy strategy has been updated such that it is performed under the non-inferiority null-hypothesis	This has been done to preserve the conservatism of the primary analysis and is aligned with feedback received from health authority
Section 1.3 Flowchart – PK sampling Section 10.2 Appendix 2: Clinical laboratory tests	The sampling time range in footnote ‘c’ and Table 10-4 has been changed from ‘96 to 119 hours’ to ‘96 to 144 hours’	This has been done to correct the time range for sampling
Section 4.3 Justification for dose	The wordings have been corrected in order to clarify that the target maintenance dose of 1.0 mg will be performed during the first 8 weeks after randomisation	This has been done to maintain consistency between Section 4.3 and Section 6.1
Section 10.10 Appendix 10 Abbreviations	The abbreviations ‘AIC’ and ‘MMRM’ has been removed	This has been removed as it is no longer defined in protocol

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Protocol Attachment II Country list of key staff and relevant departments

1 Protocol summary

1.1 Synopsis

This is an interventional, 28-week, multinational, multicentre, double-blinded, randomised, active controlled study with two treatment arms.

Rationale:

The aim of this clinical comparability study is to establish non-inferiority of semaglutide drug product based on the proposed drug substance manufacturing process (semaglutide J s.c.) against the currently approved semaglutide drug product based on the approved drug substance manufacturing process (semaglutide B s.c.) based on efficacy when measured by HbA_{1c} (%) and also to evaluate any potential risk for unexpected differences in safety, in participants with type 2 diabetes (T2D).

Semaglutide, a potent human glucagon like peptide-1 receptor agonist is approved in many countries for the treatment of T2D, and in several countries including the United States, it is moreover approved in adults with T2D and established cardiovascular disease to reduce the risk of major adverse cardiovascular events. Other benefit of semaglutide s.c. in patients with T2D is reduction in body weight.

To ensure adequate manufacturing capacity and safeguarding supply of semaglutide for the market, the manufacturing process of the drug substance used for the approved semaglutide drug product for s.c. use will be optimised by replacing the currently used *Saccharomyces cerevisiae* yeast strain with a more productive *Saccharomyces cerevisiae* yeast strain which has been enhanced to generate a higher yield and is currently used for manufacturing of semaglutide drug substance approved for oral administration. The drug product using the drug substance manufactured by the proposed process conform to the specifications approved for semaglutide s.c. The drug product manufacturing process from drug substance including excipients, which are already used in the approved semaglutide drug product, will remain unchanged.

Objectives, endpoints and estimands:

Primary objective

- To establish non-inferiority of semaglutide J s.c. against semaglutide B s.c. on change from baseline in HbA_{1c} at week 28 in participants with T2D as add-on to stable dose of metformin.

Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline visit (visit 2; week 0) to end of treatment visit (visit 10; week 28)	%-point

Secondary objective

- To compare the effect of semaglutide J s.c. and semaglutide B s.c. on change from baseline in body weight at week 28 in participants with T2D as add-on to stable dose of metformin

- To compare the number of treatment AEs between semaglutide J s.c. and semaglutide B s.c. in participants with T2D as add-on to stable dose of metformin
- To compare the development of anti-semaglutide antibodies between semaglutide J s.c. and semaglutide B s.c. in participants with T2D as add on to stable dose of metformin

Key supportive secondary endpoint

Endpoint title	Time frame	Unit
Change in body weight	From baseline visit (visit 2; week 0) to end of treatment visit (visit 10; week 28)	kg

Primary estimand

The primary clinical question of interest for the primary objective is to evaluate whether semaglutide J s.c. is non-inferior to semaglutide B s.c. in its effect on change from baseline to week 28 in HbA_{1c} (%-points) with a threshold margin of 0.3%-points in patients with T2D irrespective of treatment discontinuation and use of rescue medication.

The primary estimand is defined by the following five attributes as defined in ICH E9(R1):[2]

- Population: Patients with T2D.
- Endpoint: Change in HbA_{1c} (%-points) from baseline to week 28.
- Intervention condition: Except for trial product, the treatment regimen evaluated is the same for both intervention groups and is defined as the trial product taken for up to 28 weeks with or without initiation of glycaemic rescue medications. The treatment regimen is add-on to background metformin including possible changes in dose.
- Remaining intercurrent events: No further events are identified. The three intercurrent events are addressed in the intervention condition attributes. Treatment discontinuation for any reason, initiation of rescue medication, and changes to metformin dose is handled by the treatment policy strategy.
- Population-level summary: Difference in mean changes between semaglutide J s.c. and semaglutide B s.c.

Additional estimand

An additional clinical question of interest is to evaluate whether semaglutide J s.c., if taken for the planned 28 weeks, is non-inferior to semaglutide B s.c. in its effect on change from baseline to week 28 in HbA_{1c} (%-points) with a threshold margin of 0.3%-points in patients with T2D had they not required glycaemic rescue medication.

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

- Intervention condition: Except for trial product, the treatment regimen evaluated is the same for both intervention groups and is defined as the trial product taken for 28 weeks without initiation of glycaemic rescue medications. The treatment regimen is add-on to background metformin including possible changes in dose.
- Remaining intercurrent events: No further events are identified. The three intercurrent events are addressed in the intervention condition attributes. Treatment discontinuation for

any reason and initiation of rescue medication is handled with the hypothetical strategy. Changes to metformin dose is handled by the treatment policy strategy.

Overall design:

The study consists of:

- a 2-week screening period
- a 28-week intervention period
- a 5-week follow-up period

The intervention period comprises an 8-week dose escalation period with dose escalation every 4 weeks followed by a 20-week maintenance period.

Study intervention groups and duration:

Participants will be randomised in a 3:1 manner to receive either semaglutide J s.c. or semaglutide B s.c. An unbalanced randomisation with a higher proportion of participants randomised to receive semaglutide J s.c. is applied in order to maximise the exposure, and thereby the number of observations available to evaluate any unexpected adverse clinical consequences related to semaglutide J s.c.

The maximum duration of the intervention is 28 weeks, and the maximum duration of study is 35 weeks.

Investigational medicinal products

- Semaglutide J 1.34 mg/mL, s.c., solution for injection, 1.5 mL PDS290 prefilled pen injector.
- Semaglutide B 1.34 mg/mL, s.c., solution for injection, 1.5 mL PDS290 prefilled pen injector

Number of participants:

Approximately 475 participants will be screened to achieve 380 participants randomly assigned to receive either once-weekly semaglutide J s.c. or semaglutide B s.c.

Participant characteristics:

The participants will be male or female, aged between 18-64 years at the time of signing informed consent who meet the following key inclusion criteria and none of the following key exclusion criteria:

Key inclusion criteria

1. Diagnosed with T2D mellitus ≥ 180 days before screening.
2. Stable daily dose(s) ≥ 90 days prior to the day of screening of metformin ≥ 1500 mg or maximum tolerated or effective dose.
3. HbA_{1c} of 7.0-10.5% (53-91.3 mmol/mol) (both inclusive).

Key exclusion criteria

1. Known or suspected hypersensitivity to study intervention(s) or related products.

2. 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 and prior insulin treatment for gestational diabetes are allowed.
3. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within 90 days before screening or in the period between screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for nondilated examination.

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

Data monitoring committee: No

1.2 Flowchart

Procedure	Protocol Section	Screening	Randomisation	Intervention period							End of treatment	End of study
				Dose escalation			Maintenance period					
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Timing of visit/study day (weeks)		-2	0	2	4	8	12	16	20	24	28	33
Visit window (days)		Up to -14 days		±1	±1	±3	±3	±3	±3	±3	±3	+7
Informed Consent and Demography[a]	10.1.3	X										
Tobacco use	5.3.2	X										
Eligibility Criteria	5.1 and 5.2	X	X									
Randomisation	6		X									
Discontinuation criteria	7.1			X	X	X	X	X	X	X		
Attend Visit Fasting	5.3.1		X					X			X	X[b]
Medical History/ Concomitant Illness	8.2	X	X									
Concomitant Therapy	6.8	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	8.2.2	X	X	X				X			X	

Procedure	Protocol Section	Screening	Randomisation	Intervention period							End of treatment	End of study
				Dose escalation			Maintenance period					
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Timing of visit/study day (weeks)		-2	0	2	4	8	12	16	20	24	28	33
Visit window (days)		Up to -14 days		±1	±1	±3	±3	±3	±3	±3	±3	+7
Physical Examination	8.2.1	X									X	
Body Measurements	8.2.1	X	X	X	X	X	X	X	X	X	X	
Childbearing Potential	8.2.6 and 10.4	X										
Pregnancy Test	8.2.6 and 10.2	X	X								X	X
Laboratory Assessments	10.2	X	X	X	X	X	X	X	X	X	X	X
PK sampling (For details see separate flowchart in Section 1.3)	8.4 and 10.2			X	X	X	X	X	X	X	X	X
Antibodies	8.7 and 10.2		X		X	X	X				X	X
Eye Examination	8.2.3	X									X	
Adverse Event	8.3 and 10.3			X	X	X	X	X	X	X	X	X

Procedure	Protocol Section	Screening	Randomisation	Intervention period							End of treatment	End of study
				Dose escalation			Maintenance period					
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Timing of visit/study day (weeks)		-2	0	2	4	8	12	16	20	24	28	33
Visit window (days)		Up to -14 days		±1	±1	±3	±3	±3	±3	±3	±3	+7
Hypoglycaemic episodes	8.3 and 10.7			X	X	X	X	X	X	X	X	X
Training in Devices	6.1		X		X		X					
Drug Dispensing Visit	6.1		X		X		X		X			
Drug Accountability	6.2		X		X		X		X		X	
Dosing History	8			X	X	X	X	X	X	X	X	
Remind the participant about when to administer their last treatment before next visit	6.1			X	X	X	X	X	X	X	X	

Note:

[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] Fasting is defined as at least 2 hours prior to the visit 11 without food or liquid, except for water (see Section 5.3.1).

Abbreviation: V = visit.

1.3 Flowchart – PK sampling

Procedure	Protocol Section	Intervention period							End of treatment	End of study
		Dose escalation			Maintenance period					
Visit		V3	V4	V5	V6	V7	V8	V9	V10	V11
Dosing window (days)		±1	0	±1	0	±1	±1	0	±1	+7
PKsampling 10.1.3										
Trough[a]	10.2 and Table 10-2		X		X			X		
Peak[b]	10.2 and Table 10-2	X		X		X			X	
Decline[c]	10.2 and Table 10-2						X			
No requirement	10.2 and Table 10-2									X

Note:

The dosing windows for PK sampling is optimised to ensure that the weekly fluctuation in PK can be characterised (for more details; see Section 6.1).

[a] Sampling prior to treatment administration on a planned dosing day.

[b] Sampling 24 to 71 hours after dosing (from 1 to 3 days after dosing).

[c] Sampling 96 to 144 hours after dosing (from 4 to 6 days after dosing).

2 Introduction

2.1 Study rationale

Semaglutide is a potent human glucagon like peptide-1 (GLP-1) analogue that acts as a GLP-1 receptor agonist (RA), with a long half-life (approximately 1 week) suitable for once-weekly dosing. Semaglutide subcutaneous (s.c.) is approved in many countries for the treatment of type 2 diabetes (T2D). In several countries including the United States (US), semaglutide s.c. is moreover approved in adults with T2D and established cardiovascular disease to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction (MI) or nonfatal stroke). Other benefits from treatment with semaglutide s.c. in T2D patients are reduction in bodyweight and due to its glucose dependent mode of action, a low risk of hypoglycaemic episodes.[3, 4]

To ensure adequate manufacturing capacity and safeguarding supply of semaglutide for the market, the manufacturing process of the drug substance (DS) used for the approved semaglutide drug product (DP) for s.c. use will be optimised. The currently used *Saccharomyces cerevisiae* yeast strain will be replaced with a more productive *Saccharomyces cerevisiae* yeast strain which has been optimized to generate a higher yield and which is currently used for manufacturing of semaglutide DS approved for oral administration. Hence, the corresponding fermentation process and subsequent recovery process currently used for manufacturing of semaglutide DS approved for oral administration will be implemented in the manufacturing process of semaglutide DS for s.c. administration. The DP using the DS manufactured by the proposed process conform to the specifications approved for semaglutide s.c. The DP manufacturing process from DS including excipients, which are already used in the approved semaglutide s.c. DP, will remain unchanged.

Throughout this document, semaglutide J s.c. will refer to the semaglutide DP based on the proposed DS manufacturing process and semaglutide B s.c. will refer to the currently approved semaglutide DP based on the approved DS manufacturing process.

This clinical comparability study is designed to establish non-inferiority of semaglutide J s.c. against semaglutide B s.c. based on efficacy when measured by glycosylated haemoglobin (HbA_{1c} (%)) and also to evaluate any potential risk for unexpected differences in safety. Hereby ensuring that the safety and efficacy of semaglutide s.c. is not affected by the manufacturing change.

2.2 Background

Semaglutide J s.c. has been evaluated according to the Food and Drug Administration (FDA) Guidance for Industry 'Changes to an approved New Drug Application (NDA) or Abbreviated New Drug Application (ANDA)' and European Medicines agency's (EMA) 'Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process'.[5, 6]

Based on appropriate comparison of relevant quality attributes, the DP manufactured by proposed and approved DS manufacturing process are highly similar and considered comparable, i.e., no adverse impact on safety or efficacy profiles is foreseen.[6] The impurities specific to the proposed process has previously been clinically and non-clinically qualified without any issues related to immunogenicity being observed.

In brief, semaglutide J s.c. and semaglutide B s.c. are comparable based on the available data. Hence, the Chemistry, Manufacturing, and Controls (CMC) comparability studies are considered adequate to support implementation of the proposed DS manufacturing process for semaglutide s.c.

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 (AEs) of semaglutide s.c. may be found in the investigator's brochure (IB)[7] and any updates thereof.

2.3.1 Risk assessment

Table 2-1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study interventions (semaglutide J s.c. and semaglutide B s.c.)		
GI disorders	Consistent with other GLP-1 RAs, the most frequent AEs with semaglutide s.c. are GI (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 GI symptoms. Participants with GI symptoms are recommended to drink plenty of fluids to avoid volume depletion.
Hypoglycaemia	There is a low risk of hypoglycaemic episodes when semaglutide s.c. is used as monotherapy. Participants treated with semaglutide s.c. in combination with metformin may have an increased risk of hypoglycaemia.	The risk of hypoglycaemia can be lowered by reducing the dose of metformin when initiating treatment with semaglutide s.c.
Diabetic retinopathy complications	In a 2-year clinical study with semaglutide s.c. (NN9535-3744) involving 3,297 participants with T2D, high CV risk, long duration of diabetes and poorly controlled blood glucose, EAC-confirmed events of diabetic retinopathy complications occurred in more participants treated with semaglutide s.c. (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 semaglutide s.c. 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 semaglutide s.c. (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.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Hypersensitivity reactions	As with all protein-based pharmaceuticals, treatment with semaglutide s.c. may evoke hypersensitivity reactions, including serious hypersensitivity reactions such as anaphylactic reactions.	As a precaution, participants with known or suspected hypersensitivity to semaglutide s.c. 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 intervention 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 s.c. should be discontinued. If confirmed, semaglutide s.c. should not be restarted. For details on discontinuation of study intervention, see Section 7.1.
Neoplasms (malignant and non-malignant)	Participants with T2D, as well as participants 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 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.	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 and any carcinoma *in-situ* is allowed.
Pancreatic cancer	Participants with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from nonclinical 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 s.c. intervention 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.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Medullary thyroid cancer	Thyroid C-cell tumours were seen in mouse and rat carcinogenicity studies after daily exposure to semaglutide s.c. for 2 years. The rodent C-cell tumours are caused by a nongenotoxic, 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 MEN2 are excluded from clinical studies with semaglutide s.c.
Other		
Pregnancy and fertility	Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide s.c. in pregnant women.	Semaglutide s.c. 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 (Section 10.4.2)). If a participant wishes to become pregnant, or pregnancy occurs, semaglutide s.c. should be discontinued (please refer to Appendix 4 (Section 10.4) for further guidance). The effect of semaglutide s.c. on fertility in humans is unknown.
Study procedures		
Potential risk: COVID-19 infection in relation to participation in 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 given country.	The risk of COVID-19 transmission in relation to site visits is overall considered to be low, however this may vary between geographical areas. To minimise the risk as much as possible, the following measures have been taken: • 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).

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
		• Appendix 8 (Section 10.8) includes mitigations that can be implemented to ensure participant safety and data integrity in case a major emergency (e.g. COVID-19 outbreak) leads to lock-down of sites which affects the ability to perform study-related procedures.

Abbreviations: AEs = adverse events; COVID-19 = coronavirus disease 19; CV = cardiovascular; EAC = event adjudication committee; EMA = European Medicines Agency; GI = gastrointestinal; GLP-1 RA = glucagon like peptide-1 receptor agonists; MEN2 = multiple endocrine neoplasia type 2; s.c. = subcutaneous; T2D = type 2 diabetes

2.3.2 Benefit assessment

Eligible participants will receive thorough medical attention and every enrolled participant would 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.

The active-controlled study design means that all participants will receive and potentially benefit from intensified T2D management.

Investigational medicinal products (IMPs) and auxiliary supplies including medical device not under investigation will be provided free of charge (please see Section 6; for more details).

2.3.3 Overall benefit-risk conclusion

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

Taking into account the measures taken to minimise risk and burden to participants participating in this study, the potential risks identified in association with once-weekly semaglutide s.c. are justified by the anticipated benefits that may be afforded to participants with T2D.

3 Objectives, endpoints and estimand

3.1 Objectives and endpoints

The primary and secondary objectives and the primary and supportive secondary endpoints are presented in Table 3-1.

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
To establish non-inferiority of semaglutide J s.c. against semaglutide B s.c. on change from baseline in HbA_{1c} at week 28 in participants with T2D as add-on to stable dose of metformin	Primary:		
	Change in HbA_{1c}	From baseline visit (visit 2; week 0) to end of treatment visit (visit 10; week 28)	%-point
Secondary	**Title**	**Time frame**	**Unit**
To compare the effect of semaglutide J s.c. and semaglutide B s.c. on change from baseline in body weight at week 28 in participants with T2D as add-on to stable dose of metformin	Supportive		
	Change in body weight	From baseline visit (visit 2; week 0) to end of treatment visit (visit 10; week 28)	kg
To compare the number of treatment AEs between semaglutide J s.c. and semaglutide B s.c. in participants with T2D as add-on to stable dose of metformin	Supportive		
	Number of treatment-emergent AEs	From the time of first dosing to end of study visit (visit 11; week 33)	Count
To compare the development of anti-semaglutide antibodies between semaglutide J s.c. and semaglutide B s.c. in participants with T2D as add-on to stable dose of metformin	Supportive		

	Occurrence of anti-semaglutide antibodies (yes/no)
	• *In vitro* neutralising anti-semaglutide antibodies
	  • Anti-semaglutide binding antibodies cross-reacting with endogenous GLP-1
	  ○ *In vitro* neutralising cross-reacting antibodies to endogenous GLP-1
		From baseline visit (visit 2; week 0) to end of study visit (visit 11; week 33)	Count of participant

	Anti-semaglutide antibodies level	From baseline visit (visit 2; week 0) to end of study visit (visit 11; week 33)	(%B/T and titre)

Abbreviations: AEs = adverse events; GLP-1 = glucagon like peptide-1; HbA_{1c} = glycated haemoglobin; s.c. = subcutaneous, T2D = type 2 diabetes

The population pharmacokinetics of semaglutide J s.c. and semaglutide B s.c. in participants with T2D as add-on to stable dose of metformin will be addressed based on a modelling analysis plan and all PK assessments will be presented in a comprehensive modelling report (See Section 9.3.6).

3.1.1 Primary estimand

The primary clinical question of interest for the primary objective is to evaluate whether semaglutide J s.c. is non-inferior to semaglutide B s.c. in its effect on change from baseline to week 28 in HbA_{1c} (%-points) with a threshold margin of 0.3%-points in patients with T2D irrespective of treatment discontinuation and use of rescue medication.

The primary estimand is defined by the following five attributes as defined in ICH E9(R1):[0 2]

- Population: Patients with T2D.
- Endpoint: Change in HbA_{1c} (%-points) from baseline to week 28.
- Intervention condition: Except for trial product, the treatment regimen evaluated is the same for both intervention groups and is defined as the trial product taken for up to 28 weeks with or without initiation of glycaemic rescue medications. The treatment regimen is add-on to background metformin including possible changes in dose.
- Remaining intercurrent events: No further events are identified. The three intercurrent events are addressed in the intervention condition attributes. Treatment discontinuation for any reason, initiation of rescue medication, and changes to metformin dose is handled by the treatment policy strategy.
    - Population-level summary: Difference in mean changes between semaglutide J s.c. and semaglutide B s.c.

3.1.2 Additional estimand

An additional clinical question of interest is to evaluate whether semaglutide J s.c., if taken for the planned 28 weeks, is non-inferior to semaglutide B s.c. in its effect on change from baseline to week 28 in HbA_{1c} (%-points) with a threshold margin of 0.3%-points in patients with T2D had they not required glycaemic rescue medication.

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

- Intervention condition: Except for trial product, the treatment regimen evaluated is the same for both intervention groups and is defined as the trial product taken for 28 weeks without initiation of glycaemic rescue medications. The treatment regimen is add-on to background metformin including possible changes in dose.
- Remaining intercurrent events: No further events are identified. The three intercurrent events are addressed in the intervention condition attributes. Treatment discontinuation for any reason and initiation of rescue medication is handled with the hypothetical strategy. Changes to metformin dose is handled by the treatment policy strategy.

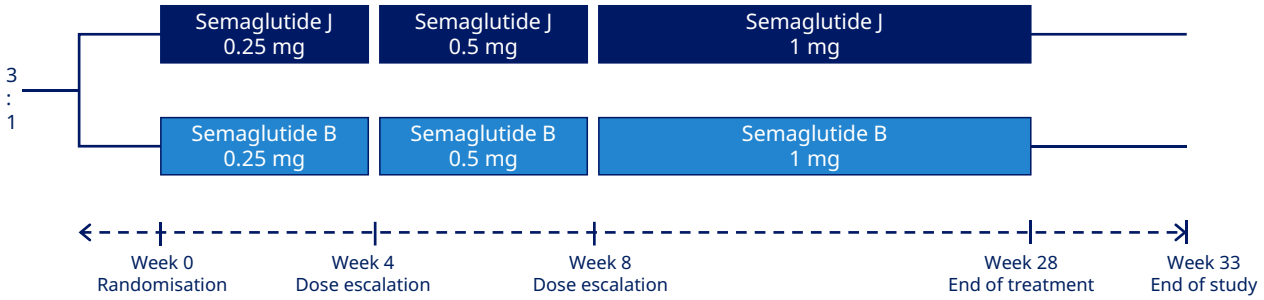
4 Study design

4.1 Overall design

This is an interventional, 28-week, multinational, multicentre, double-blinded, randomised, active controlled study comparing semaglutide J s.c. with semaglutide B s.c. in participants with T2D inadequately controlled on a stable dose of metformin with a baseline HbA_{1c} of 7.0–10.5%.

A total of 380 participants will be randomised in a 3:1 manner to receive either semaglutide J s.c. or semaglutide B s.c. The study consists of a 2-week screening period, a 28-week intervention period followed by a 5-week follow-up period. The intervention period comprises an 8-week dose escalation period with dose escalation every 4 weeks followed by a 20-week maintenance period. The planned study duration for the individual participant will be approximately 35 weeks (including screening period). The study design is illustrated in Figure 4-1.

Figure 4-1 Study design



4.2 Scientific rationale for study design

The primary objective is to establish non-inferiority on efficacy when measured by HbA_{1c} (%) of semaglutide J s.c. against semaglutide B s.c. with a non-inferiority margin of 0.3%-points. This margin is considered acceptable as it is in line with the 'Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus' and within the range of previously approved applications.[8]

Randomisation and double blinding are applied to minimise bias in the non-inferiority evaluation. An unbalanced randomisation (3:1) with a higher proportion of participants randomised to receive semaglutide J s.c. is applied in order to maximise the exposure, and thereby the number of observations available to evaluate any unexpected adverse clinical consequences related to semaglutide J s.c.

The 28-week intervention period is sufficient for evaluation of the primary endpoint. A 5-week follow-up period (corresponding to roughly 5 times $t_{1/2}$) is implemented to avoid drug interference in the anti-drug antibody assays.

4.3 Justification for dose

Semaglutide s.c. 0.5 mg and 1.0 mg are currently approved for treatment of patients with T2D (Ozempic®). Participants will be initiated at a once-weekly dose of 0.25 mg and follow the approved fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5 mg/week and 1.0 mg/week), until the target maintenance dose of 1.0 mg is reached during the first 8 weeks after randomisation (i.e., at visit 5 or the first dosing date after visit 5).

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 they have completed all periods of the study including the last visit.

The primary endpoint is evaluated from visit 2 (week 0) to visit 10 (week 28). The primary completion date (PCD) is defined as the date of visit 10 (week 28) 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 10 (week 28). The PCD determines the deadline for results disclosure at clinicaltrials.gov according to the Food and Drug Administration Amendment Act (FDAAA) (Section 10.1.7).

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 participant's medical records, including handing out participant information, as well as database review. Any pre-screening activities must be documented 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 T2D mellitus ≥ 180 days before screening.
5. Stable daily dose(s) ≥ 90 days prior to the day of screening of metformin ≥ 1500 mg or maximum tolerated or effective dose.
6. HbA_{1c} of 7.0-10.5% (53-91.3 mmol/mol) (both inclusive).

For country specific requirements in Canada, please refer to Appendix 9 (Section 10.9).

5.2 Exclusion criteria

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

1. Known or suspected hypersensitivity to study intervention(s) or related products.
2. Previous participation in this study. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using adequate contraceptive method, as defined in Appendix 4 (Section 10.4).
4. Participation in any clinical study of an approved or non-approved IMP within 30 days before screening.
5. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.[a]
6. Presence or history[a] of pancreatitis (acute or chronic).
7. Renal impairment with estimated Glomerular Filtration Rate (eGFR) < 30 ml/min/1.73 m^2 at screening.
8. Impaired liver function, defined as alanine aminotransferase (ALT) ≥ 2.5 times or bilirubin >1.5 times upper normal limit at screening.
9. Inadequately treated blood pressure defined as systolic ≥180 mmHg or diastolic ≥110 mmHg at screening.
10. MI, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within 180 days before screening.
11. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.
12. Planned coronary, carotid or peripheral artery revascularisation.

13. 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 and prior insulin treatment for gestational diabetes are allowed.
14. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within 90 days before screening or in the period between screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for nondilated examination.
15. 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.
16. Use of any medication with unknown or unspecified content within 90 days before screening.
17. Any disorder which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.

[a]As declared by the participant or reported in the medical records.

5.3 Lifestyle considerations

5.3.1 Meals and dietary restrictions

- Participants must attend the visits fasting according to the flowchart (Section 1.2).
- Fasting is defined as at least 6 hours prior to the visit (visit 2, 7 and 10) without food or liquids, except for water.
- For end of trial visit (visit 11) fasting is defined as at least 2 hours prior to the visit without food or liquid, except for water.
- If the 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 done.

5.3.2 Tobacco use

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

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, eligibility criteria, and any serious adverse event (SAE).

A screen failure session must be performed in the 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 samples), re-sampling is allowed for the affected parameters.

5.5 Randomisation criteria

Not applicable for this study.

6 Study intervention(s) and concomitant therapy

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

Trial product comprise IMP(s), including comparator(s), non-investigational medicinal product(s) (NIMP(s)) and medical devices.

6.1 Study intervention(s) administered

Table 6-1 provides an overview of the study interventions.

Table 6-1 Study interventions

Intervention/Arm name	**Semaglutide J**	**Semaglutide B**
Intervention name	Semaglutide J.	Semaglutide B.
Intervention type	IMP, test product.	IMP, reference product.
Pharmaceutical form	Solution for injection.	
Route of administration	s.c.	
Medical device	Not applicable. See 'Packaging' for device constituent.	
Trial product strength	1.34 mg/mL (1.5 mL).	
Dose and dose frequency	Visit 2-4: 0.25 mg once-weekly (initiated at V2). Visit 4-5: 0.5 mg once-weekly (initiated at V4). Visit 5-10: 1.0 mg once-weekly (initiated at V5).	
Dosing instructions and administration	s.c. (into the thigh, upper arm or abdomen).	
Sourcing	Manufactured and supplied by Novo Nordisk A/S.	
Packaging	1.5 mL PDS290 prefilled pen injector. The device constituent is not under investigation.	
Labelling	Labelled and packaged by Novo Nordisk A/S. Labelled in accordance with Annex 13,[9] local regulations and study requirements.	

Abbreviations: IMP = investigational medicinal product; s.c. = subcutaneous.

The investigator must document that training in device was given to the participant verbally and in writing as directions for use (DFU) documents at the first dispensing visit (visit 2). It must also be documented that verbal training in device was given at visit 4 and visit 6 (as specified in the flowchart; see Section 1.2). If the investigator finds it relevant, additional training and handout of DFUs can also be given at other visits during the study. Training is the responsibility of the

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

The investigator should remind participants of dosing instructions throughout the study, as applicable. A dose reminder card will be handed out to the participants from the first dispensing visit (visit 2) to visit 9, to remind the participant of the dose to be taken until next site visit. Approximately a week before the next scheduled visit, the investigator should contact the participant and remind them about when to administer the next dose according to Section 1.3 and a reminder for the same will be included in the participant's diary as well (see flowchart; Section 1.2).

Investigational medicinal products (IMP)

The study interventions are listed in Table 6-1.

Dosing instructions

Participants will be instructed to inject the trial product subcutaneously once-weekly in the abdomen, thigh, or upper arm. The injection site can be changed without dose adjustment.

Participants must be trained in handling the pen-injector when dispensed the first time and training must be repeated during the study as indicated in the flowchart (Section 1.2). The investigator may choose to observe the participant when administering the first dose.

The injection can be administered at any time of the day irrespective of meals, but on the same day of the week. The day of weekly administration can be changed if necessary if the time between two doses is at least 2 days (≥48 hours) or in accordance with the local label. After selecting a new dosing day, once-weekly dosing should be continued.

Visits with blood sampling for PK are planned with specific timing in connection with trial product administration. The timing of visits is optimised to ensure that the weekly fluctuation in PK can be characterised with population PK modelling.

In order to ensure correct timing of PK sampling in relation to trial product administration, the visits after randomisation should be scheduled within the allowed visit window according to the PK flowchart (Section 1.3). Blood sampling should always be collected prior to trial product administration if the visit is planned on a dosing day. If blood sampling is not planned on a dosing day, it is important to perform the visit and the blood sampling within the allowed number of hours/days after dosing. Guidance for the timing of visits and blood sampling is outlined in Table 10-4.

If the participant by mistake has administered trial product outside the ranges specified, the visit should be rescheduled (within the visit window). If this is not possible, Investigator should try to change the PK sample e.g. from a trough sample to a peak or a decline sample (whatever is feasible compared to when the dose was taken).

Dose escalation

Dose escalation to the target maintenance dose of semaglutide s.c. 1.0 mg should take place during the first 8 weeks after randomisation. All participants will initiate semaglutide s.c. 0.25 mg on the

day of randomisation (visit 2). Dose escalation of semaglutide s.c. should take place every 4 weeks after randomisation, as illustrated in Figure 4-1. The maintenance dose of 1.0 mg will be reached at week 8 and will continue for the remaining treatment duration. If a participant does not tolerate the designated target dose, the participant may stay at a lower dose level. This should only be allowed if the participant would otherwise discontinue trial product completely and if considered safe to continue trial product at a lower dose, as per the investigator's discretion.

Missed doses

If a semaglutide s.c. dose is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 2 days (≥48 hours). If a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the participant should not administer the missed dose. A missed dose should not affect the scheduled dosing day of the week.

If ≥ 2 consecutive doses of trial product are missed, and if the participant does not meet any of the discontinuation criteria (Section 7.1), the participant should be encouraged to recommence the treatment if considered safe as per the investigator's discretion. The trial product should be continued as early as the situation allows. The missed doses should not affect the scheduled dosing day of the week. The start dose for re-initiation of trial product is at the investigator's discretion. In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk global medical experts. If doses are missed, blood glucose should be more closely monitored if judged necessary by the investigator.

Non-investigational medicinal products (NIMP)

Antidiabetic background medication (metformin) and rescue medication are considered NIMP(s) and will not be supplied by Novo Nordisk.

Auxiliary supplies including medical devices not under investigation

Blood glucose (BG) meters will be provided by Novo Nordisk through a vendor while the other auxiliary supplies (Table 6-2) will be provided by Novo Nordisk.

Table 6-2 Auxiliary supplies

Auxiliary supplies	Details
Needles	Needles for PDS290 pen-injector. Details will be provided in the TMM. Only needles approved and provided by Novo Nordisk and with a maximum length of 6 mm must be used for administration of trial product.
DFU	DFUs for PDS290 pen-injector. DFUs are not included in the dispensing unit and must be handed out separately.
BG meter and related auxiliaries	A FreeStyle Precision Neo/FreeStyle Optium Neo/Optium Xido Neo/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.

Abbreviations: BG = blood glucose; DFU = direction for use; TMM = trial materials manual.

The PDS290 pen-injector (device constituent) is used for administration of semaglutide and is a prefilled pen-injector which is not under investigation in this study. The PDS290 pen-injector is a dial-a-dose prefilled device integrated with a 1.5 mL cartridge (filled with

semaglutide 1.34 mg/mL). The PDS290 pen-injector for semaglutide 1.34 mg/mL can deliver the doses of 0.25 mg, 0.5 mg and 1.0 mg (dose dialled on pen-injector).

Risk assessment has been conducted for the PDS290 pen-injector for semaglutide 1.34 mg/mL complying with EN International Organisation for Harmonisation (ISO) 14971:2019: Medical devices - Application of risk management to medical devices. A device risk assessment has been performed to ensure safe and accurate handling and dosing of semaglutide s.c. when using the PDS290 pen-injector in participants with T2D. All identified risks associated with using PDS290 pen-injector for semaglutide 1.34 mg/mL according to the clinical procedures specified in this protocol have been reduced as far as possible and are acceptable, taking into account the current state of the art. The use of PDS290 pen-Injector for semaglutide 1.34 mg/mL in this study is therefore considered to be of nonsignificant risk.

6.2 Preparation, handling, storage and accountability

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

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

Instructions on how to use the PDS290 pen-injector will be provided in the DFU.

For selected countries and if permitted by local regulations, the investigator may offer to send study intervention from the study site or pharmacy to the participant's home by courier service. The process for sending study intervention from the study site or pharmacy to a participant's home is described in the "Study site/pharmacy instruction for shipment of trial product to participant's homes" document. This document contains detailed instructions for preparing, packaging, and setting up the pick-up of study intervention, handover of study intervention from the study site or pharmacy staff to the courier, required temperature monitoring of study intervention, delivery to and receipt of study intervention by the participant. The process for returning study intervention to the study site or pharmacy by courier is also described in this document. Investigators, study site/pharmacy staff and participants who will be involved in shipment of study intervention to the participant's home will be adequately trained in this process.

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

All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.

The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product 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 trial product accountability and record maintenance (i.e., receipt, accountability and final disposition records). Drug accountability must be performed by registering pen-injectors as returned either as used/partly used, unused or as lost. Drug accountability should also be performed in the RTSM/IWRS.

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 products. The in-use time can be found in the TMM and the labels of the trial products.

Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor. Destruction of trial product must be documented in the RTSM/IWRS.

All returned (used or un-used), expired or damaged trial products (for technical complaint samples, see Appendix 5 (Section 10.5) must be stored separately from non-allocated trial products. No temperature monitoring is required.

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

Each single pen should be accounted for.

Acceptable temperature ranges and conditions for storage and handling of each trial product when not in use and when in use are described in the TMM.

6.3 Measures to minimise bias: Randomisation and blinding

Participants will be screened and centrally randomised using an RTSM/IWRS and assigned to the next available treatment according to the randomisation schedule. Trial products will be allocated by the RTSM/IWRS and dispensed by the investigator at the study visits summarised in the flowchart (Section 1.2). Once the participant has been assigned a randomisation number, the number must not be re-assigned to another participant.

This is a double-blind study in which participants, care providers and investigators are blinded to trial product allocation.

To preserve the blinding of the current study in the event of interim evaluation, only a minimum number of Novo Nordisk personnel are allowed to see the randomisation table and treatment assignments before the study is completed.

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 trial product 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 study intervention unless this could delay emergency treatment of the participant.

If a participant's trial product 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.

Unblinded participants may continue with trial product if there are no safety concerns at the discretion of the investigator.

6.4 Study intervention 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 trial product at home, compliance with trial product administration will be assessed, and the assessment documented in source documents at each visit where information is available. If any suspicion of noncompliance 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:

- Drug accountability information; counting returned trial product, visual inspection of pens.
- Review of diaries including self-measured plasma glucose (SMPG) profiles, semaglutide s.c. doses and hypoglycaemia.
- Evaluating glycaemic control and adherence to the visit schedule.
- Trial product start and stop dates will be recorded in the electronic case report form (eCRF).

6.5 Dose modification

Deviations from the planned doses (see Table 6-1) are not allowed. Please refer to Section 6.1 for description of missed doses.

In order to minimise the risk of gastrointestinal AEs the participants should follow the recommended dose escalation regimen described in Section 6.1. In case of tolerability issues, the dose of semaglutide s.c. can be adjusted as described in Section 6.1.

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 antidiabetic treatment after discontinuation of study intervention.

6.7 Treatment of 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.

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 IB[7] and any updates thereof.

Overdoses of up to 4.0 mg of semaglutide s.c. in a single dose/in one week have been reported in clinical studies. The most commonly reported adverse reaction was nausea. All participants recovered without complications. In the event of overdose, appropriate supportive treatment should be initiated according to the participants' clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of semaglutide of approximately one week.

Please consult the current version of the semaglutide (IB)[7] and any updates thereof for more information on overdose of semaglutide s.c.

6.8 Concomitant therapy

Any medication or vaccine that the participant is receiving at the time of screening visit (visit 1) or receives until end of study visit (visit 11)-must be recorded along with:

- Primary indication.
- Dates of administration including start and stop dates and total daily dose.

Changes in concomitant therapy must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 8.3.

6.8.1 Rescue medicine

Intensification of background oral antidiabetic treatment and/or initiation of new antihyperglycaemic treatment, should be implemented at the discretion of the investigator in case of persistent hyperglycaemia.

Rescue medication should be selected according to American Diabetes Association (ADA)/ European Association for the Study of Diabetes (EASD) guideline[10,11] (excluding GLP-1 RAs, dipeptidyl peptidase-4 (DPP-4) inhibitors and amylin analogues).

Participants that are prescribed rescue medication should continue to follow the protocol-specified visit schedule and stay on study intervention unless the investigator judge that it jeopardises participants' safety.

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

The site will not supply any rescue medication but will be reimbursed, as long as the participant is participating in the study, if required, according to local requirements.

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

Study intervention 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.

If a participant discontinues study intervention, the participant should be transferred to a commercially available treatment, at the investigator's discretion.

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 study intervention.

The study intervention must be discontinued, if any of the following applies for the participant:
1. Safety concerns related to study intervention or unacceptable intolerability, as judged by the investigator.
2. Confirmation of acute pancreatitis.
3. Pregnancy.
4. Intention of becoming pregnant.
5. Simultaneous use of an approved or non-approved IMP in another clinical study.

See the flowchart (Section 1.2) for data to be collected at the time of study intervention discontinuation (early discontinuation visit) and follow-up and for any further evaluations that need to be completed.

The participants should continue with the remaining scheduled visits and assessments until the time of the originally scheduled 'end of treatment' visit (visit 10) and "end of study" visit (visit 11).

All efforts should be made to have the participant attend at least the 'end of treatment' clinic visit containing the final data collection of primary and confirmatory secondary efficacy endpoints, and the "end of study" visit.

If the participant does not wish to attend the scheduled clinic visits efforts should be made to have the remaining visits converted to phone contacts.

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

7.1.1 Temporary discontinuation of study intervention

The participant should adhere to the study intervention to the extent possible. Exceptions to this could be in the case of safety concerns or AEs, as judged by the discretion of the investigator.

In case of suspicion of acute pancreatitis, the study interventions should promptly be interrupted. Discontinuation of treatment should not be completed in RTSM/IWRS before diagnosis of acute pancreatitis is confirmed (according to the Atlanta criteria)[12]. Appropriate actions should be initiated.

If acute pancreatitis is confirmed, the study interventions should not be restarted, and discontinuation of treatment must be made in RTSM/IWRS. If the Atlanta criteria are not fulfilled and thus, the suspicion of acute pancreatitis is not confirmed, study interventions may be resumed.

If a participant has temporarily discontinued study interventions due to an AE or a safety concern, they are allowed to restart, unless any of the discontinuation criteria specified in Section 7.1 applies. The participant should follow the guide for missed doses in Section 6.1. Similarly, a participant who discontinues study interventions on their own initiative should be encouraged to resume the study interventions.

Treatment discontinuation and treatment resume must be registered in RTSM/IWRS when a participant discontinues or resumes study intervention.

7.1.2 Rescue criteria

Participants with persistent and unacceptable hyperglycaemia should be offered treatment intensification. To allow time for dose escalation to maximum dose and to observe the expected effect of treatment on glycaemic parameters, rescue criteria will be applied at 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 ADA/EASD guidelines[10,11] (excluding GLP-1RAs, DPP-4 inhibitors and amylin analogues).

Rescue medication should be offered from week 12 to week 33 to:

- Participants with persistent poor glycaemic control, as expressed by a stable 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. Refer to Section 6.8.1 for description of rescue medication.

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, they 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 or is withdrawn by the investigator after randomisation, the investigator must ask the participant if they are willing, as soon as possible, to have assessments performed according to visit 10 and visit 11. See the flowchart (Section 1.2) for data to be collected.

Final trial product accountability must be performed even if the participant is not able to come to the site. Discontinuation of treatment must be made in RTSM/IWRS. The primary reason for discontinuation of study intervention should be specified in the end of IMP treatment form in the eCRF.

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, they 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 their 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 study intervention, withdraws consent or is withdrawn by the investigator, they will not be replaced.

7.3 Lost to follow-up

A participant will be considered lost to follow-up if they repeatedly fail 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, the participant will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

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 (Section 1.2), is essential and required for study conduct.

Assessments should be carried out according to the clinic's standard of practice unless specified in the current section. Efforts should be made to limit the bias between the assessments. The suggested order of assessments:

- Blood sampling (especially when collection fasting blood samples)
- Other assessments

A visit-specific diary for collection of detailed hypoglycaemic episodes, dosing history and AEs must be handed out at each site visit from randomisation (visit 2) to end of treatment (visit 10) included.

Review of diaries, 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 Clinical efficacy assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the flowchart (Section 1.2) 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.

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.

The following concomitant illness/medical history should be recorded in the eCRF:
- T2D including date of diagnosis.
- History of cardiovascular disorders and procedures.
- History of dyslipidaemia.
- History of kidney diseases.
- History of eye diseases.
- History of neuropathy.
- History of gallbladder diseases and procedures.
- History of pancreatic diseases.
- Other relevant concomitant illness/medical history including malignant neoplasms and coronavirus disease 19 (COVID-19).

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 the:
- Head, ears, eyes, nose, throat, neck,
- Respiratory system,
- Cardiovascular system,
- Gastrointestinal system including mouth,
- Musculoskeletal system,
- Central and peripheral nervous system,
- Skin.

Abnormal, clinically significant findings at screening should be recorded as concomitant illness in the eCRF. At the following visits, any new abnormal, clinically significant findings or clinically significant deteriorations after randomisation should be reported as AEs, see Appendix 3 (Section 10.3).

Body measurements (e.g., height and weight) will also be measured and recorded as specified in the flowchart (Section 1.2).

Height will be measured and recorded at the screening visit (visit 1). Body weight will be measured and recorded according to the flowchart (Section 1.2).

- Body weight should be measured in kilograms (kg) or pounds (lb) in participants wearing only light clothing. Body weight will be recorded to one decimal place, with a precision of 1/10 unit, (e.g. 45.2 kg / 137.2 lb). Body weight should be assessed with the same equipment throughout the study, if possible.
- Height should be measured in centimetres (cm) or inches (in) without shoes. Height will be recorded to the nearest ½ cm or ¼ inch.

From the body weight and height, the BMI will be calculated in the eCRF at visit 1 and recorded in the participant's medical records.

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

8.2.2 Vital signs

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

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 and pulse rate are collected at the time points mentioned in the flowchart (Section 1.2).

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 (Section 5.2) 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 should be performed as a fundus photography (e.g., 2-field 60 degree or better, colour or red-free) or by slit-lamp bio-microscopy examination (e.g., using a precorneal 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 at visit 10 as per protocol flowchart (Section 1.2). The investigator should indicate the outcome of each eye examination.

Eye examinations required at visit 10 can be performed within 3 weeks prior to visit 10, provided no clinical symptoms suggestive of eye disease have occurred in the meantime. Results should be available for evaluation at visit 10. 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 and Appendix 3 (Section 10.3) for details. Participants who discontinued treatment should also have their eye examinations performed in relation to the end of treatment visit (visit 10).

8.2.4 Self-measured plasma glucose

Plasma glucose (PG) should always be measured using a BG meter and recorded in the diary and eCRF when a hypoglycaemic episode is suspected. For more information on reporting of hypoglycaemic episodes, see Appendix 7 (Section 10.7).

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’ or ‘SMPG’ are the terms 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.

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

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

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 (Section 1.2)

8.2.6 Pregnancy testing

Women of childbearing potential (WOCBP) should only be included after a negative, highly sensitive urine pregnancy test (refer to Appendix 2 (Section 10.2)) at visits 1 and 2. Urine pregnancy test will also be conducted at visit 10 and 11, according to flowchart (Section 1.2).

Pregnancy testing should also be performed whenever a menstruation is missed or when pregnancy is otherwise suspected. The results of the urine pregnancy tests should be entered in the eCRF.

Additional pregnancy testing should be performed during the treatment period, if required locally, refer to Appendix 9 (Section 10.9).

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. Some AEs require additional data collection on a specific event form. The relevant events 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
Medication error	X	
Misuse and abuse	X	
Acute gallbladder disease	X	
Hypersensitivity reactions	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 7 (Section 10.7) for hypoglycaemic episodes.

8.3.1 Time period and frequency for collecting AE information

All AEs and SAEs must be collected from the first administration of study intervention 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 study intervention 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). All SAEs must be recorded and reported to Novo Nordisk or designee within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk or designee 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 under investigation 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).

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading 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).

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk or designee 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, institutional review board (IRB)/institutional ethics committee (IEC), and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR).

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

8.3.5 Pregnancy

Details of pregnancies in female participants will be collected after first exposure to IMP and until the new-born is one month of age. 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 J s.c. as well as semaglutide B s.c. The date, exact time and dose of all the administrations of trial product (dosing history) will be recorded in the diary along with the location of the injection site (see flowchart, Section 1.2). Site will transfer the information from the diary to the eCRF. The blood sampling for PK analyses will be collected in accordance with Section 1.3 and Table 10-4.

- Single-blood samples for measuring plasma concentration of semaglutide J s.c. and semaglutide B s.c. will be drawn on visits specified in the flowchart.
- The exact timing of obtaining the pharmacokinetic (PK) sample must be recorded on the laboratory form.
- The purpose of measuring plasma semaglutide levels is to conduct exposure-response, to evaluate the dose response and the adherence to the treatment.
- Blood samples for PK assessments must be collected, handled and shipped according to the description in the laboratory manual supplied by the central laboratory. The bioanalysis of semaglutide PK will be performed by a special laboratory. Semaglutide PK samples will be stored at the special laboratory responsible for PK until final clinical study report (CSR) in case Novo Nordisk requests further analysis of the PK samples. Details of the bioanalysis will be outlined in a bioanalytical study plan issued by the special laboratory.

8.4.2 Pharmacodynamics

Not applicable for this study.

8.5 Genetics

Not applicable for this study.

8.6 Biomarkers

Not applicable for this study.

8.7 Immunogenicity assessments

Blood samples will be drawn pre-dosing for measurement of serum anti-semaglutide antibodies according to the flowchart (Section 1.2). For antibody samples collected at visit 2 and visit 11, the participant must be fasting (For details, see Section 5.3.1).

The samples will be analysed by a special laboratory assigned by Novo Nordisk, please refer to Attachment I. Confirmed antibody positive samples will be further characterised for cross reactivity to native GLP-1 and titrated to estimate the magnitude of the response. Samples taken at visit 11 which are positive for anti-semaglutide antibodies will be further characterised for *in vitro* neutralising effect towards semaglutide s.c. In addition, samples taken at visit 11 which are positive for cross reactivity to native GLP-1 will be further analysed for *in vitro* neutralising effect towards native GLP-1. The *in vitro* neutralising antibody assays will be performed by Novo Nordisk.

The investigator will not be able to review the results of antibody measurement during the study as this may not be performed until after LPLV and the results will only be available after DBL.

8.8 Human biosamples for future research

Not applicable for this study.

8.9 Health economics

Not applicable for this study

9 Statistical considerations

The statistical analysis plan (SAP) will be finalized prior to the partial (interim) database lock (DBL) 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 key secondary endpoints.

9.1 Statistical hypotheses

Non-inferiority will be declared if the following two one-sided null hypothesis is rejected. Let the treatment difference of change from baseline to week 28 in HbA_{1c} between semaglutide J s.c. and semaglutide B s.c. be defined as μ = "change in HbA_{1c} for semaglutide J s.c." minus " change in HbA_{1c} for semaglutide B s.c.".

- H_0: μ ≥ 0.3%-points against H_a: μ < 0.3%-points.

The non-inferiority margin of 0.3%-points is justified in Section 4.2.

9.1.1 Multiplicity adjustment

The type 1 error probability will be controlled at 2.5% under the aforementioned one-sided null-hypothesis, and as the study has only one primary analysis, and no confirmatory secondary analyses, adjustment for multiplicity is not applicable.

9.2 Analysis sets

The following participant analysis sets are defined:

Participant analysis set (PAS)	Description
Full analysis set (FAS)	All randomised study participants. Participants will be included in the analyses according to the randomised intervention.
Safety analysis set	All participants who are exposed to study intervention. Participants will be included in the analyses according to the intervention they actually received for the majority of the period being treated.

The following data points sets are defined:

Defined data points set (DPS)	Description
DPS1 – in study	All observed data points from randomisation until the first date of: end of study visit (visit 11) or death or withdrawal of informed consent or 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 – in study or the end of study visit (visit 11) or last trial product administration +42 days.
DPS3 – on treatment without rescue	All observed data points from first drug date until the first date of: initiation of rescue medication or last trial product administration +7 days

The FAS and DPS1 are used to estimate the primary estimand (defined in Section 3.1.1).

The FAS and DPS3 are used to estimate the additional estimand (defined in Section 3.1.1).

The safety analysis set and DPS2 are used to present safety data with a long lag-time (AEs, hypoglycaemic episodes, anti-semaglutide antibodies and eye examination).

Safety analysis set and a modified DPS2 are used to present safety data with an acute onset (vital signs, laboratory assessments, physical examination). For these summaries, the DPS2 is modified by having an end date at date of last trial product administration +7 days or date of end of DPS1, whichever occurs first.

9.3 Statistical analyses

9.3.1 General considerations

A baseline assessment will be defined as the most recent measurement at randomisation. Missing baseline values will be imputed by the average of the non-missing baseline values.

The frequency and timing of intercurrent events as defined in Section 3.1.1 will be presented descriptively.

9.3.2 Primary endpoint analyses

9.3.2.1 Primary estimand analysis

The primary estimand, presented in Section 3.1.2, will be estimated based on the FAS and DPS1.

Missing end of treatment data will be imputed using multiple imputation (MI) assuming that missing data are missing at random (MAR). The imputation will be performed, under the non-inferiority null-hypothesis, by imputing missing end of treatment data separately within each to the four groups defined by randomised treatment and treatment status at end of treatment:

- semaglutide B s.c. and on-treatment at end of treatment,
- semaglutide B s.c. and off-treatment at end of treatment,
- semaglutide J s.c. and on-treatment at end of treatment,
- semaglutide J s.c. and off-treatment at end of treatment.

For each group an analysis of covariance (ANCOVA) with region as a factor and baseline HbA_{1c} as a covariate will be fitted to the observed end of treatment values. The estimated location and dispersion parameters will then be used to impute 500 values for each participant with missing end of treatment data. Furthermore, for participants randomised to semaglutide J s.c. a penalty of 0.3, corresponding to the non-inferiority margin, is added to the imputed values.

The 500 complete datasets will be analysed using an ANCOVA with randomised treatment and region as factors and baseline HbA_{1c} as a covariate. Rubin's rule[13] will then be applied to combine these estimates and draw inference.

In case of sparse data, defined as less than 5 participants with available end of treatment data, in some groups, the imputation model will be thinned by region. If this is not sufficient the imputation will be based on participants randomised to the same treatment regardless of treatment status using the imputation model region as a factor and baseline HbA_{1c} as a covariate. If this is still not sufficient, the imputation model may be thinned again in the aforementioned order.

9.3.2.1.1 Sensitivity analysis

A two-way tipping point sensitivity analysis will be performed by repeating the ANCOVA described in Section 9.3.2.1. However, prior to analysis, penalties are added to the imputed end of treatment values in both intervention arms simultaneously. A range of penalties will be explored for both treatment groups, and the impact on the conclusion will be assessed through a contour plot of the p-values. This sensitivity analysis evaluates the robustness of the non-inferiority conclusions to violations in missing data assumptions in both intervention arms.

9.3.2.2 Additional estimand

The additional estimand, presented in Section 3.1.1, will be estimated based on the FAS and DPS3.

Missing end of treatment data will be imputed using multiple imputation (MI) assuming that missing data are missing at random (MAR). The imputation will be performed separately within each treatment group. First, intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) 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. The imputation model will include region as a factor 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 randomised treatment and region as factors and associated baseline HbA_{1c} as a covariate. Rubin's rule[13] will then be applied to combine the estimates and draw inference.

9.3.2.2.1 Sensitivity analysis

A two-way tipping point sensitivity analysis as described in Section 9.3.2.1.1 will be performed.

9.3.3 Secondary endpoint analyses

9.3.3.1 Secondary supportive endpoints

9.3.3.1.1 Change in body weight (kg)

Primary estimand

A similar analysis as described in Section 9.3.2.1 will be performed, but with values of body weight instead of HbA_{1c}, and where no penalty (or rather a penalty of 0, corresponding to a superiority test) is added to imputed values for participants that are randomised to semaglutide J s.c.

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}.

9.3.3.1.2 Number of treatment-emergent AEs

For details on analyses of number of treatment emergent AEs, please refer to the SAP.

9.3.3.1.3 Anti-semaglutide antibodies

For details on analyses of anti-semaglutide antibodies, please refer to the SAP.

9.3.4 Exploratory endpoints analysis

Not applicable for this study.

9.3.5 Safety analyses

The AEs will be summarised by treatment arm by number of participants experiencing at least one event, proportion of participants in the safety analysis set experiencing at least one event, the number of events, and the rates of events (number of events per person-years of exposure).

The occurrence of anti-semaglutide antibodies (positive/negative) will summarised descriptively. This will be supported by a listing on anti-semaglutide antibody levels.

For further details on summaries of safety, please refer to the SAP.

9.3.6 Other analyses

Pharmacokinetic and/or pharmacodynamic modelling

The 8 PK samples for each participant will be used to fit a 1-compartment population PK model. In the visit schedule, 3 PK visit window types have been defined (see Table 10-4) ensuring that PK sampling times relative to dosing times are distributed across the weekly dosing interval, allowing for estimation of the absorption rate, the volume of distribution, and the clearance rate for each participant in the population PK model, and from this C_{max}, C_{min} and C_{avg} will be estimated for each participant. Lastly, a comparison of C_{max}, C_{min} and C_{avg} between semaglutide J s.c. and semaglutide B s.c. will be made.

Additional population PK/PD exposure-response analyses may be included for exploratory pharmacodynamic analysis as needed.

The modelling will include data from all enrolled participants that were exposed to semaglutide s.c. in this study and might be performed as a meta-analysis. Actual dose, date, time and injection site of all the administrations of trial product before PK sampling will be registered in the eCRF and used in the analysis, together with actual time point for PK sampling. The analysis will be further specified in a modelling analysis plan (MAP) that is to be prepared before unblinding at the partial (interim) database lock. The modelling analyses will be performed by Pharmacometrics at Novo Nordisk A/S and will be reported separately from the CSR.

9.4 Interim analysis

This study will be subject to a partial (interim) database lock (DBL) at the end of the treatment period for all participants, i.e. after the date of the last participant last treatment (LPLT) visit. A full DBL will be performed, as per the usual procedures, after last participant last visit. The partial DBL is implemented to allow for an early submission to Agency and thereby securing the stable supply of the semaglutide molecule to meet the current high demand. Novo Nordisk employees not involved in data cleaning will become unblinded to potentially both participant level data and comparative results at the time of the partial database lock, whereas participants and investigators will remain blinded until after last participant last visit (LPLV). All efficacy analyses will be performed based on the data from the partial DBL and analysis of safety will primarily be based on the full DBL. No efficacy assessments are collected after LPLT and in turn the efficacy results cannot be biased by the early unblinding. The potential impact on safety is considered negligible, as most participants will have completed the follow-up visit at the time of the partial DBL.

9.5 Sample size determination

The study is designed to have a marginal power of at least 80% of confirming a non-inferior effect of semaglutide J s.c. against semaglutide B s.c. on change from baseline to week 28 in HbA_{1c} (%-point).

The power calculation is based on a 1-sided t-test with a significance level of 0.025, a 3:1 randomisation, an expected treatment difference (TD) of 0%-points and standard deviation (SD) of 0.9%-points. Under these assumptions **380** participants (285:95) are required to be randomised, and the actual power is 80.1%.

The powers sensitivity to number of participants is show in Figure 9-1. The powers sensitivity to assumed treatment difference and standard deviation is sown in Table 9-1

Figure 9-1 Power sensitivity to number of participants

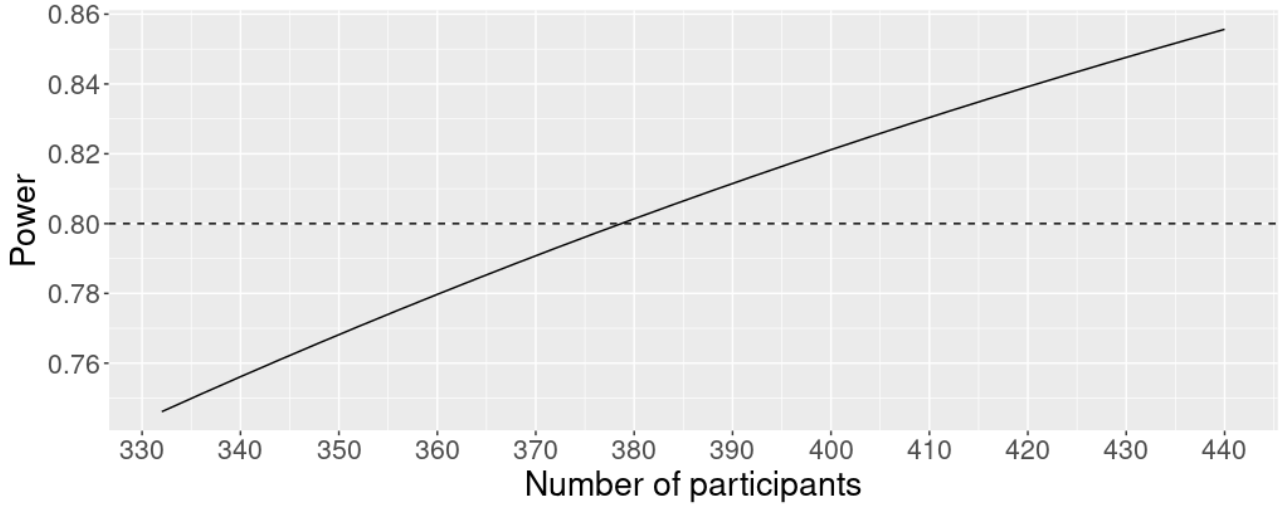


Table 9-1 Power sensitivity to treatment effect and standard deviation assumptions

TD\SD	0.85	0.9	0.95	1
0.01	0.867	0.826	0.784	0.742
0	0.844	0.801	0.758	0.714
-0.01	0.819	0.774	0.729	0.685

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[14] and applicable International Council of Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[15]
- Applicable laws and regulations

The protocol, informed consent form, IB (as applicable) and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the 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

For country specific requirements in US and Slovakia, please refer to Appendix 9 (Section 10.9).

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[15] guidelines, Declaration of Helsinki,[14] 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 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 CSR. 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. The safety committee may recommend unblinding of any data for further analysis and in this case an internal study-independent ad hoc group may be established in order to maintain the blinding of the study personnel.

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,[14] the International Committee of Medical Journal Editors (ICMJE),[16] the FDAAA,[17] European Commission Requirements[1, 18, 19] 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 eCRF on a regular basis during the conduct of the study as well as at the end of the study, as described in the eCRF completion guideline.

All participant data relating to the study will be recorded on eCRFs unless transmitted electronically to Novo Nordisk or designee (e.g., laboratory and diary data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The following will be provided as paper CRFs:

- Pregnancy forms

The following will be provided as paper CRFs to be used when access to the eCRF is revoked or the eCRF is temporarily unavailable:

- AE forms
- Safety information forms
- Technical complaint forms

Corrections to the eCRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF 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 eCRF, the eCRF must be signed and dated again by the investigator.

The investigator must ensure that data is recorded in the eCRF 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 eCRF 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[15], 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 CSR.

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 CRF 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, eCRF and other participant data will be provided in an electronic readable format to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. Site-specific CRFs and other 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.

For country specific requirements in Canada and US, please refer to Appendix 9 (Section 10.9).

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 they have 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 they move or retire), 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.

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.[20]

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, Table 10-2, Table 10-3 and Table 10-4 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.

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.

Laboratory results that could unblind the study will not be reported to the sites until the study has been unblinded.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism Assessments performed at V1, V2, V3, V4, V5, V6, V7, V8, V9, and V10 unless otherwise indicated	• Fasting plasma glucose[a] (V2, V7, V10) • HbA_{1c}
Notes: V – visit [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)).	

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology Assessments performed at V1 and V10	• Basophils • Eosinophils • Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Lymphocytes • Monocytes • Neutrophils • Thrombocytes
Biochemistry[a] Assessments performed at V1 and V10	• Alanine Aminotransferase (ALT) • Alkaline phosphatase • Amylase • Aspartate Aminotransferase (AST) • Bilirubin • Creatinine • Lipase • Potassium • Sodium • Urea
Pregnancy Testing[b] Assessments performed at V1, V2, V10 and V11	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test
Other tests Assessment performed at V1 and V10	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation
Antibodies[c,d] Assessments performed at V2, V4, V5, V6, V10 and V11 unless otherwise indicated	• Anti-semaglutide Antibody Screening (% B/T) • Anti-Semaglutide Antibody Confirmation (Positive/Negative) • Anti-semaglutide Antibodies level (Titer) • Antibodies cross reacting with native GLP-1 (Positive/Negative) • Semaglutide AB (neutralising effect) (Positive/Negative) (only at V11) • Antibodies neutralising native GLP-1 (Positive/Negative) (only at V11)

Notes:
V – visit
[a]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 3 (Section 10.3) (Hy's Law) and Protocol Section 7.1 'discontinuation of study intervention'.
[b]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).
[c] All the analyses will be performed by a laboratory contracted by Novo Nordisk, with the exception of neutralising antibodies assessment, which will be performed by Novo Nordisk laboratory.
[d] Results will not be provided to the investigator, as these results will not be used for any clinical evaluation during the study.

Table 10-3 Protocol-required PK assessments

Laboratory assessments	Parameters
Pharmacokinetics[a, b] Assessments performed at V3, V4, V5, V6, V7, V8, V9, V10 and V11	Semaglutide plasma concentrations
Notes: V – visit [a] Analysis performed by special laboratory contracted by Novo Nordisk [b] Results will not be provided to the investigator, as these results will not be used for any clinical evaluation during the study.	

Table 10-4 Timing of visits and PK blood sampling

Visit	Timing of visit
3	24 to 71 hours after dosing (from 1 to 3 days after dosing): Peak
4	Prior to treatment administration on a planned dosing day: Trough
5	24 to 71 hours after dosing (from 1 to 3 days after dosing): Peak
6	Prior to treatment administration on a planned dosing day: Trough
7	24 to 71 hours after dosing (from 1 to 3 days after dosing): Peak
8	96 to 144 hours after dosing (from 4 to 6 days after dosing): Decline
9	Prior to treatment administration on a planned dosing day: Trough
10	24 to 71 hours after dosing (from 1 to 3 days after dosing): Peak
11	No specific requirement.

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

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 an 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 ALT or aspartate 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.

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
  Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in administration of wrong drug.
- wrong route of administration, such as intramuscular instead of subcutaneous

- accidental administration of a lower or 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.

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

Hypersensitivity reactions
Events of hypersensitivity reactions.

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 nonserious 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 AE 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 diseases, 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 IB for the assessment. For each AE/SAE, the investigator must document in the medical records that they have 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 they 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.

New or updated information should be recorded in the eCRF.

10.3.5 Reporting of SAEs

AE and SAE reporting via eCRF

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

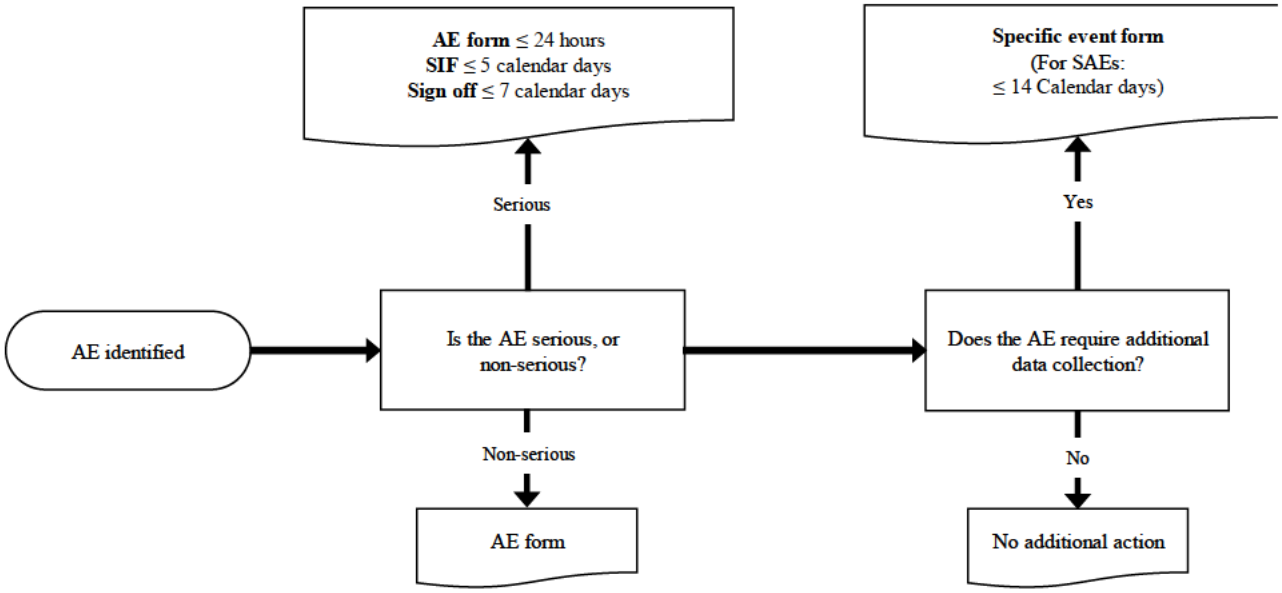
- Specific event form within 14 calendar days.

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 eCRF 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



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

Women 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 hormone replacement therapy 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 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 10-5 lists the highly effective methods of contraception allowed. Local regulations may apply, see Appendix 9 (Section 10.9).

Highly effective contraception should be utilised for a least 35 days after last dose of IMP (corresponding to time during treatment and until the end of relevant systemic exposure).

Table 10-5 Highly effective contraceptive methods allowed[21]

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
• Vasectomised partner
Vasectomised 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.

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.

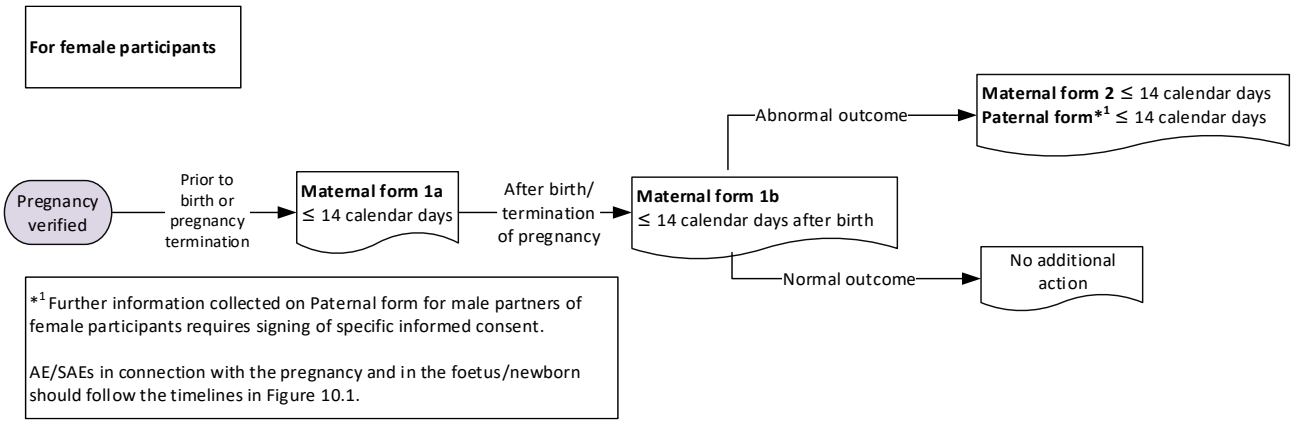
Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

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.

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.

Timelines for reporting technical complaints to Novo Nordisk

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

- 24 hours if related to an SAE
- 5 days calendar 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: Retention of human biosamples

Remaining PK samples (back-up samples and/or residual samples after PK analyses) may be retained for later re-analysis. The analyses will be performed by Novo Nordisk or a laboratory assigned by Novo Nordisk. The samples will be retained only until CSR finalisation after which they will be discarded.

Residual antibody samples may be retained for later re-analysis and/or further characterisation of antibody responses towards drug if required by health authorities or for safety reasons. The analyses will be performed by Novo Nordisk or a laboratory assigned by Novo Nordisk. Results will be documented independently and reported separately from the CSR. The samples will be retained until marked authorisation, but no longer than 15 years.

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

10.7 Appendix 7: Hypoglycaemic episodes

Table 10-6 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,[22] ADA,[23] ISPAD,[24] type 1 diabetes outcomes program,[25] ATTD.[26] Severe hypoglycaemia as defined by Seaquist[27] and ISPAD.[24]		

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.[27]

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.[27]

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.[27]

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 eCRF.

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 eCRF 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.[28, 29]

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.

10.8 Appendix 8: Mitigations to ensure participant safety and data integrity during an emergency situation

10.8.1 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 a major emergency 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.

Table 10-7 indicates the minimum requirements for assessments that should be performed during a lock-down, but 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.

10.8.2 Visits

Screening (visit 1) and randomisation/baseline (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 6, 10 and 11 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 home or off-site visits.

On-site visits (visits 3, 4, 5, 7, 8 and 9) can be converted to remote visits (video, phone or similar) or home or off-site visits.

If the end of treatment visit (visit 10) cannot be performed on-site, using remote (video, phone or similar) or home or off-site visits within the given visit window, the visit window for the assessment can be extended for up to 3 months.

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

10.8.3 Assessments

Assessments used for safety or the primary endpoints (i.e., HbA_{1c} and treatment emergent AEs) should be prioritised. The preferred order for the method of assessment is: on-site, home, video, phone visit. Specifications regarding how to perform these assessments using remote visits or as home visits will be provided by Novo Nordisk. 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, fasting plasma glucose, HbA_{1c} and eye examination 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.

Home measurements of weight, vital signs and pregnancy test can be performed if on-site visits are not possible and if deemed feasible for the participant. Only findings meeting the definition for an AE (refer to Appendix 3 (Section 10.3)) should be reported in the eCRF.

If the assessments indicated in Table 10-7 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.

10.8.4 Study intervention

Alternative dispensing methods of study intervention 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.

Table 10-7 Minimum assessments following randomisation

Procedures marked with X should be prioritised. If deemed necessary, procedures marked with C can be cancelled and procedures marked with P can be converted to phone/video visit.

Procedure	Protocol Section	Screening	Randomisation	Intervention period							End of treatment	End of study
				Dose escalation			Maintenance period					
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Timing of visit/study day (weeks)		-2	0	2	4	8	12	16	20	24	28	33
Visit window (days)		Up to -14 days		±1	±1	±3	±3	±3	±3	±3	±3	+7
Informed Consent and Demography[a]	10.1.3	X										
Tobacco Use	5.3.2	X										
Eligibility Criteria	5.1 and 5.2	X	X									
Randomisation	6		X									
Discontinuation criteria	7.1			P	P	P	X	P	P	P		
Attend Visit Fasting	5.3.1		X					C			X	X[b]
Medical History/ Concomitant Illness	8.2	X	X									
Concomitant Therapy	6.8	X	X	P	P	P	X	P	P	P	X	X

Procedure	Protocol Section	Screening	Randomisation	Intervention period							End of treatment	End of study
				Dose escalation			Maintenance period					
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Timing of visit/study day (weeks)		-2	0	2	4	8	12	16	20	24	28	33
Visit window (days)		Up to -14 days		±1	±1	±3	±3	±3	±3	±3	±3	+7
Vital Signs	8.2.2	X	X	P				P			X	
Physical Examination	8.2.1	X									X	
Body Measurements	8.2.1	X	X	P	P	P	X	P	P	P	X	
Childbearing Potential	8.2.6 and 10.4	X										
Pregnancy Test	8.2.6 and 10.2	X	X								X	X
Laboratory Assessments	10.2	X	X	C	C	C	X	C	C	C	X	X
PK sampling	8.4 and 10.2			C	C	C	X	C	C	C	X	X
Antibodies	8.7 and 10.2		X		C	C	X				X	X
Eye Examination	8.2.3	X									X	
Adverse Event	8.3 and 10.3			P	P	P	X	P	P	P	X	X

Procedure	Protocol Section	Screening	Randomisation	Intervention period							End of treatment	End of study
				Dose escalation			Maintenance period					
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Timing of visit/study day (weeks)		-2	0	2	4	8	12	16	20	24	28	33
Visit window (days)		Up to -14 days		±1	±1	±3	±3	±3	±3	±3	±3	+7
Hypoglycaemic episodes	8.3 and 10.7			P	P	P	X	P	P	P	X	X
Training in Devices	6.1		X		P		X					
Drug Dispensing Visit	6.1 and 6.2		X		X		X		X			
Drug Accountability	6.2		X		X		X		X		X	
Dosing History	8			P	P	P	X	P	P	P	X	
Remind the participant about when to administer their last treatment before next visit	6.1			P	P	P	X	P	P	P	X	

Note:

[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] Fasting is defined as at least 2 hours prior to the visit 11 without food or liquid, except for water (see Section 5.3.1).

Abbreviation: V = visit.

10.9 Appendix 9: Country-specific requirements

For Canada:

- **5.1 Inclusion criteria:** PK studies: Males must not have donated blood (450 mL) within 56 days of PK draws totalling 450mL; Females 84 days.

- **10.01.10 Retention of clinical study documentation:** Part C, Division 5 of the Food and Drug Regulations (C.05.012) requires a 25-year retention period

For United States:

- **10.01 Appendix 1: Regulatory, ethical, and study oversight 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.

10.01.10 Retention of clinical study documentation: In the US, 21 CFR 312.62(c) and 21 CFR 812.140(d) require 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified'. **For Slovakia:**

- **10.01.01 Regulatory and ethical considerations:**

The investigator will be responsible for:
- notifying the IRB/IEC of SAEs – only death, as required by IRB/IEC procedures and local regulations
- 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
- reporting any potential serious breaches to the sponsor immediately after discovery

The sponsor 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 according to local
- regulations and procedures established by the IRB/IEC and/or regulatory authorities

- ensuring submission of protocol, protocol amendments, ICF, investigator brochure, CSR synopsis and other relevant documents to the IRB/IEC and/or regulatory authorities

10.10 Appendix 10: Abbreviations

ADA	American Diabetes Association
AE	adverse event(s)
ALT	Alanine Aminotransferase
ANDA	Abbreviated New Drug Application
AST	Aspartate Aminotransferase
BG	blood glucose
BMI	body mass index
C_{avg}	Steady state average plasma concentration in a dosing interval
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CMC	Chemistry, Manufacturing, and Controls
COVID	coronavirus disease
CRF	case report form
CSR	clinical study report
CTFG	Clinical Trial Facilitation Group
DBL	database lock
DFU	directions for use
DP	drug product
DPP-4	dipeptidyl peptidase-4
DPS	data-point set
DS	drug substance
DUN	dispensing unit number
EAC	event adjudication committee
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendment Act
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP-1	glucagon like peptide-1
HbA_{1c}	glycosylated haemoglobin
hCG	human chorionic gonadotropin
IB	investigator's brochure
ICH	International Council of Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	institutional ethics committee
IHSG	International Hypoglycaemia Study Group
IMP	investigational medicinal product
IRB	institutional review board
ISO	International Organisation for Harmonisation

IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	Interactive Web Response System
LPLT	last participant last treatment
LPLV	last patient last visit
MAP	meta-analytic-predictive
MCMC	Markov Chain Monte Carlo
MI	myocardial infarction
NDA	New Drug Application
NIMP	non-investigational medicinal products
NN	Novo Nordisk
NYHA	New York Heart Association
PAS	participant analysis set
PCD	primary completion date
PD	pharmacodynamics
PG	plasma glucose
PK	pharmacokinetics
QTL	quality tolerance limits
RA	receptor agonist
RTSM	Randomisation and Trial Supply Management
SAE	serious adverse event(s)
SAP	statistical analysis plan
s.c.	subcutaneous(ly)
SD	standard deviation
SMPG	self-measured plasma glucose
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
T2D	type 2 diabetes
TMM	trial materials manual
UNL	upper normal limit
US	United States
WOCBP	women of childbearing potential

10.11 Appendix 16: 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 (08 April 2022), global

This amendment is considered 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.[2]

Overall rationale for preparing protocol, version 2.0:

This version of the protocol is prepared to include additional PK samples and analyses to allow PK comparability of semaglutide J s.c. and semaglutide B s.c., based on the Health Canada's feedback. Population pharmacokinetics will be addressed in a modelling analysis plan and the totality of evidence from all PK assessments will be presented as a collective whole in a comprehensive modelling report. Therefore, secondary PK objective has been removed from the protocol.

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis	Removal of secondary PK objective.	Since all PK assessments will be performed based on modelling analysis plan and will be presented in a comprehensive modelling report, the secondary PK objective has been removed from the protocol.
Section 1.2 Flowchart	• Additional PK sampling visits at visit 7, 8 and 9. • Additional row has been added to remind the participant about when the trial product should be administered .	Additional PK samples are collected to allow PK comparability and a dosing reminder has been added to ensure correct PK sampling in relation to trial product administration.
	The terminology 'administration of trial product' has been replaced with 'dosing history'.	To make it clear that we are recording the date, time, dose and injection site of trial product, the term 'administration of trial product' has been replaced with 'dosing history'.
	A footnote added to indicate that the race and ethnicity must be self-reported by the participants.	To comply with FDA requirements on self-reporting of race and ethnicity.
Section 1.3 Flow chart – PK sampling	Introduced detailed flow chart for PK sampling.	A detailed flowchart for PK sampling has been added to indicate when the trough, peak and decline samples will be collected.
Section 3.1 Objectives and endpoints	Removal of secondary objective and endpoint (Cavg), and addition of a statement that population PK will be reported in a comprehensive modelling report.	Since all PK assessments will be performed based on modelling analysis plan and will be presented in a comprehensive modelling report, the secondary PK objective and endpoint has been removed from the protocol.
Section 6.1 Study interventions administered	Addition of reminders for dosing.	This has been added to help the participants remember the dosing for PK sampling visits.

Section # and name	Description of change	Brief rationale
	A brief description on how blood sampling for PK assessments is planned for PK sampling visits.	To provide more clarity on how and when the blood sampling for PK assessments are planned.
Section 7 Discontinuation of study intervention and participant discontinuation/withdrawal	RTSM language for recording treatment discontinuation has been updated across the section.	The wording has been aligned with regards to RTSM language.
Section 8.4.1 Pharmacokinetics	Changed that the date, exact time and dose of all the administrations of trial product will be recorded in diary.	This has been changed to provide more clarity that the dosing history for all trial product administrations will be recorded.
Section 9.3.6 Other analyses	A brief summary on the PK modelling has been added.	This has been added to provide details on PK samples and assessments
Section 10.2 Appendix 2: Clinical laboratory tests	Additional table on 'timing of visits and PK sampling'.	This has been added to provide more clarity on how the timing of visits is planned for PK sampling
Section 10.8 Appendix 8: Mitigations to ensure participant safety and data integrity during an emergency situation	The flowchart in this section is updated in accordance with section 1.2.	To align with the flowchart in Section 1.2.
Section 10.9 Appendix 9: Country-specific requirements	Country specific requirements for Slovakia has been added.	This has been added based on the comments received from Regulatory Authority (RA) of Slovakia.
Section 1.1 Synopsis and Section 4.1 Study design	Retaining 'active-controlled' study instead of 'active, internal and historical controlled' study to keep it simple.	The changes have been made to provide more clarity that, we use historical information in the primary comparison which is not part of the study design but is rather a feature of the primary analysis. For this purpose, we have retained 'active-controlled study' wherever we are talking about study design. However, we have explained what internal and historical control is in further section.

Protocol version 3.0 (05 October 2022)

This amendment is considered 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]

Overall rationale for preparing protocol, version 3.0:

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis Section 2.1 Study rationale Section 3 Objectives, endpoints and estimand Section 4 Study design Section 6.3 Measures to minimise bias: Randomisation and blinding	The primary analysis has been changed from Bayesian comparability analysis utilizing historical data to a frequentist non-inferiority analysis based on data from participants enrolled in this study (concurrent data).	This change has been made to increase the robustness and acceptability of the primary assessment and is based on recommendations from Health Authority.

Section # and name	Description of change	Brief rationale
Section 9 Statistical considerations		
Section 1.1 Synopsis Section 4.1 Overall design Section 9.5 Sample size determination	An additional 48 participants will be randomised in a 3:1 manner to receive either semaglutide J s.c. or semaglutide B s.c.	This is to maintain 80% power under the non-inferiority analysis that does not utilize historical data.
Section 6.1 Study intervention compliance	A sentence has been modified to clarify that DFU will be given only at visit 2 and verbal training will be given at visit 2, 4 and 6.	This has been done to simplify and provide more clarity.
Section 10.10 Appendix 10: Abbreviations	'FAZ' has been changed to 'FAS'. 'SUSTAIN' has been removed.	This has been done to correct spelling mistake. This has been removed as it is no longer defined in the protocol.

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9.1.1 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

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

Content: Global key staff and Country key staff.