Cover Page for Protocol

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NCT number	NCT05514535
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Official title of study:	Efficacy and safety of once-weekly semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine vs titrated insulin glargine in participants with type 2 diabetes and overweight
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Protocol

Protocol Title: Efficacy and safety of once-weekly semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine vs titrated insulin glargine in participants with type 2 diabetes and overweight

Substance: Semaglutide

Universal Trial Number: U1111-1267-0312

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Study phase: 3b

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
Version 6.0	12 November 2024	Czech Republic, Greece, Italy, Portugal, Romania, Slovakia, Spain
Version 5.0	22 December 2023	All
Version 4.0	16 January 2023	All
Version 3.0	27 April 2022	All
Version 2.0	23 November 2021	All
Original protocol version 1.0	20 October 2021	All

Protocol version 6.0 (12 November 2024)

This amendment is considered to be non-substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014[1] because it neither substantially impacts the safety or rights of the participants nor the reliability or robustness of the data generated in the study.

Overall rationale for preparing protocol, version 6.0

The overall rationale for the changes implemented in the amended protocol is to ensure protocol compliance with (EU) No 536/2014 after study transition to the regulation. This protocol version is applicable for specific countries (Czech Republic, Greece, Italy, Portugal, Romania, Slovakia, Spain).

Section # and name	Description of change	Brief rationale
Front page	EU CT Number: 2024-510612-75-00 has been added and EudraCT Number: 2021-004392-13 has been deleted.	To specify (EU) No 536/2014 requirements.
Section 10.1.1 Regulatory and ethical considerations	(EU) No 536/2014 has been added.	To specify (EU) No 536/2014 requirements.
10.1.7 Dissemination of clinical study data	“euclinicaltrials.eu” has been added.	To comply with (EU) No 536/2014 requirements.

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1 Protocol summary

1.1 Synopsis

This is an interventional, 40-week, multi-national, multi-centre, randomised, parallel group, open-label, and active comparator study with two treatment arms.

Rationale:

The aim of this study is to compare the effect on glycaemic control, insulin use, body weight, safety and health related quality of life of once weekly (OW) semaglutide subcutaneous (s.c.) added to dose-reduced insulin glargine U100 versus insulin glargine U100 titrated in participants with type 2 diabetes (T2D) who are overweight and treated with a once daily basal insulin (e.g. insulin glargine U100 or U300, NPH insulin, insulin detemir, insulin degludec) up to 40 U/day and metformin with or without sodium glucose cotransporter 2 (SGLT-2) inhibitors.

Exogenous insulin has been seen to be an effective treatment option throughout the continuum of T2D but comes with its own disadvantages. These include risk of hypoglycaemia, weight gain, complexity of treatment regimens and necessity of frequent monitoring and adjustment resulting in inadequate glycaemic control in patients. This could lead to the risk of developing microvascular complications such as retinopathy, nephropathy and neuropathy. Semaglutide is a potent OW glucagon like peptide 1 (GLP-1) analogue that has demonstrated superior effects on glycaemic control and weight loss compared to widely used active comparators. Further, OW semaglutide s.c. added to basal insulin demonstrated superior effects on glycaemic control, weight loss, treatment satisfaction and reduction in basal insulin dose compared to placebo.

Once weekly (OW) semaglutide (s.c.) added to dose-reduced insulin glargine U100 using a simple dose adjustment algorithm may provide an efficacious and simpler alternative to insulin titration for participants with inadequately controlled T2D and overweight treated with a once daily basal insulin (e.g. insulin glargine U100 or U300, NPH insulin, insulin detemir, insulin degludec) up to 40 U/day, with lower risk of weight gain and hypoglycaemia.

Objectives, endpoints and estimands:

Primary objective

To confirm that efficacy as measured by change from baseline to week 40 in HbA_{1c} (%-point) of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is not unacceptably worse (i.e., non-inferior) to that of titrated insulin glargine U100 on change from baseline to week 40 in HbA_{1c} (%-point) in participants with T2D and overweight treated with a once daily basal insulin up to 40 U/day. Non-inferiority is assessed based on the clinically acceptable margin of 0.3%-point for the mean treatment difference in HbA_{1c}.

Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 40)	%-point

Confirmatory secondary objectives

- To confirm superiority of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on change from baseline to week 40 in body weight (kg) in participants with T2D, overweight and treated with a once daily basal insulin up to 40 U/day.

Confirmatory secondary endpoint

Endpoint title	Time frame	Unit
Change in body weight	From baseline (week 0) to end of treatment (week 40)	Kg

- To confirm superiority of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on relative change from baseline to week 40 in daily insulin dose (%) in participants with T2D, overweight and treated with a once daily basal insulin up to 40 U/day.

Confirmatory secondary endpoint

Endpoint title	Time frame	Unit
Relative change in daily insulin dose	From baseline (week 0) to end of treatment (week 40)	%

- To confirm superiority of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on change from baseline to week 40 in HbA_{1c} (%-point) in participants with T2D, overweight and treated with a once daily basal insulin up to 40 U/day.

Confirmatory secondary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 40)	%-point

- To confirm superiority of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on change from baseline to week 40 in Diabetes Treatment Satisfaction Questionnaire - change version (DTSQc) score in participants with T2D, overweight and treated with a once daily basal insulin up to 40 U/day.

Confirmatory secondary endpoint

Endpoint title	Time frame	Unit
Score of Diabetes Treatment Satisfaction Questionnaire – change version (DTSQc)	At end of treatment (week 40)	Score points (range -18 to +18)

Primary estimand

The primary estimand is defined by the following five attributes:

- Population: Participants with T2D and overweight.
- Endpoint: Change from baseline to week 40 in HbA_{1c} (%-point).

- Treatment condition: OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 or titrated insulin glargine U100, for up to 40 weeks with or without change in background medication.
- Remaining intercurrent events: No further intercurrent events are identified. The intercurrent events described as part of the treatment regimens will all implicitly be handled by a treatment policy strategy.
- Population level summary: Difference in mean changes between randomised treatment groups.

Additional estimand

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

- Treatment condition: OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 or titrated insulin glargine U100, for the planned treatment duration of 40 weeks with or without change in background medication.
- Remaining intercurrent events: The intercurrent event of 'randomised treatment discontinuation for any reason' will be handled by a hypothetical strategy. The intercurrent event of 'change in background medication' will implicitly be handled by a treatment policy strategy.

Overall design:

The study consists of a 2-week screening period followed by a randomisation visit and a 40-week intervention period. The intervention period of the semaglutide treatment arm will include a 12-week dose escalation period where OW semaglutide s.c. will be dose escalated at weeks 4, 8 and 12. Throughout the study, participants will be in contact with the site on a weekly basis (either at site visits or phone contacts) for adverse event (AE) assessment, electronic diary (e-Diary) review of self-measured plasma glucose (SMPG) values, doses taken of trial products and reported hypoglycaemic episodes, if any. At week 16, the visit can be conducted at the participant's home or other alternative off site location for participants who have consented to have V18 conducted as a home visit.

Continuous glucose monitoring (CGM) will be applied at screening for a 10-day period and at week 38 for a 14-day period with a change of sensor after 7 days. At week 40, the end of treatment visit (V42) is scheduled. After V42, all participants will enter a follow-up period of 5 weeks, ended by a follow up remote contact, which corresponds to the end of study visit at week 45 (P43).

Study intervention groups and duration:

Participants will be randomised 1:1 at the randomisation visit to receive either OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 or titrated insulin glargine U100. Participant's pre-study daily basal insulin doses will be switched to insulin glargine U100 in accordance with Appendix 7 (Section 10.7). Insulin glargine U100 will be administered s.c. daily. Randomisation will be stratified based on background treatment with SGLT-2 inhibitors (Yes/No). The maximum duration of the intervention is 40 weeks, and the maximum duration of the study will be approximately 47 weeks.

Investigational medicinal products

- Semaglutide 1.34 mg/mL and 2.68 mg/mL, subcutaneous, solution for injection, 1.5 and 3 mL pre-filled PDS290 pen injector.
- Insulin glargine 100 units/mL, subcutaneous, solution for injection, 3.0 mL pre-filled SoloSTAR® pen injector.

Number of participants:

Approximately 825 participants will be screened to achieve 568 participants randomly assigned to receive either OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 or titrated insulin glargine U100.

Participant characteristics:

The participants will be male or female and aged above 18 years at inclusion. They will 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. HbA_{1c} of 7-10% (53−86 mmol/mol) (both inclusive) as assessed by central laboratory on the day of screening.
3. Body mass index (BMI) ⩾25 kg/m^2 on the day of screening.
4. Stable daily dose(s) ≥90 days before screening of any of the following anti-diabetic drugs or combination regimens:
   - Any metformin formulations ≥1500 mg or maximum tolerated or effective dose.
   - Any metformin combination formulation ≥1500 mg or maximum tolerated or effective dose. The treatment can be with or without SGLT-2 inhibitors.
5. Treated with a once daily basal insulin (e.g. insulin glargine U100 or U300, NPH insulin, insulin detemir, insulin degludec) ≤40 U/day for ≥90 days before screening. Short-term bolus insulin treatment for a maximum of 14 days before screening is allowed.

Key exclusion criteria

1. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 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 non-dilated examination.
2. Potentially missed diagnosis of Type 1 diabetes (T1D) or latent autoimmune diabetes in adults (LADA) verified by C-peptide <0.26 nmol/L or 260 pmol/L (0.78 ng/mL) or antibodies to glutamic acid decarboxylase (anti-GAD) >5 units/mL, as measured by the central laboratory at screening.
3. Presence or history[a] of pancreatitis (acute or chronic).
4. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of <30 mL/min/1.73 m^2 at screening as defined by KDIGO 2012 classification.
5. Any episodes[a] of diabetic ketoacidosis within 90 days before screening.
6. Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8.

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

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	Dose escalation period			Maintenance period			End of treatment	End of study
Visit		V1A	V1B	V2	V6	V10	V14	V18[a]	V28	V40	V42	
☎ *Phone Contact (P) (For details see separate flowchart in Section 1.3)*				*P3 - P5*	*P7-P9*	*P11-P13*	*P15-P17*	*P19-P27*	*P29-P39*	*P41*		*P43*
Timing of Visit (Weeks)			-2	0	4	8	12	16	26	38	40	
Visit Window (Days)			±3	0	±3	±3	±3	±3	±3	±3	±3	
Informed Consent and Demography[b]	10.1.3 (App 1)	X	X									
Eligibility Criteria	5.1 and 5.2		X	X								
Randomisation	6			X								
Hypoglycaemia Unawareness	5.2 and 8.3		X									
Childbearing Potential	10.4 (App 4)		X									
Concomitant Medication	6.8		X	X	X	X	X	X	X	X	X	
Medical History/Concomitant Illness	8.3		X									
Pregnancy Test[c]	8.3.5 and 10.2 (App 2)		X	X							X	
Tobacco Use	5.3.1		X									
Body Measurements	8.3.1		X	X	X	X	X		X		X	

Procedure	Protocol section	Screening		Randomisation	Dose escalation period			Maintenance period			End of treatment	End of study
Visit		V1A	V1B	V2	V6	V10	V14	V18[a]	V28	V40	V42	
☎ *Phone Contact (P) (For details see separate flowchart in Section 1.3)*				*P3 - P5*	*P7-P9*	*P11-P13*	*P15-P17*	*P19-P27*	*P29-P39*	*P41*		*P43*
Timing of Visit (Weeks)			-2	0	4	8	12	16	26	38	40	
Visit Window (Days)			±3	0	±3	±3	±3	±3	±3	±3	±3	
Self measured plasma glucose	8.2.1, 10.6 (App 6) and 10.7 (App 7)			X	X	X	X	X	X	X	X	
Laboratory Assessments	10.2 (App 2)		X	X		X		X	X		X	
Adverse Events	8.4 and 10.3 (App 3)				X	X	X	X	X	X	X	
Hypoglycaemic Episodes	8.4 and 10.6 (App 6)				X	X	X	X	X	X	X	
Eye Examination	8.3.3		X								X[d]	
Physical Examination	8.3.1		X								X	
Vital Signs	8.3.2		X	X	X	X	X		X		X	
Hand Out Direction for Use	6			X								
Hand Out ID Card	6 and 10.1.5 (App 1)		X									
Hand Out and Instruct in BG-meter	6			X								

Procedure	Protocol section	Screening		Randomisation	Dose escalation period			Maintenance period			End of treatment	End of study
Visit		V1A	V1B	V2	V6	V10	V14	V18[a]	V28	V40	V42	
☎ *Phone Contact (P) (For details see separate flowchart in Section 1.3)*				*P3 - P5*	*P7- P9*	*P11- P13*	*P15- P17*	*P19- P27*	*P29- P39*	*P41*		*P43*
Timing of Visit (Weeks)			-2	0	4	8	12	16	26	38	40	
Visit Window (Days)			±3	0	±3	±3	±3	±3	±3	±3	±3	
Hand Out and Instruct in ePID (e-Diary)	6 and 8			X								
Hand Out and Instruct in CGM	8.2.2		X							X		
RTSM/IWRS Session	6 and 7	X		X	X	X	X		X		X	
Attend Visit Fasting	10.2 (App 2)		X	X							X	
Training in Trial Product, Pen-handling	6			X	X		X					
Dispensing Visit	6			X	X	X	X		X			
Drug Accountability	6				X	X	X		X		X	
SF-36 v2	8.2.4			X							X	
DTSQs	8.2.4			X							X	
DTSQc	8.2.4										X	

Abbreviations: AE = adverse events; App = appendix; BG = blood glucose; CGM = continuous glucose monitoring; IWRS = interactive web response system; RTSM = Randomisation and Trial Supplies Management; ePID = electronic patient interactive device; DTSQc = Diabetes Treatment Satisfaction Questionnaire- change version; DTSQs = Diabetes Treatment Satisfaction Questionnaire- status version; H= home visit; SF-36 v2 = Short Form 36 version 2; V = visit.

[a]This visit can be conducted at the participant's home or other alternative off site location for participants who have consented to have V18 conducted as a home visit. Please refer to Section 8.1 for details.

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

[c]Czech Republic: see local requirements in Appendix 9 (Section 10.9).

[d]Eye examination can be conducted up to 8 weeks prior to V42.

1.3 Flowchart - phone contacts

Procedure	Protocol sections	Dose escalation period				Maintenance			End of study
Visit		P3-P5	P7-P9	P11-P13	P15-P17	P19-P27	P29-P39	P41	P43
Timing of Visit (weeks)		1-3	5-7	9-11	13-15	17-25	27-37	39	End of treatment+5 weeks
Visit Window (days)		±3	±3	±3	±3	±3	±3	±3	+7
Concomitant Medication	6.8	X	X	X	X	X	X	X	X
Self-measured Plasma Glucose	8.2.1, 10.6 (App 6) and 10.7 (App 7)	X	X	X	X	X	X	X	X
Adverse Events	8.4 and 10.3 (App 3)	X	X	X	X	X	X	X	X
Hypoglycaemic Episodes	8.4 and 10.6 (App 6)	X	X	X	X	X	X	X	X
Pregnancy test	8.3.5 and 10.2 (App 2)								X

Abbreviations: App = Appendix; P = phone contacts.

2 Introduction

2.1 Study rationale

Type 2 diabetes (T2D) is a chronic metabolic disorder that follows a natural history of progressive beta-cell failure and increasing metabolic derangement. Chronic hyperglycaemia is strongly associated with the risks of microvascular events, major adverse cardiovascular (CV) events and mortality.[2] Additionally, overweight and obesity are risk factors for cardiovascular disease[3] and overall mortality.[4]

Exogenous insulin has been seen to be an effective treatment option throughout the continuum of T2D but comes with its own disadvantages. These include risk of hypoglycaemia, weight gain, complexity of treatment regimens and necessity of frequent monitoring and adjustment.

In patients treated with basal insulin, these before mentioned disadvantages can lead to insufficient titration resulting in inadequate glycaemic control and this has important consequences for the patients as the risk of developing microvascular complications such as retinopathy, nephropathy, and neuropathy is increased.[5-8]

Given these frequently observed disadvantages with insulin therapy, there is a need for an alternative glucose-lowering medication that is effective and convenient, for both patients and prescribers.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are recommended for the treatment of patients with T2D, particularly for those who have not achieved their target glycated haemoglobin (HbA_{1c}) and need to lose weight or minimise weight gain. GLP-1 RAs stimulate glucose-dependent insulin release from the pancreatic islets via the incretin effect, thus inhibiting inappropriate post-meal glucagon release and reduce food intake. They are also recommended as first line treatment in patients with high CV risk, regardless of HbA_{1c} level. Current guidelines place GLP-1 RAs as one of the first preferred injectable treatment options and they can also be safely added in patients who are already receiving basal insulin therapy.[9, 10]

Once weekly (OW) semaglutide subcutaneous (s.c.) added to dose-reduced insulin glargine U100 using a simple dose adjustment algorithm may provide an efficacious and simpler alternative insulin titration for participants with inadequately controlled T2D and overweight treated with a once daily basal insulin up to 40 U/day, with lower risk of weight gain and hypoglycaemia. The aim of this study is to compare the effect on glycaemic control, insulin use, body weight, safety and health related quality of life of OW semaglutide s.c. added to dose-reduced insulin glargine U100 versus insulin glargine U100 titrated in participants with T2D who are overweight and treated with basal insulin up to 40 U/day and metformin with or without sodium glucose cotransporter 2 (SGLT-2) inhibitors.

2.2 Background

Semaglutide

Semaglutide is a potent human GLP-1 analogue that acts as a GLP-1 RAs, with a long half-life (approximately 1 week) suitable for OW s.c. administration.[11] Across the SUSTAIN studies,

semaglutide s.c. demonstrated superior reduction in HbA_{1c} and body weight compared to widely used active comparators including GLP-1 RAs, dipeptidyl peptidase-4 (DPP-4) inhibitors and SGLT-2 inhibitors.[10, 12-19] Further, semaglutide s.c. added to basal insulin demonstrated superior effects on glycaemic control, weight loss, treatment satisfaction and reduction in basal insulin dose compared to placebo.[10] The CV safety of OW semaglutide s.c. has been established in a 2-year CV outcomes study[20] that showed clinically relevant CV risk reduction with OW semaglutide s.c. compared to placebo.[21] OW Semaglutide s.c. has a well-established safety profile based on data from the non-clinical and clinical development programmes, consistent with the safety profile of the GLP-1 RA drug class.[22, 23] Semaglutide s.c. is approved as Ozempic® in more than 80 countries worldwide for the treatment of T2D in maintenance doses of 0.5 mg and 1.0 mg. Additionally, OW semaglutide s.c. 2.0 mg is approved as a maintenance dose in some countries.

In a recent study, semaglutide s.c. 2.0 mg showed superiority over 1.0 mg in reducing HbA_{1c}, and additional body weight loss with a similar safety profile and has been selected as target dose for this study.[24]

Insulin glargine U100

For details on insulin glargine U100, please refer to the most recent version of European Medicines Agency (EMA) summary of product characteristics[25] or the most recent version of the US prescribing information[26] or the most recent version of any locally approved label.

Study population

Participants with inadequately controlled T2D (HbA_{1c} levels between 7-10%) treated with once daily basal insulin, stable dose of metformin with or without SGLT-2 inhibitors, with body mass index (BMI)≥25 kg/m^2 are the target population for inclusion in this study as they are anticipated to benefit from the treatment regimen to improve their glycaemic control and reduce the body weight. The study population is further described in Section 4.2.

2.3 Benefit-risk assessment

The main benefits and risks related to participation in the study are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of semaglutide s.c. may be found in the investigator's brochure (IB)[27] and any updates thereof. For insulin glargine U100 this information may be found in the most recent version of European Medicines Agency (EMA) summary of product characteristics[25] or the most recent version of the US prescribing information[26] or the most recent version of any locally approved label.

The identified and potential risks are based on findings from non-clinical and clinical studies with OW semaglutide s.c. as well as other GLP-1 RAs. For each of these risks, mitigating actions have been implemented to minimise the risks for participants enrolled in this study.

2.3.1 Risk assessment

Table 2-1 Risk assessment

Risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention (OW semaglutide s.c.)		
Gastrointestinal (GI) disorders	Consistent with other GLP-1 RAs, the most frequent AEs with semaglutide are gastrointestinal (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 subjects with impaired renal function as it may cause a deterioration of renal function.	Clinical studies have shown that a low starting dose and gradual dose escalation mitigates the risk of developing gastrointestinal symptoms. Participants with GI symptoms are recommended to drink plenty of fluids to avoid volume depletion.
Hypoglycemia	There is a low risk of hypoglycaemic episodes when semaglutide s.c. is used as monotherapy. Participants treated with semaglutide s.c. in combination with insulin may have an increased risk of hypoglycaemia.	The risk of hypoglycaemia can be lowered by reducing the dose of insulin when initiating treatment with semaglutide (Section 6.5)
Diabetic retinopathy complications	In a 2-year clinical study with semaglutide s.c. (NN9535-3744) involving 3,297 participants with T2D, CV risk, long duration of diabetes and poorly controlled blood glucose, EAC-confirmed events of diabetic retinopathy complications occurred in more participants treated with OW 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 s.c. semaglutide (1.7%) and comparators (2.0%).	Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Long-term glycaemic control decreases the risk of diabetic retinopathy. These participants should be monitored closely and treated according to clinical guidelines.
Allergic reactions	As with all protein-based pharmaceuticals, treatment with semaglutide may evoke allergic reactions, including serious allergic reactions such as anaphylactic reactions.	As a precaution, participants with known or suspected hypersensitivity to OW 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.

Risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
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 s.c. and comparator. Few events were confirmed; the events occurred throughout the study periods and the overall rates were similar to the rates reported in background populations.	Participants should be informed of the characteristic symptoms of acute pancreatitis and if pancreatitis is suspected, semaglutide should be discontinued. If confirmed, semaglutide should not be restarted. For details on discontinuation of treatment, 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 OW semaglutide s.c. 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 non-clinical studies, clinical studies, or post-marketing data that GLP-1 based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies. There is no indication of an increased relative risk in the semaglutide treatment groups vs. comparator, including placebo. The rates of EAC-confirmed events of pancreatic cancer were consistently low across studies.	Participants with presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) within 5 years prior to the day of screening will not be enrolled in this trial.
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 non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. No C-cell tumours were observed in monkeys after 52 weeks exposure up to 52-fold above the clinical plasma exposure at 14 mg/day. The GLP-1 receptor is not expressed in the normal human thyroid, and therefore the clinical relevance of the findings is considered to be low.	To mitigate this risk, participants with a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2) are excluded from clinical studies with semaglutide.

Risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Other		
Pregnancy and fertility	Studies in animals with OW semaglutide s.c. 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). If a participant wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued (please refer to protocol Section 8.4.5 for further guidance). The effect of semaglutide s.c. on fertility in humans is unknown.
Study intervention (insulin glargine U100)		
For further details on insulin glargine U100, please refer to the most recent version of European Medicines Agency (EMA) summary of product characteristics[25] or the most recent version, the US prescribing information[26] or the most recent version, any locally approved label.		
Study procedures		
Potential risk: COVID-19 infection in relation to participation in trial	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). • Appendix 8 (Section 10.8) includes mitigations that can be implemented to ensure participants' 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.

Risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Abbreviations: AE = adverse events; COVID-19= coronavirus disease 19; CV = cardiovascular; EAC = event adjudication committee; EMA = European Medicines Agency; GI = gastrointestinal tract; GLP-1 RA = glucagon like peptide-1 receptor agonists		

2.3.2 Benefit assessment

The study population will consist of participants with overweight and T2D insufficiently controlled on metformin and on a once daily basal insulin up to 40 U/day, with or without SGLT-2 inhibitors. For all participants in this study, the anticipated benefit includes improved glycaemic control as their anti-diabetic treatment will be intensified by either optimising insulin glargine U100 treatment or by adding on semaglutide s.c. 2.0 mg.[28,29] Also, among participants receiving semaglutide s.c., weight benefit can be anticipated, as OW semaglutide s.c. has demonstrated clinically relevant and dose-dependent improvements in body weight in participants with T2D.

Participants will receive intense medical care by means of frequent contact with the clinical sites. Safety and efficacy will be monitored regularly during the study.

All participants in this study will receive study interventions and auxiliary supplies free of charge.

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 OW semaglutide s.c. generated from the clinical and non-clinical development programme has not revealed any safety issues that would prohibit administration of OW semaglutide s.c. 2.0 mg.

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

3 Objectives, endpoints and estimands

In this section 'dose-reduced insulin glargine U100' and 'titrated insulin glargine U100' refer to algorithms for dose modification as described in Section 6.5.

3.1 Objectives and endpoints

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

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
To confirm that efficacy as measured by change from baseline to week 40 in HbA_{1c} (%-point) of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is not unacceptably worse (i.e., non-inferior) to that of titrated insulin glargine U100 on change from baseline to week 40 in HbA_{1c} (%-point) in participants with T2D and overweight treated with 40 units or less of basal insulin per day. Non-inferiority is assessed based on the clinically acceptable margin of 0.3%-point for the mean treatment difference in HbA_{1c}.	Primary		
	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 40)	%-point
Secondary	**Title**	**Time frame**	**Unit**
To confirm superiority of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on change from baseline to week 40 in body weight (kg) in participants with T2D and overweight treated with 40 units or less of basal insulin per day.	Confirmatory		
	Change in body weight	From baseline (week 0) to end of treatment (week 40)	kg
To confirm superiority of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on relative change from baseline to week 40 in daily insulin dose (%) in participants with T2D and overweight treated with 40 units or less of basal insulin per day.	Confirmatory		
	Relative change in daily insulin dose	From baseline (week 0) to end of treatment (week 40)	%
To confirm superiority of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on change from baseline to week 40 in HbA_{1c} (%-point) in participants with T2D and overweight treated with 40 units or less of basal insulin per day.	Confirmatory		
	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 40)	%-point
	Confirmatory		

Objectives	Endpoints		
To confirm superiority of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on change from baseline to week 40 in DTSQc score in participants with T2D and overweight treated with 40 units or less of basal insulin per day.	Score of Diabetes Treatment Satisfaction Questionnaire – change version (DTSQc)	At end of treatment (week 40)	Score points (range -18 to +18)
To compare the effect of OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 versus titrated insulin glargine U100 on insulin requirements, glycaemic control, hypoglycaemia, and patient reported outcome in participants with T2D and overweight treated with 40 units or less of basal insulin per day.	Supportive		
	Participants achieving: Insulin dose = 0 U	At end of treatment (week 40)	Y/N
	Participants achieving: Insulin dose reduced from baseline by at least 50%	At end of treatment (week 40)	Y/N
	Participants achieving: HbA_{1c} < 7%	At end of treatment (week 40)	Y/N
	Number of severe hypoglycaemic episodes (level 3)	From baseline (week 0) to end of treatment (week 40)	Number of episodes
	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter)	From baseline (week 0) to end of treatment (week 40)	Number of episodes
	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline (week 0) to end of treatment (week 40)	Number of episodes
	Participants achieving all of the following targets: HbA_{1c} reduced from baseline by at least 0.3%-points Insulin dose reduced from baseline No hypoglycaemic episodes (< 3.9 mmol/L (70 mg/dL) confirmed by BG meter) No weight gain	At end of treatment (week 40)	Y/N
	Change in score of Diabetes Treatment Satisfaction Questionnaire – status version (DTSQs)	From baseline (week 0) to end of treatment (week 40)	Score points (range: 0 to 36)
	Change in score of Short Form 36 version 2 (SF-36 v2)	From baseline (week 0) to end of treatment (week 40)	Score points (range: 0 to 100)

Abbreviations: BG = blood glucose; HbA_{1c} = glycated haemoglobin; T2D= type 2 diabetes; OW = once weekly.

3.2 Estimands

The estimands and their rationale are described in detail for each of the confirmatory objectives in Sections 3.2.1 and 3.2.2. The estimands account for the following intercurrent events:

- premature treatment discontinuation for any reason (AE or other)

- change in background medication

3.2.1 Addressing the primary objective

3.2.1.1 Primary estimand

For participants with T2D and overweight who are treated with 40 U or less of basal insulin per day, the primary clinical question is concerned with evaluating efficacy as measured by change from baseline in HbA_{1c} between the two treatment regimens:

- Once weekly semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 as per treatment guideline in Appendix 7 (Section 10.7).
- Titrated insulin glargine U100 as per treatment guideline in Appendix 7 (Section 10.7).

The two treatment regimens are compared based on non-inferiority testing (margin 0.3%-points) irrespective of premature treatment discontinuation and/or change in background medication. Titration of insulin glargine U100 will be guided by titration guideline and adjusted as per investigator's discretion.

A non-inferiority margin of 0.3%-point for the HbA_{1c} treatment difference is judged as being a clinically acceptable loss of efficacy versus titrated insulin glargine U100 in context of expected benefits in terms of a greater weight loss. This is supported by the fact that insulin glargine is a well-established comparator that has been extensively evaluated in superiority studies. Furthermore, titration of insulin glargine U100 is expected to result in at least 0.5%-points improvement in HbA_{1c}, justifying the smaller margin of 0.3%-point specified as threshold for the primary objective in this study.[30-32]

The primary estimand is defined by the following five attributes as defined in ICH E9(R1):[33]

- Population: Participants with T2D and overweight.
- Endpoint: Change from baseline to week 40 in HbA_{1c} (%-point).
- Treatment condition: OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 or titrated insulin glargine U100 for up to 40 weeks with or without change in background medication.
- Remaining intercurrent events: No further intercurrent events are identified. The intercurrent events described as part of the treatment condition will all implicitly be handled by a treatment policy strategy.
- Population level summary: Difference in mean changes between randomised treatment groups.

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

3.2.1.2 Additional estimand

An additional question of interest for the primary objective is concerned with evaluating the two treatment regimens as described under the primary estimand, had participants remained on treatment irrespective of change in background medication. The estimand attributes: population, endpoint, and population-level summary are the same as for the primary estimand. The remaining estimand attributes are:

- Treatment condition: OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 or titrated insulin glargine U100 for the planned treatment duration of 40 weeks with or without change in background medication.
- Remaining intercurrent events: The intercurrent event of 'randomised treatment discontinuation for any reason' will be handled by a hypothetical strategy. The intercurrent event of 'change in background medication' will implicitly be handled by a treatment policy strategy.

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

3.2.2 Addressing the secondary objectives

3.2.2.1 Change in body weight (kg)

The main clinical question of interest for this secondary confirmatory objective is to evaluate whether the treatment regimen described under the primary estimand with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms of change from baseline in body weight (kg).

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

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

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

3.2.2.2 Change in body weight (kg) – Additional

An additional clinical question of interest for this secondary confirmatory objective is concerned with evaluating whether the treatment regimen described under the additional estimand for primary objective with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms of change from baseline in body weight (kg).

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

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

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

3.2.2.3 Relative change in daily insulin dose (%)

The main clinical question of interest for this secondary confirmatory objective is to evaluate whether the treatment regimen described under the primary estimand with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms of relative change from baseline in daily insulin dose.

The estimand attributes: population, treatment condition, and remaining intercurrent events are the same as for the primary estimand. The remaining estimand attributes are:

- Endpoint: Relative change from baseline to week 40 in daily insulin dose (%).
- Population level summary: Difference in mean relative changes between randomised treatment groups.

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

3.2.2.4 Relative change in daily insulin dose (%) – Additional

An additional clinical question of interest for this secondary confirmatory objective is concerned with evaluating whether the treatment regimen described under the additional estimand for the primary objective with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms of relative change from baseline in daily insulin dose.

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

- Endpoint: Relative change from baseline to week 40 in daily insulin dose (%).
- Population level summary: Difference in mean relative changes between randomised treatment groups.

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

3.2.2.5 Change in HbA_{1c} (%-point)

The main clinical question of interest for this secondary confirmatory objective is to evaluate whether the treatment regimen described under the primary estimand with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms of change from baseline in HbA_{1c}.

The estimand attributes are the same as for the primary estimand.

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

3.2.2.6 Change in HbA_{1c} (%-point) – Additional

An additional clinical question of interest for this secondary confirmatory objective is concerned with evaluating whether the treatment regimen described under the additional estimand for the primary objective with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin

glargine U100 is superior to titrated insulin glargine U100 in terms of change from baseline in HbA_{1c}.

The estimand attributes are the same as for the additional estimand for the primary objective.

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

3.2.2.7 DTSQc (score)

The main clinical question of interest for this secondary confirmatory objective is to evaluate whether the treatment regimen described under the primary estimand with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms of participant satisfaction.

The estimand attributes: population, treatment condition, and remaining intercurrent events are the same as for the primary estimand. The remaining estimand attributes are:

- Endpoint: Diabetes Treatment Satisfaction Questionnaire – change version (DTSQc) score at week 40.
- Population level summary: Difference in mean score between randomised treatment groups.

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

3.2.2.8 DTSQc (score) – Additional

An additional clinical question of interest for this secondary confirmatory objective is concerned with evaluating whether the treatment regimen described under the additional estimand for primary objective with OW semaglutide s.c. 2.0 mg as add-on to dose-reduced insulin glargine U100 is superior to titrated insulin glargine U100 in terms participant satisfaction.

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

- Endpoint: DTSQc score at week 40.
- Population level summary: Difference in mean score between randomised treatment groups.

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

4 Study design

4.1 Overall design

This is an interventional, 40-week, randomised, open-label, two-armed, multi-national, parallel group, multi-centre, active comparator study comparing insulin glargine U100 (IGlar) (reduced) + semaglutide (sema): OW semaglutide s.c. 2.0 mg as an add-on to dose-reduced insulin glargine U100 (Section 10.7) with IGlar (titrated): titrated insulin glargine U100 (Section 10.7) in participants with T2D and overweight using basal insulin up to 40 U/day and metformin with or without SGLT-2 inhibitors, with a baseline HbA_{1c} of 7–10% (both inclusive).

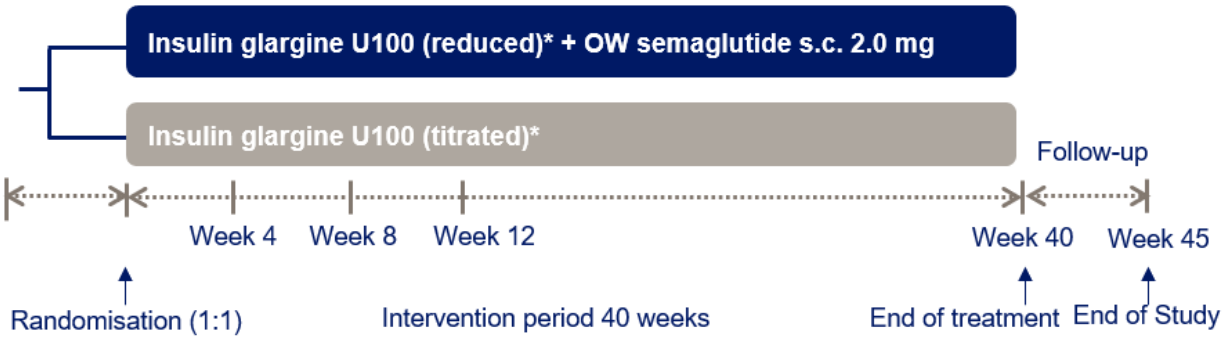
A total of 568 participants will be randomised in a 1:1 manner to receive either OW semaglutide s.c. 2.0 mg and insulin glargine U100 which will be reduced or insulin glargine U100 which will be titrated as per the treatment algorithm described in Appendix 10.7).

Randomisation will be stratified based on background treatment with SGLT-2 inhibitors (Yes/No).

The study consists of a 2-week screening period followed by a randomisation visit and a 40-week intervention period. The intervention period of the semaglutide treatment arm will include a 12-week dose escalation period where OW semaglutide s.c. will be dose escalated at weeks 4, 8 and 12. Throughout the study, participants will be in contact with the site on a weekly basis (either at site visits or phone contacts) for adverse event (AE) assessment, electronic diary (e-Diary) review of self-measured plasma glucose (SMPG) values, doses taken of trial products and reported hypoglycaemic episodes, if any. Participants will use an e-Diary to report SMPG values, dose of trial products taken and hypoglycaemic episodes, if any. At week 16, the visit can be conducted at the participant's home or other alternative off site location for participants who have consented to have V18 conducted as a home visit.

Continuous glucose monitoring (CGM) will be applied at screening for a 10-day period and at week 38 for a 14-day period with a change of sensor after 7 days. After the end of treatment visit (V42) at week 40, all participants will enter a follow-up period of 5 weeks, ended by a follow-up remote contact, which corresponds to the end of study at week 45 (P43). The planned study duration for the individual participant will be approximately 47 weeks (including screening). The study design is illustrated in Figure 4-1.

Figure 4-1 Study design



*See Appendix 7 (Section 10.7).

4.2 Scientific rationale for study design

A randomised, active comparator, two-armed, multi-centre, multi-national study design is chosen to minimise bias and to secure a comparison in the assessment of the efficacy and safety of the two treatment regimens: OW semaglutide s.c. 2.0 mg as an add-on to dose reduced insulin glargine U100 versus titrated insulin glargine U100. The open-label design is applied due to the different approaches to insulin titration in the two arms.

Insulin glargine U100 has been chosen as the once daily basal insulin, as it is a well-established comparator that has been extensively evaluated.

The treatment duration of the study is 40 weeks, with an additional 5 weeks of follow-up. A follow up phone contact that will take place 5 weeks after the end of treatment visit (V42) is included to account for the exposure and long half-life of semaglutide. A 40-week treatment duration is sufficient time to ensure appropriate adjustment of trial products and will provide robust data for the evaluation of efficacy and safety parameters.

Visit 1A is included to ensure participants give informed consent prior to attending V1B in a fasting state. A screening visit (V1B) is included to assess participant eligibility. After the randomisation visit (V2), site visits are scheduled every 4 weeks during semaglutide dose escalation. Throughout the study, phone contacts will be conducted at regular intervals for e-Diary review and AE assessment. At V1B a visit is scheduled for insertion of the CGM device and to collect CGM profiles for a 10-day period before the initiation of treatment with study interventions. At V40 a visit is scheduled for insertion of CGM device to collect CGM profiles for a 14-day period with a change of sensor at home after 7 days. The CGM profile is measured in line with international standards and Novo Nordisk recommendations.[34],[35]

The study population will consist of participants with T2D treated with basal insulin up to 40 U/day on top of metformin with or without SGLT-2 inhibitors, in need of further glycaemic control. The lower HbA_{1c} limit of 7% was chosen to select a population that may benefit from additional glycaemic control. The upper HbA_{1c} limit of 10% was chosen in view of the guideline recommendation that insulin treatment should be strongly considered in participants with high levels of HbA_{1c},[9, 36] while the study design applies a reduction in insulin glargine U100 dose in the OW semaglutide s.c. arm. Participants with BMI≥25 kg/m^2 will be included as they are anticipated to particularly benefit from the effect on body weight when advancing to a higher dose of OW semaglutide s.c. Screening for missed diagnosis of type 1 diabetes (T1D) or latent autoimmune diabetes in adults (LADA) based on C-peptide and antibodies to glutamic acid decarboxylase (anti-GAD) is applied to avoid inclusion of insulin dependent participants into the study. The selected population represents a clinically relevant population, as it is likely to benefit from the better glycaemic control, as well as from the anticipated body weight loss and potential simplification of treatment.

4.3 Justification for dose

Dose-dependent effects of OW semaglutide s.c. 2.0 mg for the treatment of T2D have been demonstrated in relation to glycaemic control and body weight.[24]

Results from the phase 2 dose-finding study showed that the OW semaglutide s.c. 0.3 mg once daily dose was the most effective in terms of both glycaemic control and weight management, while displaying an acceptable tolerability profile.[29] The daily dose of 0.3 mg corresponds to a weekly dose of 2.1 mg.

The target dose of 2.0 mg has been selected for this study as the study population could potentially benefit from the additional glycaemic control this provides and it is approved in some countries as an intended 3rd maintenance dose of OW semaglutide s.c. for glycaemic control in T2D, in addition to the already approved 0.5 mg and 1.0 mg doses. The added benefit of significantly greater weight loss observed with higher doses[14] would also allow clinicians to meet the needs of the participants with T2D treated with basal insulin.

Participants will be initiated at a OW dose of 0.25 mg and follow a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0 and 2.0 mg/week), until the target maintenance dose of 2.0 mg is reached after 12 weeks. The dose of insulin glargine U100 will concomitantly be reduced based on the algorithm described in Appendix 7 (Section 10.7).The 10 U increment reduction is deemed adequate to address the risk of hypoglycaemia and will correspond to a 25% reduction for participants on the maximum allowed 40 U insulin glargine U100, similar to the 20% reduction used as a guiding principle in the insulin studies in the phase 3a programme (i.e. SUSTAIN 5).[10]

An interventional arm in which participants receive insulin glargine U100, titrated according to an algorithm based on current guidelines[9,37] and described in Appendix 7 (Section 10.7), is included to compare the effect on glycaemic control, body weight and safety between the two different treatment regimens.

4.4 End of study definition

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

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

The primary endpoint is evaluated from week 0 to week 40. The primary completion date (PCD) is defined as the date of V42 (week 40) on which the last participant in the clinical study has an assessment for the primary endpoint. If the last participant is withdrawn early, the PCD is considered the date when the last participant would have completed V42. 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 medical records, including handing out participant information, as well as database review. Any pre-screening activities must be documented on site by the investigator.

5.1 Inclusion criteria

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

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Male or female.
3. Age above or equal to 18 years at the time of signing informed consent.
4. Diagnosed with T2D mellitus ⩾180 days before screening.
5. HbA_{1c} of 7-10% (53−86 mmol/mol) (both inclusive) as assessed by central laboratory on the day of screening.
6. BMI ≥25 kg/m^2 on the day of screening.
7. Stable daily dose(s) ≥90 days before screening of any of the following anti-diabetic drugs or combination regimens:
   - Any metformin formulation ≥ 1500 mg or maximum tolerated or effective dose.
   - Any metformin combination formulation ≥ 1500 mg or maximum tolerated or effective dose.

   The treatment can be with or without SGLT-2 inhibitors
8. Treated with a once daily basal insulin (e.g. insulin glargine U100 or U300, NPH insulin, insulin detemir, insulin degludec) ≤ 40 U/day ≥ 90 days before screening. Short term bolus insulin treatment for a maximum of 14 days before screening is allowed.

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 in this study is defined as signed informed consent.
   If the participant previously has been screen failed due to HbA_{1c} of 7-10% (53−86 mmol/mol) and/or C-peptide levels <0.5 nmol/L (1.5 ng/mL), one re-screening is allowed.
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 (i.e., randomised or exposed to intervention (whichever comes first)) in any other interventional, clinical study within 90 days before screening.
   Note: Simultaneous participation in a study (only coronavirus disease 2019 (COVID-19 related study) with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions

is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening in the current study.
5. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days before screening.
6. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).
7. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 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 non-dilated examination.
8. Potentially missed diagnosis of T1D or LADA verified by C-peptide <0.26 nmol/L or 260 pmol/L (0.78 ng/mL) or anti-GAD >5 units/mL, as measured by the central laboratory at screening.
9. Any disorder, except for conditions associated with T2D, which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.
10. Anticipated change in lifestyle (e.g., eating, exercise or sleeping pattern) during the study.
11. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma[a].
12. Presence or history[a] of pancreatitis (acute or chronic).
13. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days before screening.
14. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.
15. Planned coronary, carotid or peripheral artery revascularisation.
16. Renal impairment measured as estimated glomerular filtration rate (eGFR) value of <30 mL/min/1.73 m^2 at screening as defined by KDIGO 2012 classification.[38]
17. Any episodes[a] of diabetic ketoacidosis within 90 days before screening.
18. Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8.[39]
19. Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator.
20. 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.
21. Use of any medication with unknown or unspecified content within 90 days before screening.
22. Use of CGM at screening.

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

Portugal and Czech Republic: see local requirements in Appendix 9 (Section 10.9).

5.3 Lifestyle considerations

5.3.1 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). Individuals who do not meet the criteria for participation in this study may not be rescreened, unless they fulfil the conditions mentioned in Section 5.4.1. 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, for HbA_{1c} values between 6.7%–6.9% and 10.1%–10.3% one re-sampling is allowed. Also, in case of technical issues (e.g., haemolysed or lost samples), re-sampling is allowed for the affected parameter(s). Please see Section 8.2.2 regarding CGM in screening failure participants.

A screen failure session must be performed in the system (randomisation and trial supplies management system (RTSM)/interactive web response system (IWRS)).

5.4.1 Rescreening

Participants who have previously screen failed due to HbA_{1c} of 7-10% and/or C-peptide levels < 0.5 nmol/L can be rescreened to assess if they are eligible according to the updated exclusion criterium 8 (see section 5.2).

Rescreening will be allowed once.

Reasons for rescreening must be documented in participant's medical records. Rescreening should only be performed if the investigator considers it likely the participants would be eligible based on the new screening. Previously randomised participants cannot be rescreened. During rescreening the participants must have all visit 1B assessments repeated (see section 1.2).

Participants who are rescreened are required to sign a new informed consent form and provided with a new subject ID. Rescreening must be registered in the RTMS/IWRS.

5.5 Randomisation criteria

Not applicable for this study.

6 Study interventions and concomitant therapy

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

Trial product(s) comprise investigational medicinal products (IMPs) including comparators and non-investigational medicinal products (NIMPs).

6.1 Study interventions administered

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

Table 6-1 Study interventions

Intervention/Arm name	**IGlar (reduced) + sema**		**IGlar (titrated)**
Intervention name	Semaglutide	Insulin glargine U100	Insulin glargine U100
Intervention type	IMP, test product	IMP, background therapy	IMP, reference therapy
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) for doses: 0.25 mg, 0.5 mg, 1.0 mg. 2.68 mg/mL (3.0 mL) for 2.0 mg.	100 units/mL	100 units/mL
Dose and dose frequency	OW. Please refer to Appendix 7 (Section 10.7)	OD. Please refer to Appendix 7 (Section 10.7)	OD. Please refer to Appendix 7 (Section 10.7)
Dosing instructions and administration	s.c. (into the thigh, upper arm or abdomen)	s.c. (into the thigh, upper arm or abdomen)	s.c. (into the thigh, upper arm or abdomen)
Sourcing	Manufactured and supplied by Novo Nordisk A/S.	Manufactured by Sanofi A/S. Supplied by Novo Nordisk A/S.	Manufactured by Sanofi A/S. Supplied by Novo Nordisk A/S.
Packaging	1.5 mL PDS290 pre-filled pen injector. 3 mL PDS290 pre-filled pen injector. The device constituent is not under investigation.	3 mL SoloSTAR® pre-filled pen-injector	3 mL SoloSTAR® pre-filled pen-injector
Labelling	Labelled and packaged by Novo Nordisk A/S. Labelled in accordance with Annex 13[40], local regulations and study requirements.		

Abbreviations: IMP = investigational medicinal product; OW = once weekly; OD = once daily; s.c. = subcutaneous.

The investigator must document that directions for use (DFU) were given to the participant verbally and in writing at the first dispensing visit (V2) (as specified in the flowchart in Section 1.2). The investigator should remind participants of dosing instructions throughout the study, as applicable, and dose reminders will be sent through the e-Diary. A pen differentiation guide should also be provided to participants at the first dispensing visit.

Investigational medicinal products (IMP)

The study interventions are listed in Table 6-1.

During the study, starting at randomisation (V2), participants must be instructed to report date, dose and time of OW semaglutide s.c. and/or once daily insulin glargine U100 in the e-Diary. Please refer to Appendix 7 (Section 10.7) for more information.

The investigator must record the first and last date of trial product(s) in the electronic case report form (eCRF; Section 6.4).

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

Participants must be trained in handling the pen-injectors 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.

Insulin glargine U100 and semaglutide dosing instructions

For insulin glargine U100 and semaglutide dosing instructions please refer to Appendix 7 (Section 10.7). The investigator prescribes insulin glargine U100 and semaglutide through the healthcare professionals (HCP) portal to the participant e-Diary (Appendix 7, Section 10.7.2).

Non-investigational medicinal products (NIMP)

Anti-diabetic background medication (metformin with or without SGLT-2 inhibitors) are considered NIMP and will not be supplied by Novo Nordisk A/S.

After randomisation the dose of metformin with or without SGLT-2 inhibitors should be maintained at the same level and with the same frequency unless a safety concern related to the background medication arises. Other oral antidiabetic drugs (OAD) should not be administered during the study.

Auxiliary supplies including medical devices not under investigation

Auxiliary supplies (Table 6-2) will be provided by Novo Nordisk.

Table 6-2 Auxiliary supplies

Auxiliary supply	Details
Needles	Needles for pre-filled pen-injectors. Only needles provided and approved by Novo Nordisk must be used for administration of trial products.
Direction for use (DFU)	Information about the PDS290 pre-filled pen-injector can be found in the DFU provided in the e-Diary.

Auxiliary supply	Details
	Information about the SoloSTAR® pre-filled pen-injector can be found in the approved label for insulin glargine U100.
Blood glucose (BG) meter and related auxiliaries	At V2 participants must be instructed in how to use the blood glucose (BG) meter and the BG meter should be linked to the e-Diary as described in the e-Diary guide. Please refer to the Roche manufacturer's guide.
Continuous glucose monitoring (CGM) system	At screening (V1B) and at V40 participants must be instructed in handling of the CGM. Please refer to the CGM participant guide provided.
e-Diary	Participant Mobile Application, healthcare professional (HCP) Web Portal & Cloud Service. Please refer to the e-Diary site guide.

The PDS290 pen-injector (device constituent) is used for administration of semaglutide and is a pre-filled, single-participant-use pen-injector which is not under investigation in this study. The PDS290 pen-injector is a dial-a-dose pre-filled device integrated with a 1.5 mL cartridge (containing semaglutide 1.34 mg/mL) or a 3 mL cartridge (containing semaglutide 2.68 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) and the PDS290 pen-injector for semaglutide 2.68 mg/mL can deliver the dose of 2.0 mg (dose dialled on pen-injector).

Risk assessment has been conducted for the PDS290 pen-injector for semaglutide 1.34 mg/mL and 2.68 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 when using the PDS290 pen-injector in participants with T2D. No additional risks were associated with using the PDS290 pen-injector for semaglutide 1.34 mg/mL and 2.68 mg/mL according to the clinical procedures specified in this protocol, compared with using the PDS290 pen-injector within its approved intended use and indication for use. The use of the PDS290 pen-injector in this study is therefore considered to be of non-significant 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 and administer study intervention.

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

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all 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 to return all trial products (both used and un-used) at the next dispensing 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 products 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 and trial product label.

6.3 Measures to minimise bias: Randomisation and blinding

All 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).

This is an open-label study; however, the specific trial products for a participant will be assigned using an RTSM/IWRS. The site will access the RTSM/IWRS before the start of trial product administration for each participant. Potential bias will be reduced by central randomisation.

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(s) at home, compliance with trial product administration will be assessed by cross checking the following sources and comparing these to the expected use:

- Drug accountability information; counting returned trial product(s), visual inspection of pens.
- Weekly review of e-Diary including SMPG profiles, insulin glargine U100 and semaglutide doses and hypoglycaemia reporting.
- Evaluating glycaemic control and adherence to the visit schedule.
- If any suspicion of non-compliance arises the site must enter into a dialogue with the participant, re-emphasising the importance of compliance and uncover barriers to compliance. This dialogue must be documented.
- Trial product start and stop dates will be recorded in the eCRF.

6.5 Dose modification

Dose modification of insulin glargine U100 doses should be considered adjusted on a weekly basis according to SMPG values as described in Appendix 7 (Section 10.7).

Participants randomised to OW semaglutide s.c. should follow the recommended dose escalation regimen as described in Appendix 7 (Section 10.7) in order to lower the risk of gastrointestinal AEs. In case of tolerability issues, the dose of semaglutide can be adjusted as described in Appendix 7 (Section 10.7).

6.6 Continued access to study intervention after end of study

When discontinuing study intervention, the participant should be transferred to a suitable marketed product at the discretion of the investigator. The long half-life of semaglutide must be taken into consideration when selecting anti-diabetic treatment after discontinuation of 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 8.4 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.

Insulin glargine U100

A specific overdose for insulin glargine U100 cannot be defined; however, hypoglycaemia may develop over sequential stages if too high doses relative to the participant's requirement are administered. Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose of the insulin glargine U100, meal patterns, or physical activity may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/s.c. glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

Semaglutide

Overdoses of up to 4.0 mg of semaglutide 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)[27] and any updates thereof for more information on overdose of OW semaglutide s.c.. For insulin glargine U100, this information may be found in the most recent version of European Medicines Agency (EMA) summary of product characteristics[25] or the most recent version of the US prescribing information[26] or the most recent version of any locally approved label.

6.8 Concomitant medication

Any medication that the participant is receiving at the time of screening visit (V1B) or receives until end of study visit (P43) must be recorded along with:

- Primary indication
- Dates of administration including start and stop dates and total daily dose (glucose-lowering medications)
- Relevant for participants in COVID-19 studies: Type of study and type of drug

Changes in concomitant medication must be recorded at each contact. If a change is due to an AE, then this must be reported according to Section 8.4.

7 Discontinuation of study intervention and participant 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 semaglutide, then they should also discontinue study insulin glargine U100. The participant should be transferred to a commercially available treatment which may include insulin glargine U100, 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 concern 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. Note: Simultaneous participation in a study with the primary objective of evaluating an approved or non-approved IMP for prevention or treatment of COVID-19 disease or post-infectious conditions is allowed at the investigator's discretion without discontinuation of study intervention if simultaneous participation is allowed by local authorities.
6. Lack of efficacy, defined as fulfilment of ALL criteria (a, b and c) below after week 12 and onwards:
    a. Mean of pre-breakfast SMPG values of 3 consecutive weeks are above 15 mmol/L (270 mg/dL), AND
    b. no treatable intercurrent cause for the hyperglycaemia (e.g. non-compliance) has been identified.
    c. In such case, the participant must be called for a confirmatory fasting plasma glucose (FPG) measurement as soon as possible. A confirmatory FPG must be obtained and analysed by the central laboratory. If this FPG exceeds 15 mmol/L (270 mg/dL), participant fulfils the lack of efficacy criteria.

To allow time for up-titration of the study intervention and to observe the expected effect of study intervention on glycaemic parameters, lack of efficacy criteria will be applied on week 12 and onwards.

The participants should continue with the remaining scheduled visits and assessments until the time of the originally scheduled end of treatment visit (V42) and end of study visit (P43). CGM assessment at V40 should not be done for participants who have discontinued study intervention.

Participants who prematurely discontinue study interventions can keep and use the e-Diary and BG meters and should return it at the end of study visit (P43).

The phone contacts listed in Section 1.3 can be skipped following the participant's discontinuation except for end of study visit (P43). 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 planned end of treatment visit (V42) is the most important visit to be conducted at site, if possible.

If a participant is unwilling to attend any of the remaining visits, information about the attempts to follow-up with the participant must be documented in the participant's medical record.

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

The investigator should change participant status in the HCP web portal to 'Follow-up' if the participant discontinues to ensure that the participant should no longer report study intervention doses.

7.1.1 Temporary discontinuation of study interventions

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, semaglutide 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[41]). Appropriate actions should be initiated.

If acute pancreatitis is confirmed, semaglutide should not be restarted, and discontinuation of study interventions should be completed in RTSM/IWRS. If the Atlanta criteria are not fulfilled and thus, the suspicion of acute pancreatitis is not confirmed, semaglutide 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 Appendix 7 (Section 10.7). Similarly, a participant who discontinues study interventions on their own initiative should be encouraged to resume the study interventions.

7.1.2 Rescue criteria

Not applicable for this study.

7.2 Participant withdrawal from the study

A participant may withdraw consent at any time at their 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.

For further details of handling of CGM in case of withdrawals, please refer to Section 8.2.2.

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.

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 the RTSM/IWRS. The primary reason for discontinuation of study intervention must be specified in the end of IMP treatment form in the eCRF.

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'.
- If the participant has not been reached by their planned last visit date then they will be considered as lost to follow-up.

8 Study assessments and procedures

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

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

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

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

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

Adherence to the study design requirements, including those specified in the flowchart (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 the assessments at the randomisation visit (V2) is as follows:

- Laboratory sample collection.
- Physical assessment of body weight, vital signs and AEs.
- Randomisation in RTSM/IWRS.
- The investigator should create a participant profile and record administrative information (e.g. subject ID, year of birth and gender) and treatment arm in the HCP web portal
- Participants should be provided with an e-Diary and instructed in how to use it. Please see Section 10.7.2 for details.
- The BG meter should be connected with the e-Diary and the participant should indicate whether the SMPG value was "pre-breakfast" or "other".
- A SMPG should be measured using the BG meter.
- The investigator should ensure that the patient reported outcome (PRO) questionnaires: Diabetes Treatment Satisfaction Questionnaire- status version (DTSQs) and then 36-Item Short-Form Survey version 2 (SF-36 v2) is completed in the e-Diary by the participant.
- Dispensing and training of administration of study intervention.
- Confirm last total daily dose of non-IMP basal insulin (e.g. insulin glargine U100 or U300, NPH insulin, insulin detemir, insulin degludec) before randomisation, document in participant notes and record in eCRF. This should be used to determine the dose prescription of IMP insulin glargine U100 according to Section 10.7.
- The investigator should prescribe the treatment in the HCP web portal and demonstrate to participant how they receive this in the e-Diary.
- The investigator should remove the CGM device, upload CGM data and check the total amount of data on the device to identify which participants need further training at V40 (week 38) when they next receive the CGM device.

For information regarding the e-Diary and HCP web portal, please refer to the site guide.

Please refer to Section 6.4 for study intervention compliance.

All data entered in the e-Diary is considered source data. The investigator should review all the data of the participants through the HCP web portal, before or during each visit/phone contact.

Review of e-Diary, laboratory reports, CGM data (proportion of CGM data received and not CGM values), must be documented in the source documents or the participant's medical record. If clarification of entries or discrepancies in the e-Diary is needed, the participant must be questioned, and a conclusion made in the participant's source documents. Data entry corrections can be made by the participant in the e-Diary, if necessary. Care must be taken not to bias the participant.

8.1 Home visit

At week 16, there is a visit that can be conducted at the participant's home or other alternative off site location for participants who have consented to have V18 conducted as a home visit (Section 1.2). This visit can be performed by the investigator or other delegated qualified persons. This will be according to local legislations. Detailed procedure and specific requirements should be available for relevant site staff in a written instruction.

If there are local challenges with completing a home visit, then the investigator can perform the visit as a site visit.

8.2 Efficacy assessments

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

8.2.1 Self-measured plasma glucose

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 'self-measured plasma glucose' (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 and auxiliaries provided by Novo Nordisk should be used for the measurements required in the protocol.

Participants should be instructed to measure their pre-breakfast SMPG daily from randomisation (V2) to end of treatment visit (V42) and to transfer the measured SMPG values into the e-Diary.

A baseline SMPG value should be collected using the BG meter at V2. If the SMPG is measured fasting this should be indicated by selecting "pre-breakfast", otherwise "other" should be selected.

8.2.2 Continuous glucose monitoring

Participants will be equipped with CGM devices at the CGM measurement periods: week -2 (V1B) and at week 38 (V40). The CGM system used in this study will be the Dexcom G6®. The CGM readings will be blinded to both the participant and investigator and will not be used for any insulin dose titration or hypoglycaemic episode reporting.

If a participant withdraws consent during the study at a timepoint where they wear CGM or is a screening failure, a site visit should be scheduled in order to remove the CGM sensor and upload the data from the receiver. If this is not possible the participant can choose to remove it themselves and return the devices to the site. If the screen failed participant would like to receive the CGM data, they should keep the CGM device on for the 10 days in order to get a full dataset. The investigator will be able to obtain the results from the CGM in order to support any future treatment plans.

CGM fitting and training

The site staff will closely supervise and assist on fitting of the sensor and transmitter on the participant during the site visits. Training in the CGM is the responsibility of the investigator or site staff at the relevant visits. For information on fitting, and removing of the CGM parts, please refer to the Investigator's CGM manual and CGM participant guide provided. If a participant is to have an x-ray, magnetic Resonance Imaging, computed tomography scan or high-frequency electrical heat (diathermy), the Dexcom G6® sensor, transmitter, and receiver should be removed during this treatment.

CGM sensor check

The CGM sensor has an in-use period of 10 days. The sensor will automatically stop recording data exactly 10 days after sensor insertion and start.

The site staff should ensure that the sensor is fitted correctly and that the CGM receiver is working. This will be done during the clinic visit, as specified in the flowchart (Section 1.2). At Visit 40, the site should ensure the participant can change the sensor at home after 7 days.

CGM data upload

CGM data must be uploaded to the CGM software at the site by the site staff following the instruction provided to the sites. The upload will be documented by the system directly.

The serial number of the CGM receiver must be recorded in the eCRF at the start of each CGM period. In case the CGM receiver is being replaced, the serial number should be updated.

8.2.3 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.

8.2.4 Clinical outcome assessments

The PRO questionnaires are to be completed by the participant without assistance of the site personnel and should preferably be completed after all fasting-related activities are completed, but

before any other visit related procedures are conducted. It takes approximately five minutes to complete the questionnaires.

The following PRO questionnaires will be supplied in the e-Diary in a linguistically validated version in all languages relevant for this study:

- DTSQs: The questionnaire has been designed to measure satisfaction with diabetes treatment regimens in participants with diabetes. The DTSQs questionnaire will be measured as specified in the flowchart (Section 1.2).
- DTSQc: The questionnaire has been designed to measure the change in the level of satisfaction with diabetes treatment regimens in participants with diabetes who have had a recent intervention. The DTSQc questionnaire will be measured at end of treatment visit (V42) as specified in the flowchart (Section 1.2). (Note: DTSQc should be administered after DTSQs, if administered at the same visit).
- SF-36 v2: The SF-36 will be used to measure differences in quality of life and mental well-being. Data will be collected as specified in the flowchart (Section 1.2). (Note: SF-36 should be administered as the last clinical outcome assessment at a given visit.).

8.3 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 CV 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 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.

Information on hypoglycaemia unawareness will be recorded according to Clarke's questionnaire, question 8.[39] The investigator must ask the participant in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" Participants answering 'never, rarely or

sometimes' are considered to have impaired awareness of hypoglycaemia, whereas those answering 'often or always' are not.

8.3.1 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 (height and weight) will also be measured and recorded in the eCRF as specified in the flowchart (Section 1.2). Height will be measured and recorded at the screening visit (V1B). 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 V1B and recorded in the participant's medical records.

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

8.3.2 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.

8.3.3 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 biomicroscopy examination (e.g., using a pre-corneal or corneal contact lens examination). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

If the participant had such an eye examination performed within 90 days prior to screening (V1B), the investigator may base their evaluation upon the results of that examination. The examination must be repeated before the randomisation visit (V2) 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 at end of treatment visit (V42) as per the protocol flowchart (Section 1.2). Eye examinations required at V42 can be performed within 8 weeks prior to V42. Results should be available for evaluation at V42. 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 8.4 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 (V42).

8.3.4 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).

8.3.5 Pregnancy testing

Woman of childbearing potential (WOCBP) should only be included after a negative, highly sensitive serum pregnancy test performed at V1B (Section 1.2; Appendix 2 (Section 10.2)). Serum pregnancy tests will also be conducted at V2 and V42 and urine pregnancy tests should be conducted at P43 (Appendix 2 (Section 10.2)).

Urine pregnancy testing should 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).

8.4 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 the 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	
Neoplasms (malignant and non-malignant)	X	
Hypoglycaemic episodes[a]		X

[a] Hypoglycaemic episodes will be recorded in the e-Diary (Appendix 3 (Section 10.3.3), Appendix 6 (Section 10.6)).

Definitions and reporting timelines for the events mentioned in the above table can be found in Appendix 3 (Section 10.3) and Appendix 6 (Section10.6) for hypoglycaemic episodes.

8.4.1 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 (P43) 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 (Section 8.3).

AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3). All SAEs must be recorded and reported to Novo Nordisk within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

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

8.4.2 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 non-leading verbal questioning of the participant is the preferred method to inquire about events.

8.4.3 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).

8.4.4 Regulatory reporting requirements for SAEs

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

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB)/independent 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.

8.4.5 Pregnancy

Details of pregnancies in female participants will be collected after first exposure to IMP and until the new-born infant is one month of age. For details regarding the collection and reporting of pregnancy information, please refer to Appendix 4 (section 10.4).

8.4.6 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.

8.5 Pharmacokinetics and pharmacodynamics

Not applicable for this study.

8.6 Genetics

Not applicable for this study.

8.7 Biomarkers

Not applicable for this study.

8.8 Immunogenicity assessments

Not applicable for this study.

8.9 Human biosamples for future research

Not applicable for this study.

9 Statistical considerations

The statistical analysis plan (SAP) will be finalised prior to first participant first visit 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 primary and secondary confirmatory endpoints.

9.1 Statistical hypotheses

For the primary and secondary estimands with primary endpoint, change from baseline to week 40 in HbA_{1c} (%-point), the following confirmatory 1-sided hypotheses are planned to be tested. Let the mean treatment difference be defined as μ = ([mean change for IGlar (reduced) + sema] minus [mean change for IGlar (titrated)]).

Non-inferiority with a non-inferiority margin of 0.3 (primary estimand):

H_0: $\mu \geq 0.3$%-points against H_A: $\mu < 0.3$%-points

Superiority (secondary confirmatory estimand):

H_0: $\mu \geq 0.0$%-points against H_A: $\mu < 0.0$%-points

For the secondary estimand with secondary endpoint, change from baseline to week 40 in body weight (kg), the following confirmatory 1-sided hypothesis is planned to be tested. Let the mean treatment difference be defined as above.

Superiority (secondary confirmatory estimand):

H_0: $\mu \geq 0.0$kg against H_A: $\mu < 0.0$kg

For the secondary estimand with secondary endpoint, relative change from baseline to week 40 in daily insulin dose (%), the following confirmatory 1-sided hypothesis is planned to be tested. Let the mean treatment difference be defined as μ = ([mean relative change for IGlar (reduced) + sema] minus [mean relative change for IGlar (titrated)]).

Superiority (secondary confirmatory estimand):

H_0: $\mu \geq 0.0$%-points against H_A: $\mu < 0.0$%-points

For the secondary estimand with secondary endpoint, DTSQc score at week 40, the following confirmatory 1-sided hypothesis is planned to be tested. Let the mean treatment difference be defined as μ = ([mean score for IGlar (reduced) + sema] minus [mean score for IGlar (titrated)]).

Superiority (secondary confirmatory estimand):

H_0: $\mu \leq 0$ score points against H_A: $\mu > 0$ score points

Operationally the hypotheses will be evaluated by two-sided tests.

9.1.1 Multiplicity adjustment

The type I error will be controlled in the strong sense using a hierarchical (fixed sequence) testing procedure. This is based on priority ordering of the null hypotheses and testing them in this order using the two-sided 95% confidence interval approach until an insignificant result appears. Consequently, a null hypothesis will only be tested if the previous null hypothesis of the test hierarchy has been rejected in favour of IGlar (reduced) + sema.

The steps in the hierarchical testing procedure are as follows:

Step 1: Change from baseline to week 40 in **HbA_{1c} (%-point) non-inferiority** of IGlar (reduced) + sema versus IGlar (titrated).

Step 2: Change from baseline to week 40 in **body weight (kg) superiority** of IGlar (reduced) + sema versus IGlar (titrated).

Step 3: Relative change from baseline to week 40 in **daily insulin dose (%) superiority** of IGlar (reduced) + sema versus IGlar (titrated).

Step 4: Change from baseline to week 40 in **HbA_{1c} (%-point) superiority** of IGlar (reduced) + sema versus IGlar (titrated).

Step 5: **DTSQc score** at week 40 **superiority** of IGlar (reduced) + sema versus IGlar (titrated).

9.2 Analysis sets

The following participant analysis sets are defined:

Participant Analysis Set (PAS)	Description
Full analysis set (FAS)	All randomised participants. Participants will be included in the analyses according to the planned 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.

The following data points sets are defined:

Data points set (DPS)	Description
DPS1 – in-study	All observed data points from randomisation until the first date of: • end of study visit (P43) • death • withdrawal of informed consent • last contact as defined by investigator for participants that are lost to follow up
DPS2 – on-treatment	All observed data points from first drug date until the first date of: • end of DPS1 – in study • last IMP administration +42 days

Full analysis set (FAS) and DPS1 are used to estimate the primary estimand and the secondary estimands for the five confirmatory objectives.

FAS and DPS2 are used to estimate the additional estimands for the five confirmatory objectives.

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

Safety analysis set and a modified DPS2 are used to present safety data with an acute onset (vital signs, laboratory assessments and physical examination). The DPS2 is modified by having an end date as date of last IMP administration +7 days (due to the dosing interval of semaglutide s.c.) or date of end of DPS1, whichever occurs first.

9.3 Statistical analyses

9.3.1 General considerations

The resulting comparisons of the statistical analyses will, unless otherwise specified, be presented as point estimates, two-sided 95% confidence intervals, and the associated two-sided p-values for IGlar (reduced) + sema versus IGlar (titrated) derived under the assumption of no difference.

A baseline assessment is defined as the most recent measurement available at the randomisation visit (V2). Participants with missing baseline values will not contribute to any analysis that adjust for the given baseline.

The randomisation is stratified based on background treatment with SGLT-2 inhibitors (Y/N).

9.3.2 Primary estimand analysis

The primary estimand, presented in Section 3.2.1, 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 by imputing missing end of treatment data separately within groups defined by randomised treatment and treatment status at end of treatment, in total, four groups as follows:

i. IGlar (reduced) + sema and on-treatment at end of treatment.
ii. IGlar (reduced) + sema and off-treatment at end of treatment.
iii. IGlar (titrated) and on-treatment at end of treatment.
iv. IGlar (titrated) and off-treatment at end of treatment.

For each group an analysis of covariance (ANCOVA) with SGLT-2 inhibitor use (Y/N) and region as factors 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.

The 500 complete datasets will be analysed using an ANCOVA with randomised treatment, SGLT-2 inhibitor use (Y/N) and region as factors and baseline HbA_{1c} as a covariate. Rubin's rule will then be applied to combine these estimates and draw inference.

In case of sparse data, defined as less than 5 participants, in some groups, the imputation model will be thinned by region followed by SGLT-2 inhibitor use (Y/N). 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 with SGLT-2 inhibitor use (Y/N) and region as factors and baseline HbA_{1c} as a covariate. Finally, if this is still not sufficient the imputation model may be thinned again in the aforementioned order.

9.3.2.1 Sensitivity analysis

A two-way tipping point sensitivity analysis will be performed by repeating the ANCOVA described in Section 9.3.2. 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 analysis

The additional estimand for the primary objective, presented in Section 3.2.1, will be estimated based on the FAS and DPS2.

Missing end of treatment data will be imputed using MI assuming that missing data are 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 SGLT-2 inhibitor use (Y/N) and region as factors 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, SGLT-2 inhibitor use (Y/N) and region as factors and associated baseline HbA_{1c} as a covariate. Rubin's rule[42] will then be applied to combine the estimates and draw inference.

Sensitivity analysis

A two-way tipping point sensitivity analysis as described in Section 9.3.2.1 will be performed.

9.3.3 Secondary estimands analyses

9.3.3.1 Confirmatory

9.3.3.1.1 Change in body weight (kg)

A similar analysis as described in Section 9.3.2 will be performed, but with values of body weight instead of HbA_{1c}.

Sensitivity analysis

A two-way tipping point sensitivity analysis as described in Section 9.3.2.1 will be performed, but with values of body weight instead of HbA_{1c}.

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 Relative change in daily insulin dose (%)

Relative change from baseline to week 40 in insulin dose (%) is computed as

$$\frac{[\text{insulin dose at week 40}] - [\text{insulin dose at baseline}]}{[\text{insulin dose at baseline}]} \times 100$$

A similar analysis as described in Section 9.3.2 will be performed, but with values of insulin doses instead of HbA_{1c}. Furthermore, the model will assume a different residual variance across the two treatment arms.

Sensitivity analysis

A two-way tipping point sensitivity analysis as described in Section 9.3.2.1 will be performed, but with values of insulin doses instead of HbA_{1c}.

Additional estimand

A similar analysis as described in Section 9.3.2.2 will be performed, but with values of insulin doses instead of HbA_{1c}. Furthermore, the model will assume a different residual variance across the two treatment arms.

9.3.3.1.3 Change in HbA_{1c} (%-point)

A similar analysis as described in Section 9.3.2 will be performed.

Sensitivity analysis

A two-way tipping point sensitivity analysis as described in Section 9.3.2.1 will be performed.

Additional estimand

A similar analysis as described in Section 9.3.2.2 will be performed.

9.3.3.1.4 DTSQc score

A similar analysis as described in Section 9.3.2 will be performed, but with scores of DTSQs instead of HbA_{1c}.

Sensitivity analysis

A two-way tipping point sensitivity analysis as described in Section 9.3.2.1 will be performed, but with scores of DTSQs instead of HbA_{1c}.

Additional estimand

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

9.3.3.2 Supportive endpoints

Details on analyses of supportive secondary endpoints will be described in the SAP.

9.3.4 Exploratory endpoints analyses

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

9.3.5 Other safety analyses

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

9.3.6 Other analyses

Exploratory analyses of CGM derived variables.

Additionally, exploratory analyses of cardiovascular and renal risk markers may be performed.

Further details will be described in the SAP.

9.4 Interim analysis

This study will be subject to a partial 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 LPLT. Only Novo Nordisk employees from Medical & Science and Biostatistics will be blinded during this open-label study. These skill areas will be unblinded at the partial DBL. All efficacy analyses will be performed based on the data from the partial DBL. No efficacy assessments are collected after LPLT. In turn, efficacy results cannot be biased by the early unblinding. The impact on safety is considered minor, as most participants will have completed the follow-up visit. Analysis of safety will be performed after the full DBL. As previously stated, the SAP will be finalised prior to first participant first visit.

9.5 Sample size determination

The study has five confirmatory objectives that are tested in accordance to the test hierarchy specified in Section 9.1.1, but it is designed to have a marginal power of at least 90% of confirming the superior effect on change from baseline to week 40 in HbA_{1c} (%-point) of IGlar (reduced) + sema versus IGlar (titrated).

The power calculation is based on a 1-sided t-test with a significance level of 0.025, a 1:1 randomisation, an expected treatment difference (TD) of -0.3%-points and standard deviation (SD) of 1.1%-points (based on data from the SUSTAIN studies). Under these assumptions 568 participants are required to be randomised, and the actual power is 90.1%.

The powers for superiority on HbA_{1c} by various treatment effect sizes are found in Table 9-1.

Table 9-1 Power for superiority on HbA_{1c} by treatment effect size

TD	Power
-0.25	77.1%

TD	Power
-0.275	84.5%
-0.3	90.1%
-0.325	94.0%
-0.35	96.6%

With 568 participants a power of >99.9%, of confirming a non-inferior effect (with a non-inferiority margin of 0.3%-points) on change from baseline to week 40 in HbA_{1c} (%-point) of IGlar (reduced) + sema versus IGlar (titrated), is obtained.

Similarly, 568 randomised participants yield a power of >99.9% of confirming the superior effect on change from baseline to week 40 in body weight (kg) of IGlar (reduced) + sema versus IGlar (titrated), when assuming a TD of -6.3 kg and a SD of 4.0 kg (based on data from the SUSTAIN studies).

With 568 participants a power of 89.9%, when assuming a SD of 73.5%-points and a modest TD of -20%-points, is obtained of confirming the superior effect on the relative change from baseline to week 40 in daily insulin dose (%) of IGlar (reduced) + sema versus IGlar (titrated). The SD is chosen conservatively based on observed data from two studies (NN1436-4466 and NN9535-3627). Similarly, a TD of 20%-point reduction in insulin dose is considered conservative, and a greater reduction is expected given the nature of the two treatment arms being compared, though it is difficult to quantify more accurately due to limited historical data on insulin titration in the treatment arm with semaglutide. So, the endpoint is very well powered based on the number of randomised participants.

Lastly, 568 randomised participants yield a power of 84.5% of confirming the superior effect on DTSQc score at week 40 of IGlar (reduced) + sema versus IGlar (titrated) when assuming a TD of 1.5 score points and a SD of 6 score points (based on the study NN2211-1572).

Assuming that the power for the first three hypotheses in the test hierarchy is close to 100%, the overall power for meeting HbA_{1c} superiority is 90.1%, and the overall power for all hypotheses is 76.1%. These calculations are made assuming independence between the five tests.

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[43] and applicable International Council of Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[44]
- Applicable laws and regulations
- (EU) No 536/2014

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 clinical study report (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

Portugal and Slovakia: see local requirements in 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.

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[44] guidelines, Declaration of Helsinki,[43] 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.

Written informed consent should be taken at visit 1A so that the participant can attend the following visit (V1B) in a fasting state. If the participant normally attends their usual diabetes clinic visits in a fasting state then it is allowed to combine V1A and V1B into one visit. The site must be able to document that the participant comes to the clinic in a fasting state as part of their usual clinic practice.

For sites planning to conduct V18 as a home visit, written informed consent for home visit should be obtained before V18 so that this visit can be conducted at the participant's home or other alternative off site location.

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.

10.1.4 Information to participants during the study

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

completion of the study. Further, the participant may receive other written information during the study.

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

10.1.5 Data protection

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

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

The participant must be informed about his/her privacy rights, including that his/her personal study-related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the participant.

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

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

Spain: see local requirements in Appendix 9 (Section 10.9).

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, euclinicaltrials.eu 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,[43] the International Committee of Medical Journal Editors (ICMJE),[45] the Food and Drug Administration Amendment Act (FDAAA),[46] European Commission Requirements[47-49] and in accordance with Novo Nordisk commitment to clinical transparency. If a

participant requests to be included in the study via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the participant. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

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

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

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

The following will be provided as paper CRFs*:*

- Pregnancy forms

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

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints on study intervention not yet allocated to a participant)

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[44], and all applicable regulatory requirements, evaluating the adequacy of critical processes at site for the execution of the protocol, collection of study data, to ensure that the safety and rights of participants are being protected.

Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.

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

10.1.8.3 Protocol compliance

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

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

10.1.9 Source documents

All data entered in the eCRF must be verifiable in source documentation. Data in the service providers' database is considered source data e.g. laboratory data and CGM. For e-Diary (including PROs), data in the e-Diary database is considered source data, unless stated otherwise in source documentation agreements.

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, eCRFs 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 case report forms (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.

Spain and US: see local requirements in 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 he/she has delegated specified study-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the study. It is the investigator's responsibility to supervise the conduct of the study and to protect the rights, safety, and well-being of the participants.

A qualified physician, who is an investigator or a sub investigator for the study, must be responsible for all study-related medical decisions.

The investigator is responsible for filing essential documents (i.e., those documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced) in the investigator trial master file. The documents, including the participant identification code list must be kept in a secure locked facility so that no unauthorised persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. This also includes ensuring that no indirect sharing of user credentials for IT systems used in this study takes place (e.g., by not sharing IT equipment with others in a way where user credentials have the possibility of being shared). The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of participants to a specific qualified physician who will be readily available to participants during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g., if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

10.1.13 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical studies in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the study or by persons for whom the said site or investigator are responsible.

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.[50]

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.

US: see local requirements in Appendix 9 (Section 10.9).

10.2 Appendix 2: Clinical laboratory tests

The tests detailed in Table 10-1 and Table 10-2 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.

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, then a part of the sample may be kept for up to two years or according to local regulations.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	**Parameters**
Glucose metabolism	• HbA_{1c} (V1B, V2, V10, V18, V28, V42) • FPG (V2 and V42)[a,b] • C-peptide (V1B, V2 and V42)
Abbreviations: FPG = fasting plasma glucose [a] An FPG result <3.0 mmol/L (54 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as an AE at the discretion of the investigator (Appendix 3, Section 10.3). [b] An FPG result >16.7 mmol/L (300 mg/dL) should not be reported as a hyperglycaemic 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 V1B, V18 and V42	• Basophils • Eosinophils • Erythrocytes • Haematocrit • Haemoglobin • Leukocytes • Lymphocytes • Monocytes • Neutrophils • Thrombocytes

Laboratory assessments	Parameters
Biochemistry[a] Assessments performed at V1B, V18 and V42	• Alanine Aminotransferase (ALT) • Alkaline phosphatase • Amylase • Aspartate Aminotransferase (AST) • Bilirubin • Creatinine • Lipase • Potassium • Sodium • Urea • High Sensitive C-Reactive Protein (also V2)
Serology Assessments performed at V1B	• antibodies to GAD
Lipids	• Total Cholesterol (V2, V18 and V42) • High density lipoprotein (HDL) cholesterol (V2, V18 and V42) • Low density lipoprotein (LDL) cholesterol (V2, V18 and V42) • Triglycerides (V2, V18 and V42) • Apolipoprotein B (V2 and V42)
Hormones Assessments performed at V1B	• Calcitonin
Pregnancy Testing[b]	• Highly sensitive serum (V1B, V2, V42) and urine human chorionic gonadotropin (hCG) pregnancy test (P43)
Urinalysis Assessments performed at V2 and V42	• Albumin/Creatinine Ratio
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation (V1B and V42).
Notes: H: home visit; P: phone contact; 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 Section 7.1. [b] For women of childbearing potential, serum testing will be used except for follow up visit P43 where urine testing will be done.	

All study-required laboratory assessments will be performed by a central laboratory, with the exception of: P43 urine pregnancy test.

Czech Republic: see local requirements in Appendix 9 (Section 10.9).

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 a IMP.

Events to be reported as AEs:

- Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected
- Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected
- Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition
- Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent

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

Events NOT to be reported as AEs:

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

10.3.2 Definition of an SAE

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

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalisation or prolongation of existing hospitalisation**
  - Hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the

physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

- Hospitalisation for elective treatment (e.g., elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE.
  Note: Hospitalisations for administrative, study-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for medical or surgical procedures, planned before study inclusion, are not considered AEs or SAEs

- **Results in persistent or significant disability/incapacity**
  - The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Important medical event:**
  - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
  - The following must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:
    - Suspicion of transmission of infectious agents via IMP
    - Risk of liver injury defined as alanine aminotransferase (ALT) or 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. All AEs requiring additional data collection are collected on a specific event form. The AEs requiring additional data collection, are presented in Table 8-1.

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 or use of wrong device
  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)

Neoplasms (malignant and non-malignant)
Confirmed neoplasm by histopathology or other substantial clinical evidence

Other events requiring collection of additional information

Other AEs that also require collection of additional information, but which do not follow exactly the same reporting process as AEs requiring additional data collection include hypoglycaemic episodes (Table 8-1).

Hypoglycaemic episodes:

All hypoglycaemic episodes must be recorded by the participant in the e-Diary. Instructions on how to transfer SMPG values to the e-Diary will be given to the participants.

All hypoglycaemic episodes must be collected from the first administration of study intervention under clinical investigation and until the end of study visit (P43) in accordance with the flowchart (Section 1.2) or whenever, within the above time period, the site becomes aware of an hypoglycaemic episode. If the hypoglycaemic episode fulfils the criteria for an SAE, the AE form and the safety information form must be filled in. One AE form and safety information form can cover several hypoglycaemic episodes, if the participant has not recovered between the episodes. For more information on hypoglycaemic episodes, please refer to Appendix 6 (Section 10.6).

10.3.4 Recording and follow-up of AE and SAE

10.3.4.1 AE and SAE recording

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

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

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

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

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

Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the study, it is important that the suspected relationship is reported to Novo Nordisk, e.g., in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this 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 disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, should be considered and investigated.

The investigator should use the IB[27] and product information, for marketed products for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

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

The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the eCRF.

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

10.3.4.4 Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved**: The participant has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented.
- **Recovering/resolving**: The condition is improving, and the participant is expected to recover from the event. This term may also be applicable for AEs ongoing at the time of death (where death was due to another AE).
  Note: For SAEs, this term is only applicable if the participant has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae**: The participant has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved**: The condition of the participant has not improved, and the symptoms are unchanged, or the outcome is not known. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal**: This term is only applicable if the participant died from a condition related to the reported AE. Outcomes of other reported AEs in a participant before he/she died should be assessed as ‘recovered/resolved’, ‘recovering/resolving’, ‘recovered/resolved with sequelae’ or ‘not recovered/not resolved’. An AE with a fatal outcome must be reported as an SAE.
- **Unknown**: This term is only applicable if the participant is lost to follow-up.

10.3.4.5 Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g., severe hypersensitivity reactions, Hy’s

law). This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

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

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):

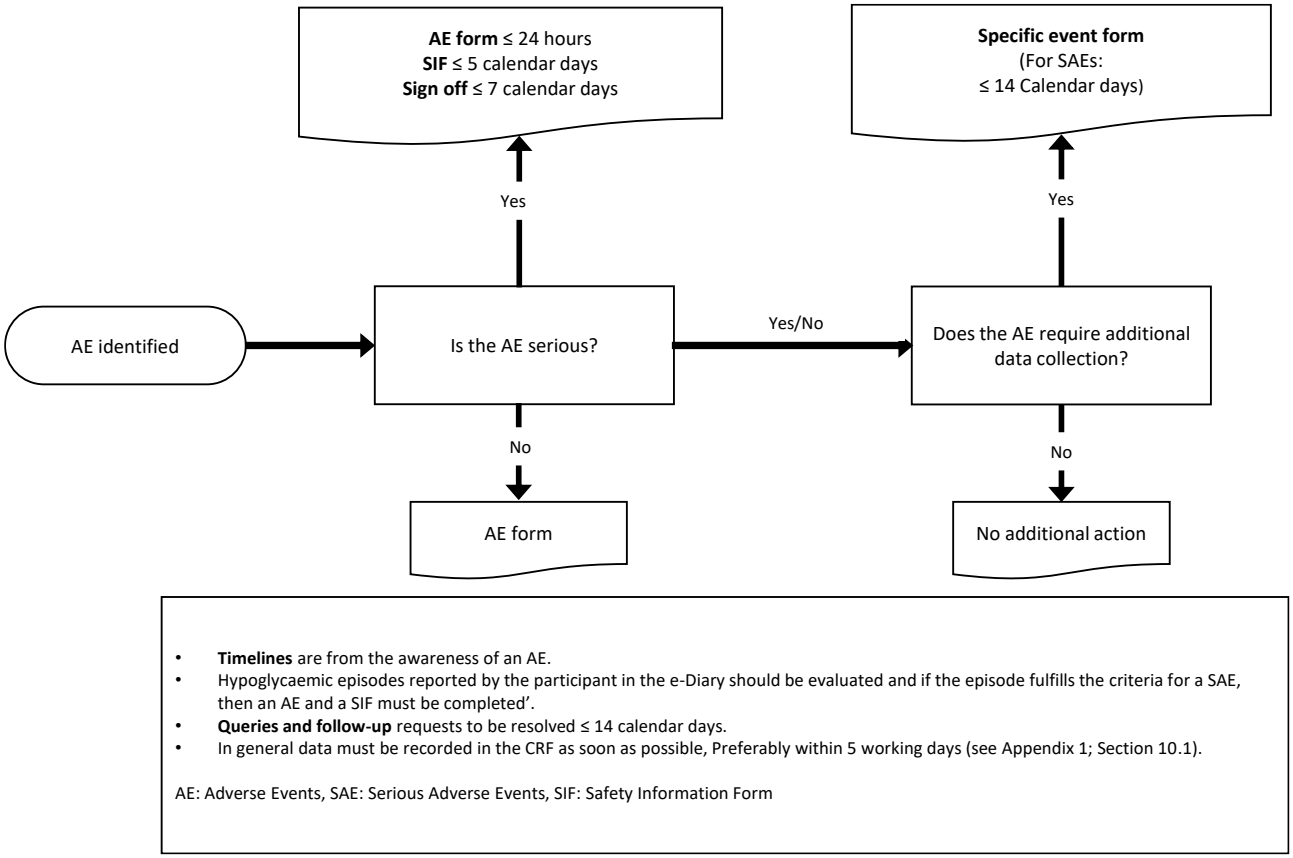
- AE form within 24 hours.
- Safety information form within 5 calendar days.
- Both forms must be signed within 7 calendar days after first knowledge by the investigator.
- Specific event form within 14 calendar days.

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

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

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



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

10.3.6 Reporting of AEs for non-Novo Nordisk medical devices

Reporting of AEs from baseline for non-Novo Nordisk medical devices provided by Novo Nordisk for use in the study

Additional reporting of AEs considered related to the BG meter and CGM: All AEs related to CGM should be reported from baseline to both the manufacturer and Novo Nordisk.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Females in the following categories are not considered WOCBP

1. Premenarcheal

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

   For females with permanent infertility due to an alternate medical cause other than the above (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining study enrolment.
3. Postmenopausal female:
   - A postmenopausal state is defined as amenorrhoea for at least 12 months without an alternative medical cause in a female > 45 years of age. Alternative medical causes for amenorrhoea include, but are not limited to, hormonal contraception or hormonal replacement therapy.
   - Females ≥ 60 years of age can be considered postmenopausal.

Females on 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 10-3 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 10-3 Highly effective contraceptive methods allowed[51]

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 Table 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.

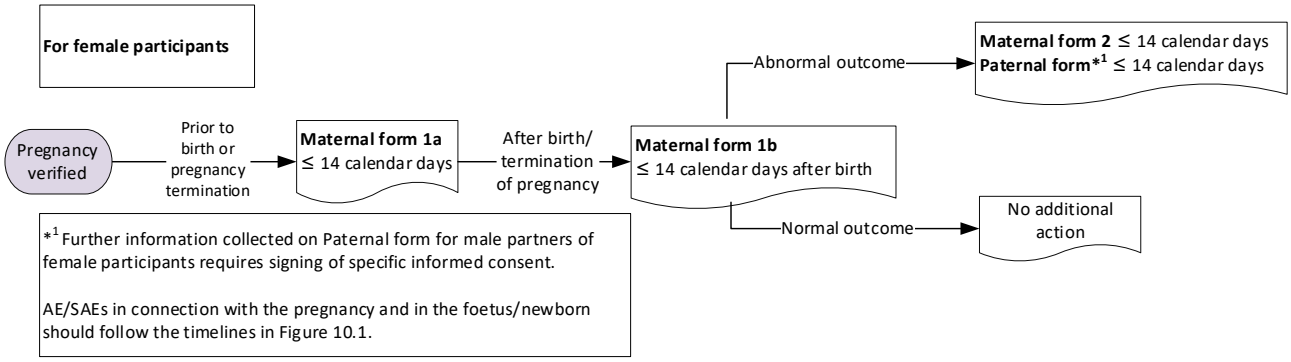
While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding 'gestational', 'pregnancy-related' or a similar term when reporting the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

Czech Republic: see local requirements in Appendix 9 (Section 10.9).

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 calendar days for all other technical complaints.

If the eCRF is unavailable, or when reporting a technical complaint on a product that is not yet allocated to a participant, the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

Follow-up of technical complaints

The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples

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

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the study intervention.

If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together.

Storage for the technical complaint sample must be done in accordance with the conditions prescribed for the product.

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: Hypoglycaemic episodes

Table 10-4 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,[52] ADA,[53] ISPAD[54], type 1 diabetes outcomes program[55], AATD.[34] Severe hypoglycaemia as defined by Seaquist[56] and ISPAD.[54] **Abbreviations**: ADA = American Diabetes Association; ATTD = Advanced Technologies & Treatments for Diabetes, ISPAD = International Society for Pediatric and Adolescent Diabetes; IHSG = The International Hypoglycaemia Study Group		

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 (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.[56]

Nocturnal hypoglycaemia

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

Reporting of hypoglycaemic episodes

PG should always be recorded in the e-Diary when a hypoglycaemic episode is suspected.

The following should be reported in the e-Diary as hypoglycaemic episodic events:

- PG values < 3.9 mmol/L (70 mg/dL)
- Severe hypoglycaemic episodes without confirmed PG values

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 e-Diary. The investigator should ensure correct reporting of the hypoglycaemic episode. Confirmation of the hypoglycaemic episode review must be documented in the e-Diary HCP web portal. In case a participant is not able to fill in the e-Diary (e.g., in case of hospitalisation), at the time of the episode, the participant can report the episode in the e-Diary retrospectively.

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.[56]

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.

If the episode was an event that required assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions, then the investigator must ensure that the participant has indicated in the e-Diary that he/she needed help to get a sugary drink, food or medicine to feel better. 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.[56]

Please refer to Section 10.3.3 for information regarding reporting of hypoglycaemia in the e-Diary.

e-Diary review

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

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.

10.7 Appendix 7: Treatment guideline for semaglutide and insulin glargine U100

Titration guidelines have been developed for insulin glargine U100, providing recommended dose adjustments at different PG levels to ensure that participants receive an optimal treatment. However, it is recognised that insulin treatment should be individualised, and the specific titration algorithms may not be applicable in certain clinical situations. Hence, it is important that other information, such as symptoms of hypo/hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the participant's level of glycaemic control, is taken into consideration when decisions on dosing are made. The investigator is responsible for the treatment of the participants and can therefore overrule the guidelines to avoid safety hazards.

10.7.1 Initiation and treatment with trial products

At randomisation all eligible participants will be transferred to receive either OW semaglutide s.c. + insulin glargine U100 or to receive insulin glargine U100.

10.7.1.1 OW semaglutide s.c.+ insulin glargine U100 arm

Semaglutide s.c. will be initiated at randomisation (V2) with 0.25 mg OW. The injection can be administered at any time of the day irrespective of meals, but on the same day of the week.

Dose escalation to the target maintenance doses of OW semaglutide s.c. 2.0 mg should take place every 4 weeks after randomisation as described in Table 10-5.

Prior daily basal insulin dose should be replaced with insulin glargine U100 at a dose reduction of 10 U at the initiation of OW semaglutide s.c. The insulin glargine U100 dose should be reduced by 10 U at each semaglutide dose escalation in accordance with Table 10-5. This is to reduce the risk of hypoglycaemic episodes.

Insulin glargine U100 dose should be adjusted based on the pre-breakfast SMPG values measured on the day of the titration and on the two days before each contact in accordance with Table 10-6.

Table 10-5 Dose escalation and maintenance of OW semaglutide s.c. dose escalation and reduction of insulin glargine U100

	Escalation step 1 Visit 2	**Escalation step 2 Visit 6**	**Escalation step 3 Visit 10**	**Maintenance Visit 14**
OW Semaglutide s.c.	0.25 mg	0.5 mg	1.0 mg	2.0 mg
Insulin glargine U100 reduction[a]	-10 U	-10 U	-10 U	-10 U

Abbreviations : OW = once weekly ; s.c. =subcutaneous; U = units

[a]Dose reduction of 10 U insulin for each escalation step should be attempted in all participants regardless if they receive less than 40 units/day at randomisation.

If a participant does not tolerate the designated target dose of semaglutide s.c., 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. The participant should make at least one attempt to re-escalate to the designated target dose, as per the investigator's discretion.

It is recommended that the investigator consults Novo Nordisk in case of persistent deviations from the planned escalation regimen.

Semaglutide missed doses

If a OW 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.

10.7.1.2 Insulin glargine U100 arm

Prior daily basal insulin should be switched to insulin glargine U100 in accordance with local insulin glargine (Lantus®) labelled text, and thereafter considered adjusted on a weekly basis according to pre-breakfast SMPG values obtained on the day of titration and on the 2 days prior to titration. The dose of insulin glargine U100 should be titrated in line with the titration algorithm described in Table 10-6.

If one or more SMPG values are missing, the adjustment should be performed on the remaining SMPG value(s).

Table 10-6 Adjustment of insulin glargine U100 dose

Pre-breakfast SMPG			**Insulin glargine U100 adjustment**
Value to use	**mmol/L**	**mg/dL**	**Units**
Lowest of the SMPG values	<4.4	<80	-3
Mean of the SMPG values	4.4-7.2	80-130	0
	>7.2	>130	+3

Abbreviations: SMPG = self-measured plasma glucose.

10.7.2 Data collection

The participant should be instructed to report the following in the e-Diary:

- Date, dose and time of insulin glargine U100 injections.
- Date, dose and time of OW semaglutide s.c. injections.
- SMPG values with an indication of "pre-breakfast" or "other" (see Section 8.2.1).
- Hypoglycaemic episodes as described in Appendix 6 (Section 10.6).

While using the HCP web portal for titration the following will be entered by investigator:

- Insulin glargine U100 and semaglutide doses prescribed at this contact.
- Reasons for deviation from the titration algorithm, if applicable.

10.7.3 Data surveillance

Surveillance of titration data will be performed centrally by Novo Nordisk in an unbiased manner. The data will be reviewed and significant changes from the titration algorithm will be followed up.

Titration data will consist of:

- Relevant SMPG values.
- Recommended insulin glargine U100 dose.
- Prescribed insulin glargine U100 dose.
- Actual semaglutide and insulin glargine U100 doses taken by the participant.
- Reason for deviation from the insulin glargine U100 titration guideline. Deviations are divided into:
    - "Hypoglycaemia"
    - "Other, please specify"
    - Hypoglycaemia information.

It is important that titration data is entered into the e-Diary and into the eCRF in a timely manner, as the aim is to reduce the time in which the participant may receive inadequate treatment.

The titration data should be reviewed by Novo Nordisk within 24 hours (on workdays). Novo Nordisk may contact the investigator by phone or via an online portal (CONNECT) after e-mail notification to clarify reasons for deviation or to request entry of missing data. When the investigator receives an inquiry, a response should be received at Novo Nordisk within 24 hours (on workdays).

Novo Nordisk will also monitor changes in HbA_{1c}. Novo Nordisk's medical staff may (virtually) visit to discuss progress in glycaemic control and titration of individual participants.

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 COVID-19 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 (V1A and V1B) and randomisation (V2) 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.

Visit V18 should be performed at the participants' home or other alternative off-site location according to the flowchart (Section 1.2), if in any way possible. If not, assessments can be conducted remotely (video, phone or similar).

On-site visits (V6, V10, V14, V28 and V40) can be converted to remote visits (video, phone or similar) or home or off-site visits.

The weekly phone contacts should be conducted according to the original flowchart (Sections 1.2 and 1.3).

The end of treatment visit (V42) should be performed as an on-site visit, if in any way possible. If not, the visit can be conducted in the following order of preference:

1. The visit can be conducted as home or off-site visit.
2. The visit window for the assessments can be extended for up to 3 months and participants should continue randomised treatment until the end of treatment visit (V42) takes place.
3. The visit can be conducted remotely (video, phone or similar).

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 and secondary confirmatory endpoints, i.e. HbA_{1c}, body weight and DTSQc, should be prioritised. Review of the e-Diary via the HCP portal data must be done to ensure that daily insulin dose (secondary confirmatory endpoint) is correctly reported.

Local laboratories or diagnostic facilities can be used for laboratory assessments 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 body weight 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 a participant cannot attend the site at a timepoint where he/she wears CGM, the site should instruct the participant in removing the sensor themselves after the CGM period is complete, and to keep the Receiver battery charged. The site staff can collect the receiver from the participant up to 4 weeks later and bring the receiver to the site for CGM data upload. It is also possible to arrange a courier to return the device back to site. At Visit 40 the site should ensure the participant can change the sensor at home after 7 days.

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

Please refer to Section 1.2 for the full flowchart.

Procedures marked with a black X should be prioritised. If deemed necessary, procedures marked with a red C can be cancelled and V6, V10, V14, V28 and V40 can be fully converted to remote visits. The phone contacts should be conducted according to the original flowchart (Sections 1.2 and 1.3).

	Protocol section	Screening		Randomisation	Dose escalation period			Maintenance period			End of treatment	End of study
Visit		V1A	V1B	V2	V6	V10	V14	V18[a]	V28	V40	V42	P43
Timing of Visit (Weeks)			-2	0	4	8	12	16	26	38	40	End of treatment+5 weeks
Visit Window (Days)			±3	0	±3	±3	±3	±3	±3	±3	±3	+7
Informed Consent and Demography[b]	10.1.3 (App 1)	X										
Eligibility Criteria	5.1 and 5.2		X	X								
Randomisation	6			X								
Hypoglycaemia unawareness	5.2 and 8.3		X									
Childbearing Potential	10.4 (App 4)		X									
Concomitant Medication	6.8		X	X	X	X	X	X	X	X	X	X
Medical History/Concomitant Illness	8.3		X									

	Protocol section	Screening		Randomisation	Dose escalation period			Maintenance period			End of treatment	End of study
Visit		V1A	V1B	V2	V6	V10	V14	V18[a]	V28	V40	V42	P43
Timing of Visit (Weeks)			-2	0	4	8	12	16	26	38	40	End of treatment+5 weeks
Visit Window (Days)			±3	0	±3	±3	±3	±3	±3	±3	±3	+7
Pregnancy Test[c]	8.3.5 and 10.2 (App 2)		X	X							X	X
Tobacco Use	5.3.1		X									
Body Measurements	8.3.1		X	X	C	C	C		C		X	
Self measured plasma glucose	8.2.1, 10.6 (App 6) and 10.7 (App 7)			X	X	X	X	X	X	X	X	X
Laboratory Assessments	10.2 (App 2)		X	X	-	C		X	C		X	
Adverse Events	8.4 and 10.3 (App 3)				X	X	X	X	X	X	X	X
Hypoglycaemic Episodes	8.4 and 10.6 (App 6)				X	X	X	X	X	X	X	X
Eye Examination	8.3.3		X								X[d]	
Physical Examination	8.3.1		X								X	
Vital Signs	8.3.2		X	X	C	C	X		C		X	
Hand Out Direction for Use	6			X								

	Protocol section	Screening		Randomisation	Dose escalation period			Maintenance period			End of treatment	End of study
Visit		V1A	V1B	V2	V6	V10	V14	V18[a]	V28	V40	V42	P43
Timing of Visit (Weeks)			-2	0	4	8	12	16	26	38	40	End of treatment+5 weeks
Visit Window (Days)			±3	0	±3	±3	±3	±3	±3	±3	±3	+7
Hand Out ID Card	6 and 10.1.5 (App 1)		X									
Hand Out and Instruct in BG-meter	6			X								
Hand Out and Instruct in ePID (e-Diary)	6 and 8			X								
Hand Out and Instruct in CGM	8.2.2		X							C		
RTSM/IWRS Session	6 and 7	X		X	X	X	X		X		X	
Attend visit fasting	10.2 (App 2)		X	X							X	
Training in Trial Product, Pen-handling	6			X	C		X					
Dispensing Visit	6			X	X	X	X		X			
Drug Accountability	6				X	X	X		X		X	
SF-36 v2	8.2.4			X							X	
DTSQs	8.2.4			X							X	

	Protocol section	Screening		Randomisation	Dose escalation period			Maintenance period			End of treatment	End of study
Visit		V1A	V1B	V2	V6	V10	V14	V18[a]	V28	V40	V42	P43
Timing of Visit (Weeks)			-2	0	4	8	12	16	26	38	40	End of treatment+5 weeks
Visit Window (Days)			±3	0	±3	±3	±3	±3	±3	±3	±3	+7
DTSQc	8.2.4										X	

Abbreviations: AE = adverse events; App = appendix; BG = blood glucose; CGM = continuous glucose monitoring; IWRS = interactive web response system; RTSM = Randomisation and Trial Supplies Management; ePID = electronic patient interactive device; DTSQc = Diabetes Treatment Satisfaction Questionnaire- change version ; DTSQs = Diabetes Treatment Satisfaction Questionnaire- status version ; SF-36 v2 = Short Form 36 version 2; V = visit.

[a]This visit can be conducted at the participant's home or other alternative off site location for participants who have consented to have V18 conducted as a home visit. Please refer to Section8.1.

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

[c]Czech Republic: see local requirements in Appendix 9 (Section 10.9).

[d]Eye examination can be conducted up to 8 weeks prior to V42.

10.9 Appendix 9: Country-specific requirements

For Portugal:

- **5.2 Exclusion criteria:** Contraception requirements based on the Recommendations related to contraception and pregnancy testing in clinical trials from Clinical Trial Facilitation Group (CTFG): http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
- **10.1.1 Regulatory and ethical considerations**: Contact of responsible person/department, with fax, email besides the address

For Spain:

- **10.1.5 Data protection**: This study will be conducted in line with European Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on data protection GDPR
- **10.1.10 Retention of clinical study documentation**: 25 years according to the new Spanish Royal Decree 1090/2015.

For United States:

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

Food and Drug Administration (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 trial.

- **10.1.10 Retention of clinical study documentation**: In the United States, 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'. Since we follow the corporate default of 15 years (Directive 2001/20/EC), we request column N be updated to '15 years' for transparency.

For Slovakia:

- **10.1.1 Regulatory and ethical considerations:**

The investigator will be responsible for:

1. notifying the IRB/IEC of SAEs – only death, as required by IRB/IEC procedures and local regulations
2. 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
3. reporting any potential serious breaches to the sponsor immediately after discovery
4. The sponsor will be responsible for:
5. 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
6. notifying the IRB/IEC of SAEs or other significant safety findings according to local
7. regulations and procedures established by the IRB/IEC and/or regulatory authorities
8. ensuring submission of protocol, protocol amendments, ICF, investigator brochure, CSR synopsis and other relevant documents to the IRB/IEC and/or regulatory authorities.

For Czech Republic:

- Section 1.2: Date of Birth: Patient's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth.
- Section 5.2 exclusion criteria no 3 and Appendix 4, 10.4: Contraceptive requirements as per EU CTFG guideline: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
- Monthly pregnancy test (urine) for female participant of childbearing potential is needed. The additional pregnancy testing will not be reported in the CRF. In case of pregnancy, trial product will be discontinued, and the investigator should follow the procedures outlined in Appendix 4, Section 10.4.

10.10 Appendix 10: Abbreviations

Abbreviation	Definition
ADA	American Diabetes Association
AE	adverse event
ANCOVA	Analysis of covariance
ATTD	Advanced Technologies & Treatments for Diabetes
BG	blood glucose
BMI	body mass index
CGM	continuous glucose monitoring
COVID-19	Coronavirus disease 2019
CRF	case report form
CRO	contract research organisation
CSR	clinical study report
CTFG	clinical trial facilitation group
CV	cardiovascular
DBL	database lock
DFU	directions for use
DPS	data points set
DPP-4	dipeptidyl peptidase
DTSQc	Diabetes Treatment Satisfaction Questionnaire- change version
DTSQs	Diabetes Treatment Satisfaction Questionnaire- status version
DUN	dispensing unit number
eCRF	electronic case report form
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ePID	electronic patient interactive device
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
GAD	glutamic acid decarboxylase
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP-1	Glucagon-like peptide
$HbA1_c$	glycated haemoglobin
HCP	Healthcare professional

IB	investigator's brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics committee
IGlar	Insulin glargine
IHSG	The International Hypoglycaemia Study Group
IMP	investigational medicinal product
IND	investigational new drug
IRB	institutional review board
ISO	International Organization for Harmonization
ISPAD	International Society for Paediatric and Adolescent Diabetes
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	interactive web response system
LADA	Latent autoimmune diabetes in adults
LPLT	last participant last visit
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MEN2	multiple endocrine neoplasia type 2
MI	Multiple imputation
NIMP	non-investigational medicinal product
NPH	Neutral protamine hagedorn
NYHA	New York Heart Association
OW	Once weekly
PAS	participant analysis set
PCD	primary completion date
PG	plasma glucose
PRO	patient reported outcome
QTL	Quality tolerance limit
RTSM/IWRS	Systems used for Randomisation and Trial Supplies Management (also Interactive Web Response System)
SAE	serious adverse event
SAP	Statistical Analysis Plan
Sema	Semaglutide s.c.
SF-36 v2	Short Form 36 version 2
SGLT-2	Sodium glucose cotransporters 2
SmPC	Summary of product characteristics

SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TD	Treatment difference
TMM	Trial Materials Manual
WOCBP	woman of childbearing potential

10.11 Appendix 10: 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 (23 November 2021), global

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, because it neither significantly impacts the safety nor physical/mental integrity of participants nor the scientific value of the study.

Overall rationale for preparing protocol, version 2.0:

This protocol amendment is done to correct the errors identified in visits related to laboratory assessments and self-measured plasma glucose (SMPG) values in flow-chart and in other relevant sections.

Section # and name	Description of change	Brief rationale
Section 1.2 Flowchart	Errors in flowchart (misplaced assessments have been corrected)	Error in laboratory assessment visits
Section 1.3 Flowchart	Errors in the flowchart (misplaced assessments have been corrected)	Errors in in the timepoint assessment of SMPG (at P24)
Section 8 Study assessments and procedures	Error in assessment schedule for physical examinations at V2	To align protocol text and flowchart

Protocol version 3.0 (27 April 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.[47]

Overall rationale for preparing protocol, version 3.0:

This version of protocol was prepared primarily to clarify home visit (V18) to be voluntary (both for site and participants), modify titration algorithm to simplify dose titration further and to ensure sufficient dose adjustments frequency is increased to weekly contacts. In addition, rationale for

incremental reduction in dose of insulin glargine has been clarified. The changes including rationales are listed in the table below.

Sections # and name	Description of change	Brief rationale
Section 1.1 Synopsis Section 1.2 Flowchart Section 4.1 Overall design Section 8.1 Home visit	Home visit (V18) has been clarified to be voluntary (both for site and participants).	Due to operational challenges and making this widely applicable.
Section 10.8.4 Study intervention	Visit numbers have been updated.	Due to additional phone visits.
Section 1.1 Synopsis Section 4.1 Overall design	Information regarding weekly contacts (either at site visits or phone contacts) for adverse event (AE) assessment, electronic diary (eDiary) review of self-measured plasma glucose (SMPG) values, doses taken of trial products and reported hypoglycaemic episodes, if any.	To ensure sufficient dose adjustments and monitoring, frequency is increased to weekly contact
Section 1.1 Synopsis Section 4.1 Overall design Section 4.2 Scientific rationale for study design Section 8.2.2 Continuous glucose monitoring Section 10.8.3 Assessments	Information regarding CGM profile for a 14-day period with a change of sensor after 7 days at week 38 has been added. Visit numbers have been updated.	In line with international standards and Novo Nordisk recommendations.
Section 1.2 Flowchart Section 8.2.2 Continuous glucose monitoring Section 10.8.4 Study intervention	The following footnote has been removed: "CGM is not applicable for the countries were the Dexcom G6® device is not approved, see Appendix 9 (Section 10.9)".	Dexcom G6® device is approved in all selected countries.
Section 1.2 Flowchart Section 1.3 Flowchart – phone contacts	Additional phone visits included. Visit numbers have been updated.	To ensure weekly contacts.
Section 1.2 Flowchart Section 10.8.4 Study intervention	A footnote added to indicate that race and ethnicity must be self reported by the participants.	To comply with FDA requirements on self-reporting of race and ethnicity.
Section 2.2 Background Section 4.3 Justification for dose	Approval status of OW semaglutide s.c. 2.0 mg has been included.	Updated information.
Section 4.3 Justification for dose	Rationale for target dose of semaglutide 2.0 mg has been added. Rationale for 10 U increment reduction in dose of insulin glargine has been added.	Clarification and updated information. Additional Clarification.
Section 6.1 Study interventions administered	Information on stable dose of pre-trial anti-diabetic background medication during the trial and not allowing addition of other oral antidiabetic drugs has been added.	Clarification
Section 6.5 Dose modification	Information on weekly dose adjustment of insulin glargine U100 doses has been added.	To allow frequent dose adjustments according to SMPG values.

Sections # and name	Description of change	Brief rationale
Section 4.4 End of study definition Section 6.8 Concomitant medication Section 10.2 Appendix 2: Clinical laboratory tests Section 10.3.3 Description of AEs requiring additional data collection and other events requiring collection of additional information Section 10.8.2 Visits	Visit number has been updated.	Due to additional phone visits.
Section 7 Discontinuation of study intervention and participant withdrawal	RTSM language update. Visit number has been updated.	In line with standards.
Section 8 Study assessments and procedures	The order of the assessments at the randomisation visit (V2) has been updated. Visit number has been updated.	To include the setup of the eDiary device.
Section 8.2.2 Continuous glucose monitoring	The following text has been removed: "The CGM will be removed by the site staff at the participant's next visit".	At V40, CGM profile for 14 days require change of sensor at home.
Section 9.3.2.2 Additional estimand analysis	The additional estimand for the primary objective will be estimated based on the FAS and DPS2.	Typo error
Section 10.1.3 Informed consent process	Informed consent process for home visit at V18 has been added.	To describe informed consent process for home visit.
Section 10.1.8.1 Case report forms	Rephrased the text related to signature of investigator in the eCRF.	Clarification
Section 10.1.10 Retention of clinical study documentation	Investigator must retain study documents for 25 years.	Based on EU CT regulation
Section 10.2 Appendix 2: Clinical laboratory tests	Deleted the text related to "investigator must keep an overview, e.g. a log of laboratory samples" Removal of Apolipoprotein B at V18.	Apolipoprotein not needed for monitoring purposes during trial conduct.
Section 10.7 Appendix 7: Treatment guideline for semaglutide and insulin glargine	Frequency and schedule for insulin glargine dose adjustments has been clarified and updated. Updated titration algorithm of insulin glargine dose (-3, 0, +3 IU) Visit number has been updated	Additional Clarification. To further simplify titration algorithm
Section 10.9 Appendix 9: Country-specific requirements	Slovakia and Czech Republic requirements have been added. Russia and Ukraine requirements have been removed.	Based on the comments received from Regulatory Authority of Slovakia. New country Czech Republic added. Russia and Ukraine removed due to current crisis within the region.
Section 1.1 Synopsis Section 1.2 Flowchart Section 2.3.2 Benefit assessment	Minor editorial changes	

Sections # and name	Description of change	Brief rationale
Section 3.2.1.1 Primary estimand Section 3.2.1.2 Additional estimand Section 4.1 Overall design Section 4.2 Scientific rationale for study design Section 5.2 Exclusion criteria Section 6.4 Study intervention compliance Section 9 Statistical considerations Section 10.1 Appendix 1 : Regulatory, ethical and study oversight considerations Section 10.4 Appendix 4:Contraceptive guidance and collection of pregnancy information Section 10.8 Appendix 8: Mitigations to ensure participant safety and data integrity during an emergency situation		

Protocol version 4.0 (16 January 2023)

This amendment is considered to be non-substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014.[1]

Overall rationale for preparing protocol, version 4.0

The overall rationale for the changes implemented in the amended protocol is to ensure the recruitment of sufficient number of participants to be included in the study.

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis Section 2.1 Study rationale Section 2.2 Background Section 2.3.2 Benefit assessment Section 3.1 Objectives and endpoints Section 3.2.1.1 Primary estimand Section 4.1 Overall design Section 4.2 Scientific rationale for study design Section 5.1 Inclusion criteria Section 6.1 Study interventions administered Section 8 Study assessments and procedures	Patients who are being treated with a daily dose of basal insulin (e.g. insulin glargine U100 or U300, NPH insulin, insulin detemir, insulin degludec) up to 40 U/day for ≥ 90 days before screening will be allowed to undergo screening for the participation in this study. This change has been implemented throughout the protocol.	To allow for a more representative population of patients with type 2 diabetes using once daily basal insulin and to ensure recruitment of the required number of participants for the study.
Section 1.1 Synopsis	The number of participants that will be screened to achieve the required number of participants has been changed *from* “757” to “825”.	To ensure recruitment of the required number of participants for the study.

Section # and name	Description of change	Brief rationale
Section 2.2 Background Section 2.3 Benefit risk assessment Section 6.7 Treatment of overdose	"For details on insulin glargine U100, please refer to the most recent version of European Medicines Agency (EMA) summary of product characteristics or the most recent version of the US prescribing information or the most recent version of any locally approved label." has been added. This change has been implemented throughout the protocol.	To guide where to find information about Insulin glargine.
Section 4.2 Scientific rationale for study design	"Insulin glargine U100 has been chosen as the once daily basal insulin, as it is a well-established comparator that has been extensively evaluated." has been added.	Added to clarify the rationale related to choosing insulin glargine as the comparator.
Section 5.2 Exclusion criteria	Exclusion criteria no 2 has been changed from "Previous participation in this study. Participation is defined as signed informed consent." to "Previous participation in this study. Participation in this study is defined as signed informed consent. If the participant previously has been screen failed due to C-peptide levels <0.5 nmol/L (1.5 ng/mL), one re-screening is allowed."	The C-peptide threshold of <0.5 nmol/L was conservative and excluding participants who had a normal range of C-peptide according to the assay used (0.26-1730 nmol/L). Due to the weekly site contacts, the former threshold is deemed obsolete.
Section 5.2 Exclusion criteria	Exclusion criteria no. 4 has been changed from "Participation (i.e., signed informed consent) in any interventional, clinical study within 90 days before screening." to "Participation (i.e., randomised or exposed to intervention (whichever comes first)) in any other interventional, clinical study within 90 days before screening."	To ensure recruitment of the required number of participants for the study.
Section 5.2 Exclusion criteria and Section 1.1 Synopsis	Exclusion criteria no. 8 has been changed from "C-peptide <0.5 nmol/L" to "C-peptide <0.26 nmol/L or 260 pmol/L (0.78 ng/mL)."	To allow for a more representative population of patients with type 2 diabetes. The C-peptide threshold of <0.5 nmol/L was conservative and excluding patients who had a normal range of C-peptide according to the assay used (0.26-1730 nmol/L). Due to the weekly site contacts, the former threshold is deemed obsolete.
Section 5.4 Screen Failures Section 5.4.1 Rescreening	A new subsection "5.4.1 Rescreening" with relevant information has been added.	To describe the participants who will be allowed to undergo rescreening and the process that will be followed. This aligns with the changes made in the inclusion and exclusion criteria and consequently ensure recruitment of the required number of participants for study.

Section # and name	Description of change	Brief rationale
Section 7.1.1 Temporary discontinuation of study intervention.	Text changed from: "In case of suspicion of acute pancreatitis, 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 criteria41). Appropriate actions should be initiated. If acute pancreatitis is confirmed, study interventions should not be restarted, and discontinuation of treatment should be completed 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." to "In case of suspicion of acute pancreatitis, semaglutide 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). Appropriate actions should be initiated. If acute pancreatitis is confirmed, semaglutide should not be restarted, and discontinuation of study interventions should be completed in RTSM/IWRS. If the Atlanta criteria are not fulfilled and thus, the suspicion of acute pancreatitis is not confirmed, semaglutide may be resumed."	Changed to clarify the procedure of discontinuation due to suspected or confirmed acute pancreatitis.
Appendix 10.7.1.1 OW semaglutide s.c.+ insulin glargine U100 arm	Information regarding the switch from other basal insulins to insulin glargine U100 has been added to reflect the current inclusion of participants on basal insulin in the study. The text has been changed from "Insulin glargine U100 should be reduced by 10 U at initiation of OW semaglutide s.c. and then again at each OW semaglutide s.c. dose escalation in accordance to Table 10-5." to "Prior daily basal insulin dose should be replaced with insulin glargine U100 at a dose reduction of 10 U at the initiation of OW semaglutide s.c. The insulin glargine U100 dose should be reduced by 10 U at each	To allow for a more representative population of patients with type 2 diabetes using basal insulin and to ensure the recruitment of the required number of participants for the study.

Section # and name	Description of change	Brief rationale
	semaglutide dose escalation in accordance with Table 10-5."	
Appendix 10.7.1.2 Insulin glargine U100 arm	Information regarding the switch from other basal insulins to insulin glargine U100 has been added to reflect the current inclusion of patients on basal insulin in the study. The text has been changed from "Insulin glargine U100 should be switched from previous treatment unit-to-unit and thereafter considered adjusted on a weekly basis according to pre-breakfast SMPG values obtained on the day of titration and on the 2 days prior to titration." to "Prior daily basal insulin should be switched to insulin glargine U100 in accordance with the local insulin glargine (Lantus®) labelled text, and thereafter considered adjusted on a weekly basis according to pre-breakfast SMPG values obtained on the day of titration and on the 2 days prior to titration."	To allow for a more representative population of patients with type 2 diabetes using basal insulin and to ensure the recruitment of the required number of participants for the successful conduct of the study.

Protocol version 5.0 (22 December 2023)

This amendment is considered to be non-substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014.[1]

Overall rationale for preparing protocol, version 5.0

The overall rationale for the changes implemented in the amended protocol is to ensure the recruitment of sufficient number of participants to be included in the study.

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis	Upper limit of HbA1c % has been changed from 7-9% (53-75 mmol/mol) to 7-10% (53-86 mmol/mol)	To ensure recruitment of the required number of participants for the study.
Section 5.1 Inclusion criterion	Upper limit of HbA1c % has been changed from 7-9% (53-75 mmol/mol) to 7-10% (53-86 mmol/mol)	To ensure recruitment of the required number of participants for the study.

Section # and name	Description of change	Brief rationale
Section 5.2 Exclusion criterion	HbA_{1c} of 7%-10% has been added along with C-peptide levels < 0.5 nmol/L in the exclusion criteria	To ensure recruitment of the required number of participants for the study.
Section 5.4 Screen failures	Change in % of upper limit of HbA1c to be aligned with inclusion criteria	To ensure recruitment of the required number of participants for the study.
Section 5.4.1 re-screening	HbA_{1c} of 7%-10% has been added along with C-peptide levels < 0.5 nmol/L	To ensure recruitment of the required number of participants for the study.

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