Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT06041217
Sponsor trial ID:	NN9536-4706
Official title of study:	Efficacy and safety of semaglutide 2.4 mg once-weekly in adults with overweight and obesity (STEP 12)
Document date*:	05 September 2024

*Document date refers to the date on which the document was most recently updated.

Protocol

Protocol Title: Efficacy and safety of semaglutide 2.4 mg once-weekly in adults with overweight and obesity (STEP 12)

Substance: Semaglutide

Redacted protocol
includes redaction of company confidential information.

Universal Trial Number: U1111-1273-4538

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Study phase: 3b

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

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in regions
Protocol version 4.0	05 September 2024	China mainland and Taiwan
Protocol version 3.0	17 May 2023	Taiwan
Protocol version 2.0	05 April 2023	China mainland and Taiwan
Original protocol version 1.0	11 November 2022	China mainland and Taiwan

Protocol version 4.0 (05 September 2024)

Overall rationale for preparing protocol, version 4.0:

The rationale for preparing the protocol amendment is to include information related to elevated liver enzymes, add a supportive secondary endpoint and to update the analysis for primary endpoint (see all changes below). This amendment is considered substantial.

Section # and name	Description of change	Brief rationale
Section 1.2: Flowchart	Deleted the RTSM transaction at visit 14	As per the RTSM guidance, the last RTSM transaction is "Dispensing Completion" at visit 12
Section 2.3: Benefit-risk assessment	Risk of intestinal obstruction has been added	Important information for the investigators including mitigation strategy
Section 3: Objectives, endpoints and estimands	Addition of 'Change in waist-height ratio' to the supportive secondary endpoints	As per the latest recommendation for Novo Nordisk obesity clinical trials
Section 7: Discontinuation of study intervention and participant discontinuation/withdrawal	Addition of new discontinuation criteria in relation to hepatic events	As per the latest requirement for Novo Nordisk clinical trials
Section 8.3: Adverse events and other safety reporting	Addition of 'elevated liver enzymes' as other event requiring collection of additional information	As per the latest requirement for Novo Nordisk clinical trials
Section 9.3.2: Primary endpoint(s)/estimand(s) analysis	The primary imputation approach for the primary estimand is updated to WO-MI	The full model of RD-MI is expected to be not fit due to small sample size. WO-MI model is more stable compared to RD-MI model, especially for small sample size

Section # and name	Description of change	Brief rationale
Section 10.2	Addition of 'very low-density lipoprotein (VLDL) cholesterol in clinical laboratory tests	VLDL is already available as per the requirements of standard laboratory assessments. An editorial error led to the omission of this parameter in the table text, and has now been included.
Appendix 3: Section 10.3.3: Description of AEs requiring additional data collection	Description of AE 'hepatic event' was updated, and description of AE 'elevated liver enzymes' was added	Additional information for the AEs to be included in the forms to have more detailed data
Appendix 5: Hepatic Safety: Actions and follow-up assessments	Information on hepatic safety was added	The collected data on the hepatic events are to be analysed by the global safety
Throughout the protocol	Updated the Appendix and section numbers wherever applicable	Due to the addition of Appendix 5: Hepatic Safety: Actions and follow-up assessments
Throughout the protocol	Minor editorial change from 'semaglutide s.c. 2.4 mg once weekly' to 'semaglutide 2.4 mg' was done wherever applicable	The editorial change is to maintain consistency

Contents

1 Protocol summary

1.1 Synopsis

This is an interventional, multi-centre, randomised, double-blind, placebo-controlled, two-armed, parallel group clinical study in adults living with overweight and obesity.

Rationale:

Globally, more than 1.9 billion adults are overweight and 650 million of them are living with obesity.[1] In China, the prevalence of overweight and obesity has similarly increased dramatically over the past four decades . Based on Chinese criteria (overweight defined as 24 -< 28 kg/m^2 and obesity as >= 28 kg/m^2), national prevalence estimates show that for 2015–19, 34.3% of adults (≥18 years) in China are overweight, and 16.4% are living with obesity.[2] Based on Taiwanese criteria[3] (overweight defined as ≥ 24 kg/m^2, and obesity as BMI ≥ 27 kg/m^2), the age-adjusted prevalence of overweight and obesity in 2017 was 29.9% and 24.9% for men, and 20.4% and 16.7% for women[4], respectively.

The risk of obesity-related complications increases with increasing BMI, and a weight loss of 5−10% has significant health benefits by improving obesity-related complications including a slower progression to developing T2D and improving physical symptoms and quality of life.[5-11] Lifestyle intervention in the form of diet and exercise is the first-line treatment of obesity, but most people living with obesity struggle to achieve and maintain their weight loss.[12-22]

Most studies that examine the risk of adverse health associated with obesity have been based on data from Europe or the United States. However, the increased health risks associated with obesity occur in people with lower BMIs in the Asia Pacific region. This has supported calls by obesity researchers for lower BMI cut-offs for overweight and obesity in Asian populations than those in the international WHO classification.[23, 24] The WHO has proposed a BMI classification for the Asia-Pacific region with lower cut-offs for overweight (≥ 23.0 kg/m^2) and obesity (p≥ 25.0 kg/m^2).[25-27] The Working Group on Obesity in China mainland defines overweight as BMI of 24.0-27.9 kg/m^2, and obesity as BMI ≥ 28.0 kg/m^2.[2] The Ministry of Health and Welfare in Taiwan defines overweight as BMI ≥ 24 kg/m^2, and obesity as BMI ≥ 27 kg/m^2.[3]

Semaglutide s.c. 2.4 mg once weekly (Wegovy®) has been approved for weight management in the USA in adults with obesity or overweight and the presence of at least one weight-related complication (such as high blood pressure, T2D, or high cholesterol). In addition, once weekly semaglutide is approved for treatment of T2D in the doses of 0.5 mg, 1.0 mg and 2.0 mg (Ozempic®).

This 44-week study is designed to demonstrate the superiority of semaglutide s.c. 2.4 mg once weekly, versus placebo, as an adjunct to diet and exercise, on weight loss, living with overweight and obesity (BMI ≥ 24.0 and < 28.0 kg/m^2 with at least one weight-related complication, or BMI ≥ 28.0 and < 30.0 kg/m^2, with or without weight-related complications). The study will also provide data on the safety and tolerability of semaglutide.

Objectives, endpoints and estimand(s):

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
To demonstrate superiority of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to relative change in body weight after 44 weeks of treatment, in adults with overweight and obesity.	**Co-primary:**		
	Relative change in body weight	From baseline (week 0) to end of treatment (week 44)	%
To demonstrate superiority of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 5% after 44 weeks of treatment, in adults with overweight and obesity.	Body weight reduction ≥ 5% (yes/no)	At end of treatment (week 44)	count of participant
Secondary	**Endpoints**	**Time frame**	**Unit**
To demonstrate superiority of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 10% after 44 weeks of treatment, in adults with overweight and obesity.	**Confirmatory secondary:**		
	Body weight reduction ≥ 10% (yes/no)	At end of treatment (week 44)	count of participant
To demonstrate superiority of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to the change in waist circumference after 44 weeks of treatment, in adults with overweight and obesity.	Change in waist circumference	From baseline (week 0) to end of treatment (week 44)	cm

Objectives	Endpoints		
	Supportive secondary:		
	Body weight parameters		
To compare the efficacy of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to body weight parameters, after 44 weeks of treatment, in adults with overweight and obesity.	Change in body weight	From baseline (week 0) to end of treatment (week 44)	kg
	Change in body mass index	From baseline (week 0) to end of treatment (week 44)	kg/m^2
	Change in waist-height ratio (WtHR)	From baseline (week 0) to end of treatment (week 44)	Not applicable
	[redacted]		
	Cardiovascular parameters		
To compare the efficacy of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to cardiovascular parameters, after 44 weeks of treatment, in adults with overweight and obesity.	Change in systolic blood pressure	From baseline (week 0) to end of treatment (week 44)	mmHg
	Change in diastolic blood pressure	From baseline (week 0) to end of treatment (week 44)	mmHg
	Change in total cholesterol	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in high-density lipoprotein (HDL) cholesterol	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in low-density lipoprotein (LDL) cholesterol	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in very low-density lipoprotein (VLDL) cholesterol	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in triglycerides	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in free fatty acids	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline

Objectives	Endpoints		
	Change in high-sensitivity c-reactive protein (hsCRP)	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Glucose metabolism parameters		
To compare the efficacy of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to glycemic status, after 44 weeks of treatment, in adults with overweight and obesity.	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 44)	%-point and mmol/mol
	Change in fasting plasma glucose	From baseline (week 0) to end of treatment (week 44)	mg/dL, mmol/L
Safety	**Endpoints**	**Timeframe**	**Unit**
To compare the safety and tolerability of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, after 44 weeks of treatment, in adults with overweight and obesity.	***All participants***		
	Number of TEAEs	From baseline (week 0) to end of study (week 49)	count of events
	Number of SAEs	From baseline (week 0) to end of study (week 49)	count of events
	Pulse	From baseline (week 0) to end of treatment (week 44)	beats/min
	Participants with T2D		
	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L) confirmed by BG meter)	From baseline (week 0) to end of study (week 49)	number of episodes

[redacted]

Co-primary estimands

The primary clinical question of interest is: What is the treatment effect of semaglutide s.c. 2.4 mg once weekly versus placebo both as adjunct to a reduced-calorie diet and increased physical activity in adults with overweight and obesity defined according to local guidelines, measured by relative change from baseline (week 0) to end of treatment (week 44) in body weight, and participants achieving a body weight reduction of ≥ 5%, at end of treatment (week 44), regardless of discontinuation or dose reduction of randomised study product, and regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery).

The co-primary estimands are described by the following attributes:

- **Population:** Adults with overweight (defined as BMI ≥ 24 and < 28 kg/m^2), with at least one weight-related complication, or with obesity (defined as BMI ≥ 28 and < 30 kg/m^2), with or without weight-related complications.

- **Endpoint**: 1) relative change from baseline to week 44 in body weight and 2) body weight reduction ≥ 5% (yes/no) at week 44.
- **Treatment condition**: Semaglutide 2.4 mg vs. placebo regardless of discontinuation or dose reduction of randomised treatment, and regardless of initiating other anti-obesity therapies.
- **Remaining intercurrent events**: None, all intercurrent events (discontinuation or dose reduction of randomised treatment and initiation of other anti-obesity therapies) are captured by the treatment condition attribute and handled by the treatment policy strategy.
- **Population-level summary**: 1) difference in mean changes and 2) odds ratio between treatment conditions.

Secondary estimands

The secondary estimands with confirmatory and supportive secondary endpoints are similar to the co-primary estimands except for the endpoint attribute. The secondary estimands with continuous endpoints for secondary objectives are similar to the co-primary estimand for relative weight change, with the exception of endpoints with units of ratio to baseline, for which the population-level summary is the ratio between treatment conditions. The secondary estimands with binary endpoints for secondary objectives are similar to the co-primary estimand for body weight reduction ≥ 5%.

Additional estimands

The additional estimands differ only by endpoint and population level summary. The additional estimands are described by the following attributes:

- **Population:** Adults with overweight and obesity defined as BMI ≥ 24 and < 28 kg/m^2 with at least one weight-related complication, or BMI ≥ 28 and < 30 kg/m^2 with or without weight-related complications.
- **Endpoint**: 1) relative change from baseline to week 44 in body weight and 2) body weight reduction ≥ 5% at week 44.
- **Treatment condition**: Semaglutide 2.4 mg vs. placebo both as adjunct to a reduced-caloric diet and increased physical activity and regardless of dose reduction of randomised treatment.
- **Remaining intercurrent events**: Treatment discontinuation and initiation of other anti-obesity therapies are both handled by the hypothetical strategy. Dose reduction of randomised treatment, addressed in the treatment condition attribute, is handled by the treatment policy strategy.
- **Population-level summary**: 1) difference in mean changes and 2) odds ratio between treatment conditions.

A similar additional estimand also applies to all confirmatory and supportive secondary endpoints.

Overall design:

The study consists of:

- a 1 to 2-week screening period
- a 16-week dose escalation period
- a 28-week maintenance period

- a 5-week follow-up period

Study intervention groups and duration:
Following a screening period of up to 2 weeks, the participants will be randomised 2:1 at the randomisation visit to either semaglutide s.c. 2.4 mg once weekly or placebo once weekly as an adjunct to a reduced-calorie diet and increased physical activity.

At the time of randomisation participants will be stratified according to the following categories:

- Participants without T2D or
- Participants with T2D

The maximum duration of the study intervention for each participant is 44 weeks. The planned total study duration for the individual participant is approximately 50 weeks (including screening). Study product is provided in a PDS290 prefilled pen-injector.

Number of participants:
Approximately 404 participants will be screened to achieve 242 participants randomised to study intervention. Of the 242 participants, [redacted]

Participant characteristics:
The participants will be adults who meet the following key inclusion criteria and none of the following key exclusion criteria:

Key inclusion criteria:

- Age ≥ 18 years at the time of signing informed consent.
- Body mass index (BMI) of ≥ 24 and < 28 kg/m^2 with the presence of at least one weight-related complication (treated or untreated): T2D, hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease or BMI ≥ 28 and < 30 kg/m^2, with or without weight-related complications at screening.
- History of at least one self-reported unsuccessful dietary effort to lose body weight.

For participants with T2D at screening:

- Diagnosed with T2D ≥ 180 days prior to the day of screening.
- Treated with either:
  - diet and exercise alone or with 1-3 marketed oral antidiabetic drugs (metformin, α-glucosidase, SU, glinides, SGLT2i or glitazone as a single agent or in combination) according to local label.
  - Treatment with oral anti-diabetic drugs should be stable (same drug(s) or active ingredient, dose, and dosing frequency) for at least 60 days before screening.
- HbA_{1c} of ≤10.0% (≤ 86 mmol/mol) as measured by the central laboratory at screening.

Key exclusion criteria:

- A self-reported change in body weight > 5 kg within 90 days before screening irrespective of medical records.
- Treatment with any medication for the indication of obesity within the past 90 days before screening.
- Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.

For participants without T2D at screening:

- $HbA_{1c} \geq 6.5\%$ (48 mmol/mol) as measured by the laboratory.

For participants with T2D at screening:

- Renal impairment with estimated Glomerular Filtration Rate (eGFR) value of < 30 mL/min/1.73 m^2 according to CKD-EPI creatinine equation as defined by KDIGO 2012 classification[28] by the central laboratory at screening.
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to 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.

Data monitoring committee: No

1.2 Flowchart

	Protocol section	Screening	Randomisation	Dose escalation period					Maintenance period						End of study intervention[a]	End of study
Visit		V1	V2	V3	V4	V5	V6	V7	V8	P9	V10	P11	V12	P13	V14	V15
Timing of Visit (Weeks)		-1	0	2	4	8	12	16	20	24	28	32	36	40	44	49
Visit Window (Days)		-7	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7
PARTICIPANT RELATED INFORMATION AND ASSESSMENTS																
Informed Consent and Demography[b]	10.1.3	X														
Medical History/Concomitant Illness	8.2	X													X	
Concomitant Medication	6.7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Eligibility Criteria	5.1 and 5.2	X	X													
Randomisation	6.3		X													
Childbearing Potential[c]	10.4.1	X														
Tobacco Use[d]	5.3.2	X														
Pregnancy Test[e]	8.2.6	X	X	X	X	X	X	X	X		X		X		X	X
Evaluation of Antihypertensive Treatment	8									X					X	
Evaluation of Glycaemic Status[f]	8		X							X					X	
Evaluation of Lipid-lowering Treatment	8									X					X	
Evaluation Oral Anti Diabetes Medication[g]	8									X					X	
Discontinuation Criteria	7.1			X	X	X	X	X	X	X	X	X	X	X		

	Protocol section	Screening	Randomisation	Dose escalation period					Maintenance period						End of study intervention[a]	End of study
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**P9**	**V10**	**P11**	**V12**	**P13**	**V14**	**V15**
Timing of Visit (Weeks)		**-1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**49**
Visit Window (Days)		**-7**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**
Surgical Procedures Form	8.2.7		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight History	8.2.1	X														
Contraceptive Counselling[e]	8.2.6	X	X	X	X	X	X	X	X		X		X		X	
Risk Factors for Skin Cancer	8.2	X														
Risk Factors for Breast Neoplasm[c]	8.2	X														
Risk Factors for Colon Neoplasm	8.2	X														
EFFICACY																
Body Measurements	8.1.1	X	X	X	X	X	X	X	X		X		X		X	
Self-measured Plasma Glucose[g]	8.1.2		X		X		X	X			X		X		X	
SAFETY																
Physical Examination	8.2.1	X													X	
Vital Signs	8.2.2	X	X	X	X	X	X	X	X		X		X		X	
Laboratory Assessments	10.2	X	X			X			X		X				X	
HbA_{1c}	10.2	X	X			X			X		X				X	
Fasting plasma glucose	10.2		X						X						X	

	Protocol section	Screening	Randomisation	Dose escalation period					Maintenance period						End of study intervention[a]	End of study
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**P9**	**V10**	**P11**	**V12**	**P13**	**V14**	**V15**
Timing of Visit (Weeks)		**-1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**49**
Visit Window (Days)		**-7**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**
Lipids	10.2		X						X						X	
Haematology	10.2		X						X						X	
Biochemistry	10.2	X	X						X						X	
Attend Visit Fasting	5.3.1		X						X						X	
Adverse Event	8.3, 10.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Breast Neoplasms Follow-up[c]	8.2														X	X
Medication Error, Misuse and Abuse	8.3			X	X	X	X	X	X	X	X	X	X	X	X	
Technical Complaint	8.3.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Eye Examination[g]	8.2.3	X													X	
Hypoglycaemic Episodes[g]	8.3.7		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Colon Neoplasm Follow-up	8.2														X	X

	Protocol section	Screening	Randomisation	Dose escalation period					Maintenance period						End of study intervention[a]	End of study
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**P9**	**V10**	**P11**	**V12**	**P13**	**V14**	**V15**
Timing of Visit (Weeks)		**-1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**49**
Visit Window (Days)		**-7**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**
STUDY MATERIAL																
Drug Dispensing	6.2		X		X	X	X	X	X		X		X			
Administration of Trial Product	6.1		X	X	X	X	X	X	X	X	X	X	X	X	X	
Semaglutide/Placebo	6.1		X	X	X	X	X	X	X	X	X	X	X	X	X	
REMINDERS																
Training in Trial Product, Pen-handling	6.1		X		X	X	X	X	X		X		X			
Barriers and Motivation Interview	8	X														
Hand Out ID Card	8	X														
Hand Out and Instruct in BG-meter[g]	8.1.2		X													
Hand Out Dose Reminder Card	6.4		X		X	X	X	X	X		X		X			
Hand Out Direction for Use	6.1		X													
Hand Out and Instruct in Diabetes Diary[g]	8.1.2	X	X	X	X	X	X	X	X		X		X		X	
Diet and Physical Activity Counselling	6.1		X	X	X	X	X	X	X	X	X	X	X	X	X	

	Protocol section	Screening	Randomisation	Dose escalation period					Maintenance period						End of study intervention[a]	End of study
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**P9**	**V10**	**P11**	**V12**	**P13**	**V14**	**V15**
Timing of Visit (Weeks)		**-1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**49**
Visit Window (Days)		**-7**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**
OTHER ASSESSMENTS																
Clinical Outcome Assessments	8.2.4	X							X						X	
Patient Health Questionnaire - 9	8.2.4	X							X						X	
C-SSRS Baseline	8.2.4	X														
C-SSRS Since Last Visit	8.2.4								X						X	
End of Treatment	6.1														X	
AE Requiring Additional Data	8.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X
End of Study	4.4															X
RTSM Transaction	6.3	X	X		X	X	X	X	X		X		X			

[a]End of study intervention includes both end of IMP treatment and end of lifestyle intervention.

[b]Demography consists of date of birth, sex, ethnicity, and race (according to local regulations).

[c]For all female participants.

[d]Smoking is defined as smoking at least one cigarette or equivalent daily.

[e]Only for women of childbearing potential. Pregnancy test at V2 to be performed before randomisation of participants.

[f]Participants without T2D at screening.

[g]Only participants with T2D.

[redacted]

Abbreviations: AE = adverse event; BG = blood glucose; C-SSRS = Columbia-Suicide Severity Rating Scale; HbA_{1c} = glycated haemoglobin; ID = identification; P = phone; RTSM = randomisation and trial supplies management system; T2D = type 2 diabetes; V = visit

2 Introduction

2.1 Study rationale

Globally, more than 1.9 billion adults are overweight; 650 million of them are living with obesity, based on global BMI classifications (defines overweight as BMI ≥ 25 kg/m^2, and obesity as BMI ≥ 30 kg/m^2).[1] In China, the prevalence of overweight and obesity have similarly increased dramatically over the past four decades. Based on Chinese criteria (overweight defined as 24 -< 28 kg/m^{2}and obesity as >= 28 kg/m^2), national prevalence estimates show that for 2015–19, 34.3% of adults (≥18 years) in China are overweight, and 16.4% are living with obesity.[2] Based on Taiwanese criteria[3] (overweight defined as ≥ 24 kg/m^2, and obesity as BMI ≥ 27 kg/m^2), the age-adjusted prevalence of overweight and obesity in 2017 was 29.9% and 24.9% for men, and 20.4% and 16.7% for women[4], respectively.

Overweight and obesity are associated with an increased risk of developing type 2 diabetes (T2D)[29, 30], dyslipidaemia, hypertension[31], cardiovascular disease, obstructive sleep apnoea[32], non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH)[33], several types of cancers[34], and increased mortality.[35, 36] The risk of obesity-related complications increases with increasing body mass index (BMI), and even a body weight loss of 5–10% has been shown to have significant health benefits in individuals with obesity in terms of decreasing the risk of developing T2D[37], improving hypertension[11], dyslipidaemia[8], NAFLD/NASH[38] and reducing cardiovascular death[39].

East Asian participants experience weight-related complications at a lower BMI than what is observed in people of other ethnic origin. As such similar to Caucasians, Asians with a BMI 25.0–29.9 kg/m^2 have significantly elevated all-cause mortality risk.[40] The WHO has proposed a BMI classification for the Asia-Pacific region with lower cut-offs for overweight (≥ 23.0 kg/m^2) and obesity (≥ 25.0 kg/m^2).[25-27] The Working Group on Obesity in China mainland defines overweight as BMI of 24.0 -27.9 kg/m^2, and obesity as BMI ≥ 28.0 kg/m^2.[2] The Ministry of Health and Welfare in Taiwan defines overweight as BMI ≥ 24 kg/m^2, and obesity as BMI ≥ 27 kg/m^2.[3]

Current standard of care consists of lifestyle counselling including reduced-calorie diets and increased physical activity. Using this first line of treatment for obesity, only one in five individuals successfully achieves clinically relevant, sustained weight loss.[41] Pharmacotherapy providing high weight loss results will allow a higher proportion of people to achieve these benefits.

The glucagon-like peptide-1 receptor agonist (GLP-1 RA) drug class is associated with multiple benefits relevant for weight management and glycaemic control; it has a well-documented safety profile, improves blood pressure, lipid profile and other cardiovascular risk factors. Semaglutide is a once-weekly GLP-1 RA with documented efficacy and safety in doses of up to 2.4 mg.

GLP-1 is a physiological regulator of appetite[42] and GLP-1 receptors are present in several areas of the brain involved in appetite regulation. Semaglutide is a long-acting GLP-1 analogue with a half-life of 160 hours, making it suitable for once weekly dosing[43]. Once weekly semaglutide s.c. 2.4 mg will be referred to as, 'semaglutide 2.4 mg' throughout this document.

Semaglutide s.c. 2.4 mg once weekly (Wegovy®) has been approved in the USA for weight management in adults with obesity, or overweight and the presence of at least one weight-related

complication (such as high blood pressure, T2D, or dyslipidemia). It has also been approved in several other regions worldwide, including EU, Canada, UK, Australia, Switzerland and India for weight management. In addition, once weekly semaglutide is approved for treatment of T2D in the doses of 0.5 mg, 1.0 mg and 2.0 mg (Ozempic®).

The present 44-week study is designed to demonstrate the superiority of semaglutide 2.4 mg, versus placebo, as an adjunct to diet and exercise, on weight loss, in participants living with overweight or obesity (BMI ≥ 24.0 and < 28.0 kg/m^2 with at least one weight-related complications, or BMI ≥ 28.0 and < 30.0 kg/m^2, with or without weight-related complications) according to the local guidelines.[44]

2.2 Background

2.2.1 Semaglutide

Semaglutide is a long-acting glucagon-like petide-1 receptor agonist (GLP-1 RA), approved for weight management in doses of 2.4 mg/week (Wegovy®). Semaglutide has a half-life of approximately 160 hours, making it suitable for once-weekly dosing.[45] GLP-1 is a physiological regulator of appetite and GLP-1 receptors are present in several areas of the brain involved in appetite regulation.[42]

Clinical[46-51] and non-clinical[52] data indicate that the body weight-reducing effect of semaglutide is mainly mediated by a reduced energy intake.

A global phase 3a clinical development programme with semaglutide s.c. 2.4 mg once-weekly has been completed (STEP programme), having enrolled approximately 4,500 adults with overweight or obesity including approximately 1,200 with T2D. The programme consists of four studies (NN9536-4373, NN9536-4374, NN9536-4375 and NN9536-4376), which demonstrated clinically significant weight loss with semaglutide 2.4 mg together with a safe and well-tolerated profile, consistent with previous findings. This phase 3a programme formed the basis of the first approvals of Wegovy®.

The safety and efficacy of semaglutide 2.4 mg has furthermore been demonstrated in an additional phase 3a study (NN9536-4382 [East Asian population]) and two phase 3b studies (NN9536-4378 [2-year efficacy] and NN9536-4576 [head-to-head with liraglutide]) and additional studies are ongoing.

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

2.2.2 Study population

The study population will consist of participants with overweight or obesity (BMI ≥ 24.0 and < 28.0 kg/m^2 with at least one weight-related complication, or BMI ≥ 28.0 and < 30.0 kg/m^2, with or without weight-related complications). These participants represent a clinically relevant population for pharmacotherapeutic weight management as they are at significant risk of weight-related complications and mortality and are likely to benefit from weight reduction.

First line treatment in weight management should always be lifestyle modification through a reduced calorie diet and increased physical activity. Thus only participants who have tried but failed a dietary weight loss intervention will be included in accordance with regulatory and clinical guidelines.[53,54,55]

Of the 242 participants, [redacted]

2.3 Benefit-risk assessment

The main benefits and risks related to participation in the study are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of semaglutide may be found in the investigator's brochure and any update hereof. The risks are based on findings in non-clinical studies and clinical studies with semaglutide (both s.c. and oral) as well as other GLP-1 RAs. For each of these risks, mitigating actions have been implemented to minimise the risks for participants enrolled in this study.

2.3.1 Risk assessment

Table 2-1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention (semaglutide)		
Identified risks		
Gastrointestinal effects and dehydration	Consistent with findings for other GLP-1 RAs, the most frequently reported AEs in clinical studies with semaglutide were gastrointestinal (GI) disorders, including nausea, diarrhoea, and vomiting. In general, these reactions are mild or moderate in severity, of short duration, and dose dependent. In adults treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating adults with impaired renal function as it may cause a deterioration of renal function.	Clinical studies have shown that a low starting dose and gradual dose escalation mitigates the risk of developing GI symptoms. A low starting dose and dose escalation steps has been implemented in the study to mitigate the risk of GI AEs. Participants with GI symptoms are recommended to drink plenty of fluids to avoid volume depletion. Thresholds for renal impairment based on the measured estimated Glomerular Filtration Rate (eGFR) for participants with and without T2D at screening are specified in Section 5.2. Adults exceeding these thresholds will not be enrolled in the study.
Acute gallbladder disease (Cholelithiasis)	Events of cholelithiasis were the most frequently reported gallbladder events in the clinical development programme for semaglutide 2.4 mg for weight management. The increased risk of cholelithiasis with semaglutide 2.4 mg s.c. appeared to be at least partly explained by the larger weight loss. Cholelithiasis may lead to complications such as cholecystitis or acute pancreatitis.	If cholelithiasis is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.
Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 RA drug class. The frequency of adjudication-confirmed acute pancreatitis reported in phase 3a clinical studies was 0.2% for semaglutide 2.4 mg and <0.1% for placebo, respectively.	Adults with a history of chronic pancreatitis or recent acute pancreatitis will not be enrolled in the study (Section 5.2). Participants should be informed of the characteristic symptoms of acute pancreatitis. In addition, in case of suspicion of acute pancreatitis, study intervention should be promptly interrupted in accordance with Section 7.1. If confirmed, semaglutide should not be restarted.
Hypoglycaemia (*for participants with T2D at screening only*)	Semaglutide and other GLP-1 RAs are in general associated with a low risk of hypoglycaemia because of their glucose-dependent mechanism of action. There is a low risk of hypoglycaemic episodes when semaglutide is used as monotherapy. Adults treated with semaglutide in combination with a sulphonyl urea (SU) or insulin have an increased risk of hypoglycaemia.	The risk of hypoglycaemia can be lowered by reducing the dose of SU when initiating treatment with semaglutide (or insulin if participants have been allowed to use insulin as rescue therapy) at the discretion of the investigator (Section 6.7).

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Diabetic retinopathy complications (*for participants with T2D at screening only*)	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. In line with previous observations in T2D populations, few episodes of diabetic retinopathy (4.0 % vs 2.7% of participants treated with semaglutide 2.4 mg s.c. for weight management vs placebo, respectively) were observed in study 4374.	As a precaution, participants with a history of uncontrolled and potentially unstable diabetic retinopathy or maculopathy will be excluded from the study, and fundus photography or slit-lamp bio microscopy examination with pharmacologically dilated pupils will be performed according to flowchart (Section 1.2).
Intestinal obstruction	There have been post-marketing cases of intestinal obstruction reported with semaglutide. Intestinal obstruction is a severe form of constipation with blocked passage of food, liquid and stool with additional symptoms such as stomach ache, bloating, vomiting etc. In serious cases, intestinal obstruction can lead to bowel ischemia and perforation.	Please refer to mitigations of gastrointestinal adverse events. Furthermore, participants should be informed of the characteristic symptoms of intestinal obstruction. If intestinal obstruction is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.
Potential risks		
Allergic reactions	As is the case with all protein-based pharmaceuticals, participants treated with semaglutide may evoke allergic reactions, including serious allergic reactions such as angioedema and anaphylactic reactions.	Adults with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this study (see Section 5.2). In addition, participants will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the study product occurs.
Neoplasms (malignant and non-malignant)	People with overweight or obesity as well as people with T2D, 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. No imbalance was observed in the semaglutide 2.4 mg for weight management phase 3a studies with regards to the proportions of participants with neoplasms (malignant and non-malignant). However, in the semaglutide s.c. as well as oral semaglutide phase 3a studies for T2D, the proportion of participants with neoplasms (malignant and non-malignant) were slightly higher with semaglutide than with comparator. The number of participants exposed to semaglutide s.c. or oral semaglutide for a longer period is considered insufficient for a thorough assessment of the risk of neoplasms.	Adults with presence or history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this study. Basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in-situ prostate cancer is allowed. (Section 5.2).

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Pancreatic cancer (*potential GLP-1 RA class risk)*	There is currently no support from non-clinical studies, clinical studies, or post-marketing data that GLP-1 RA-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies based on the unknown long-term effects on β-cell stimulation and α-cell suppression.	Adults with presence or history of malignant neoplasm within 5 years prior to screening will not be enrolled in this study (Section 5.2).
Medullary thyroid cancer (MTC) *(based on non-clinical data)*	Thyroid C-cell tumours were seen in the mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. No hyperplasia was observed in monkeys after 52 weeks exposure up to 13-fold above the clinical plasma exposure at 2.4 mg/week. 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.	Adults with a family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2) are excluded from the study (Section 5.2).
Study procedures		
Discomfort related to invasive study procedure	Venous laboratory samples drawn at screening and selected visits may be associated with slight discomfort and complicated by bruising in the region.	Experienced and properly trained site personnel will ensure minimisation of discomfort caused by study procedures.
Risk of COVID-19 infection in relation to participation in the study	Participants may be exposed to 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. Local guidance related to COVID-19 pandemic should be respected, in case a site or country are locked down and participants cannot attend on-site visits.
Risk of externally induced unforeseen events with a global impact (e.g., global pandemic)	Sites and participants may be impacted to a degree where certain parts of the protocol cannot be adhered to.	In case of externally induced unforeseen events, some deviations to the planned visit schedule will be allowed. Please reach out to monitor for guidance, as with all other unforeseen events occurring at site level. For a description of visits that should be performed as on-site visits, please refer to Section 7.1.
Other		
Pregnancy, fertility and lactation (based on non-clinical data)	Studies in animals have shown reproductive toxicity. There is limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy.	Exclusion and discontinuation criteria related to pregnancy have been implemented in this study. Women of childbearing potential are required to use highly effective contraceptive methods when participating in this study (Appendix 4, Section 10.4.1).

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	It is unknown if semaglutide affects fertility or pregnancy outcomes. Therefore, semaglutide should not be used in women wishing to becoming pregnant. In lactating rats, semaglutide was excreted in milk. A risk to a breast-fed child cannot be excluded. Semaglutide should not be used during breast-feeding.	If a participant wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Please refer to Section 7.1 for further guidance.
Risk of COVID-19 infection in relation to study intervention	Available data does not suggest an increased risk of infection or a more severe progression of infection when treated with s.c. semaglutide.	Detailed information about the known risks for s.c. semaglutide can be found in the investigator's brochure and summary of product characteristics.
Abbreviations: AEs = adverse events; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; GLP-1 RAs = Glucagon-like peptide-1 receptor agonist; MEN2 = multiple endocrine neoplasia type 2; MTC = medullary thyroid carcinoma; s.c. = subcutaneous; T2D = type 2 diabetes.		

2.3.2 Benefit assessment

The phase 3a weight management studies STEP 1 (NN9536-4373) and STEP 2 (NN9536-4374), demonstrated clinically significant weight loss with semaglutide s.c. 2.4 mg once-weekly and a safe and well-tolerated profile. Safety and tolerability was also demonstrated in East Asian participants in STEP 6 (NN9536-4382), conducted with common design features and study procedures as in STEP 1 (NN9536-4373), and in addition included a subgroup of participants with T2D. Data from STEP 6 showed 82.9% of participants on semaglutide achieving ≥5% weight loss from baseline to week 68 compared to 21.0% with placebo and overall safety and tolerability of semaglutide s.c. 2.4 mg reflected that of the GLP-1 RA class.

Data from STEP 1, 2 and 6 showed significant reductions in body weight from baseline to week 68 of 9.64-14.85% [9.67-15.33 kg] versus 2.12-3.42% [1.70-3.54 kg] in placebo.
Semaglutide s.c. 2.4 mg once weekly is expected to provide substantial weight loss benefits without jeopardising safety of participants.

In addition, it is expected that all participants will benefit from close contact with the study site and counselling by a dietician or a similar qualified healthcare professional, which will likely result in intensified weight management. It is anticipated that all participants will benefit from participation, but the effect will be greater in participants randomised to semaglutide compared to placebo.

2.3.3 Overall benefit-risk conclusion

Necessary precautions have been implemented in the design and planned conduct of the study to minimise the risks and inconveniences for participation in the study. The safety profile for semaglutide generated from the clinical and non-clinical development programme has not revealed any new safety issues that would prohibit administration of semaglutide 2.4 mg in the study population.

The overall results of the phase 3 studies (semaglutide subcutaneous) indicate that semaglutide will provide a clinically meaningful weight loss. The anticipated benefits from diet and physical activity counselling will include all participants participating in this study.

Taking into account the measures taken to minimise risk to participants in this study, the potential risks identified in association with semaglutide 2.4 mg are justified by the anticipated benefits that may be afforded to participants with obesity.

More detailed information about the known and expected benefits and risks and expected AEs of semaglutide s.c. may be found in the IB[56] and any updates hereof.

3 Objectives, endpoints and estimands

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
To demonstrate superiority of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to relative change in body weight after 44 weeks of treatment, in adults with overweight and obesity.	**Co-primary:**		
	Relative change in body weight	From baseline (week 0) to end of treatment (week 44)	%
To demonstrate superiority of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 5% after 44 weeks of treatment, in adults with overweight and obesity.	Body weight reduction ≥ 5% (yes/no)	At end of treatment (week 44)	count of participant
Secondary	**Endpoints**	**Time frame**	**Unit**
To demonstrate superiority of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 10% after 44 weeks of treatment, in adults with overweight and obesity.	**Confirmatory secondary:**		
	Body weight reduction ≥ 10% (yes/no)	At end of treatment (week 44)	count of participant
To demonstrate superiority of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to the change in waist circumference after 44 weeks of treatment, in adults with overweight and obesity.	Change in waist circumference	From baseline (week 0) to end of treatment (week 44)	cm

Objectives	Endpoints		
	Supportive secondary:		
	Body weight parameters		
To compare the efficacy of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to body weight parameters, after 44 weeks of treatment, in adults with overweight and obesity.	Change in body weight	From baseline (week 0) to end of treatment (week 44)	kg
	Change in body mass index	From baseline (week 0) to end of treatment (week 44)	kg/m^2
	Change in waist-height ratio (WtHR)	From baseline (week 0) to end of treatment (week 44)	Not applicable
	[redacted]		
	Cardiovascular parameters		
To compare the efficacy of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to cardiovascular parameters, after 44 weeks of treatment, in adults with overweight and obesity.	Change in systolic blood pressure	From baseline (week 0) to end of treatment (week 44)	mmHg
	Change in diastolic blood pressure	From baseline (week 0) to end of treatment (week 44)	mmHg
	Change in total cholesterol	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in high-density lipoprotein (HDL) cholesterol	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in low-density lipoprotein (LDL) cholesterol	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in very low-density lipoprotein (VLDL) cholesterol	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in triglycerides	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in free fatty acids	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline

Objectives	Endpoints		
	Change in high-sensitivity c-reactive protein (hsCRP)	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Glucose metabolism parameters		
To compare the efficacy of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to glycemic status, after 44 weeks of treatment, in adults with overweight and obesity.	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 44)	%-point and mmol/mol
	Change in fasting plasma glucose	From baseline (week 0) to end of treatment (week 44)	mg/dL, mmol/L
Safety	**Endpoints**	**Timeframe**	**Unit**
To compare the safety and tolerability of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, after 44 weeks of treatment, in adults with overweight and obesity.	***All participants***		
	Number of TEAEs	From baseline (week 0) to end of study (week 49)	count of events
	Number of SAEs	From baseline (week 0) to end of study (week 49)	count of events
	Pulse	From baseline (week 0) to end of treatment (week 44)	beats/min
	Participants withT2D		
	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L) confirmed by BG meter)	From baseline (week 0) to end of study (week 49)	number of episodes

[redacted]

Co-primary estimands

The primary clinical question of interest is: What is the treatment effect of semaglutide 2.4 mg vs. placebo both as adjunct to a reduced-calorie diet and increased physical activity in adults with overweight and obesity defined according to local guidelines, measured by relative change from baseline (week 0) to end of treatment (week 44) in body weight, and participants achieving a body weight reduction of ≥ 5%, at end of treatment (week 44), regardless of discontinuation or dose reduction of randomised study product, and regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery).

The co-primary estimands differ only by endpoint and population level summary. The co-primary estimands are described by the following attributes: ‘

- **Population:** Adults with overweight (defined as BMI ≥ 24 and < 28 kg/m^2), with at least one weight-related complication, or with obesity (defined as BMI ≥ 28 and < 30 kg/m^2), with or without weight-related complications.
- **Endpoint**: 1) relative change from baseline to week 44 in body weight and 2) body weight reduction ≥ 5% (yes/no) at week 44.
- **Treatment condition**: Semaglutide 2.4 mg vs. placebo regardless of discontinuation or dose reduction of randomised treatment, and regardless of initiating other anti-obesity therapies (as defined above).
- **Remaining intercurrent events**: None, all intercurrent events (discontinuation or dose reduction of randomised treatment and initiation of other anti-obesity therapies) are captured by the treatment condition attribute and handled by the treatment policy strategy.
- **Population-level summary**: 1) difference in mean changes and 2) odds ratio between treatment conditions.

Rationale for estimand: The co-primary estimands take into account both safety and efficacy and reflect clinical practice to the extent possible in a clinical study. The co-primary estimands are thus relevant to support regulatory decision-making.

Secondary estimands

The secondary estimands with confirmatory and supportive secondary endpoints are similar to the co-primary estimands except for the endpoint attribute. The secondary estimands with continuous endpoints for secondary objectives are similar to the co-primary estimand for relative weight change, with the exception of endpoints with units of ratio to baseline, for which the population-level summary is the ratio between treatment conditions. The secondary estimands with binary endpoints for secondary objectives are similar to the co-primary estimand for body weight reduction ≥ 5%.

Additional estimands

An additional clinical question of interest for the primary objective is: what is the treatment effect of semaglutide 2.4 mg vs. placebo both as adjuncts to a reduced-calorie diet and increased physical activity in adults with overweight and obesity, measured by the relative change from baseline (week 0) to week 44 in body weight, and participants achieving body weight reduction ≥ 5% at week 44, had they remained on their randomised treatment for the entire planned duration of the study and not initiated any other anti-obesity therapies (weight management drugs or bariatric surgery)?

The additional estimands differ only by endpoint and population level summary. The additional estimands are described by the following attributes:

- **Population:** Adults with overweight or obesity defined as BMI ≥ 24 and < 28 kg/m^2 with at least one weight-related complication, or BMI ≥ 28 and < 30 kg/m^2 with or without weight-related complications.
- **Endpoint**: 1) relative change from baseline to week 44 in body weight and 2) body weight reduction ≥ 5% at week 44.

- **Treatment condition**: Semaglutide 2.4 mg vs. placebo both as adjunct to a reduced-caloric diet and increased physical activity and regardless of dose reduction of randomised treatment.
- **Remaining intercurrent events**: Treatment discontinuation and initiation of other anti-obesity therapies are both handled by the hypothetical strategy. Dose reduction of randomised treatment, addressed in the treatment condition attribute, is handled by the treatment policy strategy.
- **Population-level summary**: 1) difference in mean changes and 2) odds ratio between treatment conditions

Rationale for estimand: The additional estimand aims at reflecting the treatment effect (including all doses of semaglutide) without the confounding effects of other anti-obesity therapies or study product discontinuation.

A similar additional estimand also applies to all confirmatory and supportive secondary endpoints.

4 Study design

4.1 Overall design

This is an interventional, multi-centre, randomised, double-blind, placebo-controlled, two-armed, parallel group clinical study.

Approximately 404 participants will be screened to achieve 242 participants who will be randomised 2:1 to receive either semaglutide 2.4 mg or placebo, once weekly, as an adjunct to a reduced-calorie diet and increased physical activity. About 194 participants are expected to complete. The study population consists of participants with overweight or obesity and a maximum of 20% of the participants will have T2D, in accordance with local guidelines.

At the time of randomisation participants will be stratified according to the following categories:

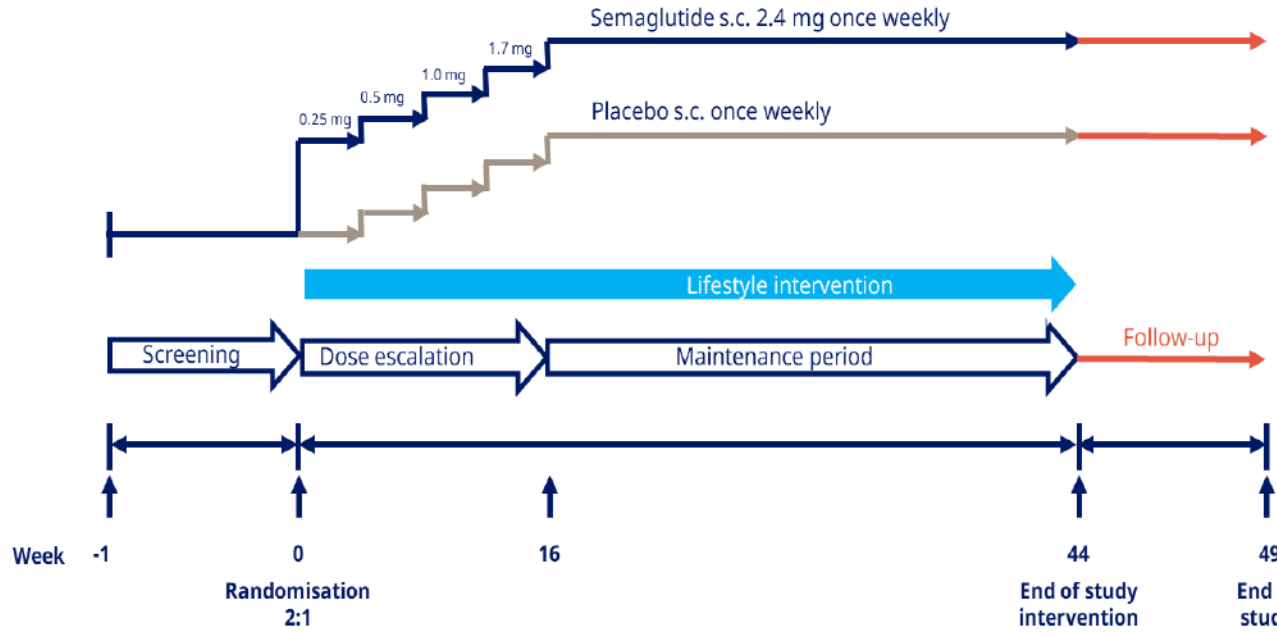
- Participants without T2D or
- Participants with T2D

The study consists of:

- a 1 to 2-week screening period
- a 16-week dose escalation period
- a 28-week maintenance period
- a 5-week follow-up period

The duration of the study intervention is 44 weeks with an additional 5-week follow-up (off study intervention) (Figure 4-1).

Figure 4-1 Study design



Note: 'End of study intervention' is defined as end of IMP and reduced calorie diet and increased physical activity.

4.2 Scientific rationale for study design

A 44-week study intervention duration (including 28 weeks on maintenance dose) is considered sufficient to assess weight loss, safety, and tolerability. Results from STEP 1 have shown clinically significant weight loss with semaglutide 2.4 mg, already at 44 weeks.[57] The 5-week follow-up period is included to account for the exposure and long half-life of semaglutide.

A randomised, double-blind, placebo-controlled, multi-centre study design is chosen to minimise bias in the assessment of the efficacy and safety of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity. Evidence indicates that Asian populations experience overweight and obesity related complications at lower BMI ranges.[40, 58-62]

This study focuses on adults with overweight and obesity in the local BMI ranges relevant for pharmacotherapy according to local guidelines, thus participants will have:

- a BMI $\geq$ 24 and < 28 kg/m^2 with the presence of at least one weight-related complication
- or BMI $\geq$ 28 and < 30 kg/m^2, with or without weight-related complication.

[redacted]

The study will aim to recruit 50% of the participants with a BMI range of 24-28 kg/m^2.

4.3 Justification for dose

A maintenance dose of semaglutide s.c. 2.4 mg once weekly was chosen in the phase 3 weight management development programme. The phase 68-week 3a weight management programme (STEP 1-4) demonstrated a clinically significant weight loss with semaglutide s.c. 2.4 mg once weekly and statistically significant improvements in waist circumference, systolic blood pressure and physical functioning. This resulted in a favourable balance between benefits and risks. Additionally, the once-weekly dosing has demonstrated to ease the burden of drug administration in clinical practice.

In STEP 1 (NN9536-4373), 1,961 participants with overweight or obesity achieved an average weight loss of 14.9% compared to 2.4% in the placebo group. In STEP 2 (NN9536-4374), 1,210 participants with overweight or obesity and T2D achieved an average weight loss of 9.6% compared to 3.4% in the placebo group. In both studies, semaglutide s.c. 2.4 mg once weekly showed a safe and well-tolerated profile, consistent with previous findings. A maintenance dose of semaglutide s.c. 2.4 mg once weekly in an Asian population is supported by the results from STEP 6 (NN9536-4382) with East Asian participants, with an estimated mean change in body weight from baseline to week 68 was 13.2% vs. 2.1%, for participants in the semaglutide 2.4 mg group vs. the placebo group.[63]

A low starting dose and fixed-dose escalation regimen is expected to mitigate the risk of developing gastrointestinal (GI) adverse events (AEs). A fixed-dose escalation regimen, with dose escalation every 4 weeks until the target dose is reached, will be followed. Participants start with a once-weekly dose of 0.25 mg and follow a fixed-dose escalation regimen, with dose increases every

4 weeks, (to 0.5, 1.0, 1.7 mg/week) to reach the target maintenance dose (2.4 mg/week) after 16 weeks.

Please refer to Section 6.1 for more details on study product doses. See Section 6.2 for dose modification.

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.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit ('end of study' according to the flowchart, Section 1.2).

The primary endpoints are evaluated from baseline (week 0) to end of treatment (week 44). The primary completion date (PCD) is defined as the date of visit 14 (week 44) on which the last participant in the clinical study has an assessment for the co-primary endpoints. If the last participant is withdrawn early, the PCD is considered the date when the last participant would have completed visit 14.

5 Study population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted. The inclusion and exclusion criteria will be assessed at the investigator's discretion unless stated otherwise.

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. Age ≥ 18 years at the time of signing informed consent.
3. BMI ≥ 24 and < 28 kg/m^2 with the presence of at least one weight-related complication (treated or untreated): T2D, hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease or BMI ≥ 28 and < 30 kg/m^2, with or without weight-related complications at screening[a].
4. History of at least one self-reported unsuccessful dietary effort to lose body weight[b].

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

5. Diagnosed with T2D ≥ 180 days prior to the day of screening.
6. Treatment with either lifestyle intervention, or treatment with 1-3 marketed oral antidiabetic drugs (metformin, α-glucosidase, SU, glinides, SGLT2i or glitazone as a single agent or in combination) according to local label. Treatment with oral anti-diabetic drugs should be stable (same drug(s) or active ingredient, dose, and dosing frequency) for at least 60 days before screening.
7. HbA_{1c} of ≤10.0% (≤ 86 mmol/mol) as measured by central laboratory at screening[c].

[a]BMI criteria: BMI as calculated in the eCRF at screening.

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

[c]Where HbA_{1c} is reported in both % and mmol/mol, the participant must fulfil the cut-off for both units.

5.2 Exclusion criteria

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

For participants **without T2D** at screening**:**

1. HbA_{1c} ≥ 6.5% (48 mmol/mol) as measured by central laboratory at screening
2. History of type 1 or type 2 diabetes mellitus[a]
3. Treatment with glucose-lowering agent(s) within 90 days before screening
4. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of < 15 ml/min/1.73 m^2 according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation as defined by kidney disease improving global outcomes defined by KDIGO 2012 classification[28] by the central laboratory at screening.

For participants **with T2D** at screening:

5. Treatment with any medication for the indication of diabetes other than stated in the inclusion criteria within the past 60 days prior day of screening.
6. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of < 30 mL/min/1.73 m^2 according to CKD-EPI creatinine equation as defined by KDIGO 2012 classification[28] by the central laboratory at screening.
7. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to 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.

The following criteria apply to all participants:

Obesity related:

8. A self-reported change in body weight > 5 kg within 90 days before screening irrespective of medical records.
9. Treatment with any medication for the indication of obesity within the past 90 days before screening.
10. Uncontrolled thyroid disease, as per investigator's discretion.
11. Previous or planned (during the study period) obesity treatment with surgery or a weight loss device. However, the following are allowed:
    - Liposuction and/or abdominoplasty, if performed > 1 year before screening
    - Adjustable gastric banding if the band has been removed > 1 year before screening
    - Intragastric balloon if the balloon has been removed > 1 year before screening
    - Duodenal-jejunal bypass liner (e.g., Endobarrier), if the liner has been removed > 1 year before screening.

Mental health related:

12. History of major depressive disorder within 2 years before screening[a].
13. Diagnosis of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder)[a].
14. A Patient Health Questionnaire-9 (PHQ-9) score of ≥ 15 at screening.
15. A lifetime history of a suicidal attempt.
16. Suicidal behaviour within 30 days before screening[a].
17. Suicidal ideation corresponding to type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the past 30 days before screening[a].

General safety:

18. Treatment with a GLP-1 RA within 180 days before screening[a].
19. Presence of acute pancreatitis within 180 days prior to screening[a].
20. History or presence of chronic pancreatitis[a].
21. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma[a].
22. Presence or history of malignant neoplasms or in situ carcinomas (other than basal or squamous cell skin cancer, low-risk prostate cancer, or in-situ carcinomas of the cervix or carcinoma in situ/high grade prostatic intraepithelial neoplasia (PIN) within 5 years before screening[a].

23. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 60 days prior to the day of screening.
24. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.
25. Surgery scheduled for the duration of the study, except for minor surgical procedures, in the opinion of the investigator.
26. Known or suspected abuse of alcohol or recreational drugs.
27. Known or suspected hypersensitivity to study intervention(s) or related products.
28. Previous participation in this study. Participation is defined as signed informed consent.
29. Use of any medication with unknown or unspecified content within 90 days before screening.
30. Other participant(s) from the same household participating in any semaglutide study.
31. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using highly effective contraceptive methods, prior to randomisation.
32. Any disorder, unwillingness, or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.
33. Participation (i.e., signed informed consent) in any interventional, clinical study within 90 days before screening.

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

5.3 Lifestyle considerations

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

5.3.1 Meals and dietary restrictions

- Participants must attend the visits fasting, if indicated, according to the flowchart.
- Fasting is defined as at least 8 hours overnight before the visit, without food or liquids, except for water. Study product and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood samples have been obtained.
- If the participant is not fasting as required, the participant should be called in for a new visit within the visit window to have the fasting procedures done. Procedures requiring participant to fast include blood sampling of FPG and lipids.

5.3.2 Caffeine, alcohol, and tobacco

Participants should avoid caffeine, alcohol, and tobacco use at least 30 minutes prior to measuring the blood pressure. Tobacco use is defined as smoking at least one cigarette or equivalent daily.

5.4 Screen failures

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

A screen failure transaction must be made in the randomisation and trial supplies management system (RTSM).

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

5.5 Run-in criteria, randomisation criteria and dosing day criteria

5.5.1 Run-in criteria

Not applicable for this study.

5.5.2 Randomisation criteria

Not applicable for this study.

5.5.3 Dosing day criteria

Not applicable for this study.

6 Study intervention(s) and concomitant therapy

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

Study products comprise the investigational medicinal products (IMPs), including placebo and comparators.

6.1 Study intervention(s) administered

Table 6-1 provides an overview of the study interventions. Table 6-2 provides an overview of the investigational medicinal products (IMPs). The investigator must document that 'directions for use' were given to the participant verbally, and in writing, as a direction for use (DFU) document at the first dispensing visit (as specified in the flowchart).

Table 6-1 Study interventions

Intervention/Arm name	Semaglutide	Placebo	Any other interventions
Intervention name	Semaglutide B	Placebo	Diet and physical activity counselling
Intervention type	IMP	IMP, reference therapy	Background intervention
Pharmaceutical form	Solution for injection	Solution for injection	
Route of administration	Subcutaneous	Subcutaneous	
Study product strength	See Table 6-2 for details.	See Table 6-2 for details.	
Dose and dose frequency	Dose: see Table 6-2 Dose frequency: once weekly	Dose: see Table 6-2 Dose frequency: once weekly	
Dosing instructions and administration	Once-weekly injection, at the same day of the week (to the extent possible) throughout the study. Injections may be administered in the thigh, abdomen, or upper arm, at any time of day irrespective of meals.	Once-weekly injection, at the same day of the week (to the extent possible) throughout the study. Injections may be administered in the thigh, abdomen, or upper arm, at any time of day irrespective of meals.	
Sourcing	Manufactured and supplied by Novo Nordisk A/S.	Manufactured and supplied by Novo Nordisk A/S.	
Packaging and labelling	• Labelled and packaged by Novo Nordisk A/S • Labelled in accordance with Annexure 13,[64] local regulations and study requirements • IMP is provided in a PDS290 pen-injector Table 6-2.	• Labelled and packaged by Novo Nordisk A/S • Labelled in accordance with Annexure 13,[64] local regulations and study requirements • IMP is provided in a PDS290 pen-injector Table 6-2.	

Investigational medicinal products (IMP)

Table 6-2 IMP provided in the PDS290 pre-filled pen-injector

Study intervention name	Dose	Volume	Value shown in dose counter[a]	Duration
Dose escalation period				
Semaglutide 0.68 mg/mL or placebo, PDS290	0.25 mg	0.37 mL	37	4 weeks
Semaglutide 1.34 mg/mL or placebo, PDS290	0.5 mg	0.37 mL	37	4 weeks
Semaglutide 1.34 mg/mL or placebo, PDS290	1.0 mg	0.75 mL	75	4 weeks
Semaglutide 2.27 mg/mL or placebo, PDS290	1.7 mg	0.75 mL	75	4 weeks
Maintenance period				
Semaglutide 3.2 mg/mL or placebo, PDS290	2.4 mg	0.75 mL	75	28 weeks

[a]Conversion to dose is calculated based on 0.01 mL/value for all strengths of semaglutide

Other interventions

All participants will receive counselling with regards to diet (approximately 500 kcal deficit per day relative to the estimated total daily energy expenditure [TEE] calculated once at randomisation) and physical activity (increasing from baseline to at least 150 min of physical activity per week is encouraged, e.g. walking or using the stairs). Counselling should be done by a dietician or similarly qualified healthcare professional according to the flowchart (Section 1.2) via visits/phone contacts.

Calculation of estimated total energy expenditure

The TEE is calculated by multiplying the estimated Basal Metabolic Rate (BMR) (see Table 6-3) with a Physical Activity Level value of 1.3.[65]

$$TEE = BMR \times 1.3$$

Table 6-3 Equation for estimated BMR

Sex	Age	BMR (kcal/day)
Men	18–30 years	15.057 × weight at randomisation in kg + 692.2
	31–60 years	11.472 × weight at randomisation in kg + 873.1
	> 60 years	11.711 × weight at randomisation in kg + 587.7
Women	18–30 years	14.818 × weight at randomisation in kg + 486.6
	31–60 years	8.126 × weight at randomisation in kg + 845.6
	> 60 years	9.082 × weight at randomisation in kg + 658.5

If a BMI ≤ 22.5 kg/m2 is reached the recommended energy intake should be recalculated with no kcal deficit (maintenance diet) for the remainder of the study. If deemed necessary, the investigator may consult Novo Nordisk to discuss when maintenance diet can be initiated.

Auxiliary supplies including medical device(s) not under investigation

Auxiliary supplies will be provided in accordance with the Trial Materials Manual (TMM) and Table 6-4.

Table 6-4 Auxiliary supplies provided by Novo Nordisk A/S

Auxiliary supply	Details
Needles	Needles for pre-filled pen-injector. Details provided in the TMM. Only needles provided and approved by Novo Nordisk must be used for administration of study product.
Direction for use (DFU)	DFU for the PDS290 pre-filled pen-injector Not included in the dispensing unit and to be handed out separately
BG meters	BG meter includes lancets, test strips, control solutions and instructions. Details are provided in the BG meter manual. Only participants with T2D at screening

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

6.2 Preparation, handling, storage and accountability

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

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

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

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

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

The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any participant before it has been

evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the TMM.

The investigator or designee is responsible for trial product accountability and record maintenance (i.e., receipt, accountability and final disposition records).

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

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

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.

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 as unused, at the latest at closure of the site.

6.3 Measures to minimise bias: Randomisation and blinding

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

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

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

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

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

Participant will continue on trial product if there are no safety concerns at the discretion of the investigator.

6.3.1 Study intervention compliance

Drug treatment compliance

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

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

- Accountability information; counting returned trial product, visual inspection of pens
- Questioning of participants

Compliance with other interventions

Compliance with diet and exercise will be monitored by the health-care providers performing the counselling. Evidence of non-compliance should result in a dialogue with the participant to re-emphasize the importance of, and uncover barriers to, compliance. This dialogue should be documented in the participant's medical record.

6.4 Dose modification

Dose escalation

Participants will be initiated at a once-weekly dose of 0.25 mg and follow a fixed-dose escalation regimen, with a dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), until the target dose is reached after 16 weeks. All participants should aim at reaching the recommended target dose of study product, or corresponding volume of placebo.

If a participant does not tolerate the recommended weekly target dose of 2.4 mg, the participant may stay at a lower dose level. This should only occur if the participant would otherwise discontinue study product completely, and the investigator considers it safe for the participant to continue study product. It is recommended that the participant make at least one attempt to re-escalate to the recommended weekly target dose (2.4 mg or the corresponding volume of placebo).

If there are persistent deviations from the planned escalation regimen, the investigator may contact Novo Nordisk for guidance.

A dose reminder card will be handed out to the participants at each site visit during the escalation period. Once the target dose has been reached, the dose reminder card is only handed out as needed.

Mitigation of GI symptoms

The investigator should support participants in escalating and maintaining their respective IMP dose. To mitigate and manage GI symptoms the investigator should:

- Advise participants to eat slowly, eat smaller meals, and stop eating when feeling full.
- In cases of persistent GI AEs, at any time during the study, symptomatic medication (e.g. antiemetic or antidiarrheal) should be prescribe, at the investigator's discretion.

Dose adjustment

If the participant reaches a BMI within the lower normal range and continues to lose weight, and there is a health concern, the investigator must consider reducing the dose of the IMP. The investigator should contact Novo Nordisk for guidance.

If the participant reaches a BMI < 18.5 kg/m^2, the dose of IMP must be reduced, and Novo Nordisk should be contacted for guidance.

Missed dose(s)

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

If ≥ 2 consecutive doses of study product are missed, the participant should be encouraged to re-commence the study product if considered safe as per the investigator's discretion and if the participant does not meet any of the discontinuation criteria (see Section 7.1). The starting dose for re-initiation of study product is at the investigator's discretion. In case of questions related to re-initiation of study product, the investigator should consult Novo Nordisk medical experts.

6.5 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.

6.6 Treatment of overdose

Overdose with semaglutide may be associated with gastrointestinal disorders which could lead to dehydration.

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

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

In the event of an overdose, the investigator should closely monitor the participant for overdose-related AE/SAE and laboratory abnormalities, and appropriate supportive treatment should be initiated according to the participants' clinical signs and symptoms. A prolonged period

of observation and treatment may be necessary, taking into account the long half-life of semaglutide of approximately one week.

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

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

6.7 Concomitant therapy

Any medication or vaccine (including over-the-counter or prescription medicines) that the participant is receiving at the time of the first visit or receives until end of study must be recorded along with:

- Trade name or generic name
- Dose (only to be recorded for oral antidiabetic drugs (OADs), anti-hypertensive and lipid-lowering medication)
- Primary indication
- Dates of administration including start and stop dates

Need for change in antihypertensive, OADs, or lipid-lowering medication should be continuously evaluated by the investigator at every visit, and any changes should be recorded as outlined above. The overall evaluation of change (i.e., either increase, decrease or no change) from randomisation should be recorded at visit 9 and end-of-treatment (visit 14) in the relevant forms (according to the flow chart in Section 1.2).

During the study, the participant should not initiate any anti-obesity medication or treatment which is not part of the study procedures. If such treatment is initiated, the participant should be instructed to stop the treatment.

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

There is no prohibited medication for participants except those included as exclusion criteria and excluded as rescue criteria (GLP-1 RAs, DPP-4 inhibitors and amylin analogues).

For participants with T2D at screening only:

If the participant receives OADs or insulin as rescue medication, the dose must be recorded in concomitant medication form.

To mitigate sulfonylurea (SU) induced hypoglycaemia, participants treated with SU (alone or in combination with other OADs) should, at the discretion of the investigator, reduce the SU dose at randomisation by approximately 50%.

Apart from the initial dose reduction of SU, background medication dose should remain at the same dose level and with the same frequency during the entire treatment period, unless glycaemic rescue

treatment is needed in case of persistent hyperglycaemia (as described in Sections 6.7.1 and 7.1.2), or a safety concern related to the use of background medications arises.

Investigators can switch anti-hyperglycaemic treatment within the same drug class e.g., in case specific drugs become unavailable.

6.7.1 Rescue medicine

For participants with T2D at screening:

Glycaemic rescue medication, i.e. intensification of background OAD treatment or addition of new OADs or insulin treatment, should be implemented at the discretion of the investigator in case of persistent hyperglycaemia as described in Section 7.1.2.

The following guidelines should be used:

1. Rescue medication according to American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD)[66] or local guidelines (excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues). Rescue medication should preferably be weight neutral.
2. If deemed necessary at the discretion of the investigator, insulin rescue therapy can be initiated, if so it should be according to ADA/EASD[66] or local guideline and as short duration as possible.

Participants that are started on rescue medication should continue to follow the protocol-specified visit schedule and stay on randomised treatment unless the investigator judges that it jeopardises safety. Rescue medication should be documented in medical records and reported in the case report form (CRF).

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

7 Discontinuation of study intervention and participant discontinuation/withdrawal

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

7.1 Discontinuation of study intervention

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

Efforts must be made to have participants attend and complete all scheduled visit procedures. 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.

If the participant does not wish to attend the scheduled clinic visits, efforts should be made to have the visits converted to phone contacts. However, all efforts should be made to have the participant attend at least the 'end of treatment' clinic visit containing the final data collection of primary and confirmatory secondary efficacy endpoints, and the 'end of study' visit.

The study intervention must be discontinued, if any of the following applies for the participant:

1. Safety concern as judged by the investigator
2. Suspicion of pancreatitis
3. Pregnancy
4. Intention of becoming pregnant
5. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study

Participants meeting discontinuation of the study intervention criteria no. 1, 2, 3 and 4 are allowed to resume study intervention, if the criteria are no longer met (see Section 7.1.1).

The primary reason for discontinuation of study intervention must be specified in the CRF, and final trial product accountability must be performed. Treatment discontinuation must be made in RTSM.

Pregnancy testing is recommended 5 weeks after premature discontinuation of study intervention (Appendix 4, Section 10.4).

7.1.1 Temporary discontinuation of study intervention

If a participant has discontinued trial product due to temporary safety concern not related to trial product and is allowed to resume, the participant should follow the guide for missed doses (Section 6.1). Similarly, a participant who discontinue trial product on their own initiative should be encouraged to resume trial product (Section 6.1).

In case of suspicion of acute pancreatitis, the study intervention should promptly be interrupted. Appropriate actions should be initiated, including local measurement of amylase and lipase (Appendix 3, Section 10.3 for AE reporting).

If acute pancreatitis is confirmed, treatment with IMP should not be resumed. If the Atlanta criteria[67] are not fulfilled, and thus, the suspicion of acute pancreatitis is not confirmed, treatment with IMP can be resumed. IMP may be resumed for participant with a gallstone-induced pancreatitis in case of cholecystectomy.

If acute pancreatitis is confirmed, randomised treatment should not be restarted, and treatment discontinuation must be made in RTSM.

Each missed dose should be recorded in the CRF, as per participant's recollection. If a treatment discontinuation previously has been made in RTSM, to indicate discontinuation of trial product, then resume treatment must be made in RTSM to resume trial product.

7.1.1.1 Hepatic events requiring temporary discontinuation of study intervention

Temporary discontinuation of study intervention is required for:

ALT or AST > 8 x upper limit of normal (ULN)

ALT or AST > 5 x ULN for more than 2 weeks

ALT (or AST) > 3 x ULN and total bilirubin > 2 x ULN (> 35% direct bilirubin) or ALT (or AST) > 3 x ULN and international normalised ratio (INR) > 1.5, which may indicate severe liver injury

ALT (or AST) > 3 x ULN with the appearance of fatigue, nausea, vomiting, anorexia, abdominal pain or tenderness, fever, rash and/or eosinophilia (>5%).

Temporary discontinuation of study intervention is also required in case of abnormal liver laboratory values not meeting protocol-specified discontinuation criteria, if the investigator deems that it is in the best interest of the participant.

Study intervention can be restarted only if an alternative aetiology is definitively identified and liver blood parameters have returned to pre-event levels. If an alternative aetiology is not definitively defined and/or liver blood parameters have not returned to pre-event levels, drug-induced liver injury (DILI) cannot be excluded, and study intervention must be permanently discontinued.

Please see Appendix 5 (Section 10.5) for follow-up information on hepatic safety.

Please also see the criteria for an AE and Hepatic Event form in Appendix 3 (Section 10.3.3).

7.1.2 Rescue criteria

For participants with T2D at screening only:

Persistent hyperglycaemia is defined by FPG or HbA_{1c} at the investigator's discretion.

Participants with persistent and unacceptable hyperglycaemia should be offered rescue medication. If any of the FPG values (including protocol scheduled fasting self-measured plasma glucose (SMPG)) exceed 15 mmol/L (270 mg/dL) and no intercurrent cause of the hyperglycaemia can be identified, a confirmatory FPG (at central laboratory) should be obtained by calling the participant for a re-test. If the confirmatory measurement also exceeds 15 mmol/L (270 mg/dL) the participant must be offered rescue medication, at the discretion of the investigator, according to the ADA/EASD[66] or local guidelines (excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues). For a description of rescue medication, please refer to Section 6.7.1.

However, when considering initiation of glycaemic rescue medication, dose escalation step, time remaining to initiation of maintenance dose, and expected effect of treatment in glycaemic parameters should be considered.

7.2 Participants discontinuing/Withdrawal from the study

A participant may withdraw consent at any time at his/her own request. The participant may also be withdrawn from the study at the discretion of the investigator.

If a participant withdraws consent, the investigator must ask the participant if he/she is willing, as soon as possible, to have assessment performed according to the 'end of treatment' visit. See the flowchart for data to be collected.

Final drug accountability must be performed even if the participant is not able to come to the trial site. The investigator must make treatment discontinuation in RTSM to discontinue trial product.

If a participant withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the medical record. If the participant withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

Although a participant is not obliged to give his/her reason(s) for withdrawing, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the end of trial form in the CRF.

7.2.1 Replacement of participants

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

7.3 Lost to follow-up

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

The following actions must be taken if a participant fails to return to the trial 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 or not the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow-up, the investigator 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). If attempts have failed, family members or other contacts consented by the participant can be contacted for alternative contact details. These contact attempts should be documented in the participant's source document.
- Should the participant continue to be unreachable at the 'end of treatment' visit, he/she will be considered to have withdrawn from the trial with a primary reason of lost to 'follow-up'.

8 Study assessments and procedures

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

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

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

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

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

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

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

Review of laboratory reports must be documented in the source documents or the participant's medical record. Care must be taken not to bias the participant.

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

8.1 Efficacy assessments

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

8.1.1 Body measurements

- Body weight should be measured at all site visits without shoes, on an empty bladder and only wearing light clothing. It should be measured on a digital scale and recorded in kilograms (rounding to one decimal e.g., x.2 or x.7) using the same scale throughout the trial. trial. The scale must be calibrated according to manufacturer's recommendation or local requirements.
- Height is measured without shoes in centimetres or inches (rounding to one decimal e.g., x.2 or x.7). BMI will be calculated in the eCRF at each clinic visit based on height at screening and body weight at the clinic visit. BMI calculated in the eCRF at screening must be in agreement with inclusion criterion no. 3 and thus verified after entry of screening results in the eCRF.

- Waist circumference is defined as abdominal circumference located midway between the lower rib margin and the iliac crest. Measures must be obtained in standing position with a non-stretchable measuring tape and to the nearest cm or inch (rounding is required). The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The participant should be asked to breathe normally. The same measuring tape should be used throughout the study. The measuring tape will be provided by Novo Nordisk to ensure standardisation.
- [redacted]

8.1.2 Self-measured plasma glucose

For participants with T2D at screening:

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 provided by Novo Nordisk A/S must be used for the measurements required in the protocol.

SMPG measurements should be taken fasting (at least 8 hours overnight before the visit) and prior to taking any diabetes medication. SMPG should be taken either on the day of the clinic visit or on the day before, according to the flowchart (Section 1.2). In case of suspicion of a hypoglycaemic event a SMPG should also be taken. Participants should be instructed in how to record the results of the SMPG values in the diaries. The record of each SMPG value should include date, time and value. All data from the diary must be transcribed into the CRF during or following the contact. If obtained via phone, and a discrepancy is later detected, the values in the CRF must be corrected.

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

8.1.3 Clinical efficacy laboratory assessments

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

8.2 Safety assessments

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

Medical history is a medical event that the participant experienced prior to the time point from which AEs are collected.

Only relevant and significant medical history as judged by the investigator should be recorded. Findings of specific medical history should de described in designated forms. As part of the medical history, information related to history of the following will be collected:

- Allergies, symptoms and predisposing conditions
- Breast neoplasm (for female participants only)
- Cardiovascular disorder and procedure
- Dyslipidaemia
- Eating disorder
- Gallbladder disease and procedure
- Gastrointestinal disorder and neoplasm
- Genitourinary tract disorder
- Glucose metabolism disorder
- Heart failure
- Kidney disease
- Liver disease
- Musculoskeletal system disorder
- Neuropathy
- Pancreatic disease
- Psychiatric disorder
- Respiratory disorder
- Skin cancer and skin disorder
- Thyroid disorder
- Weight disorder

Risk factors for breast (for female participants only), colon and skin cancer (including family history of breast, colon and/or skin cancer, age at time of diagnosis for relevant family members, predisposing factors for breast and skin cancer, menarche/menopause, breast cancer screening, hormone replacement therapy).

Information on weight-related complications will be collected as part of medical history/concomitant illness at screening and an evaluation will be done at the end of study intervention.

Weight history (including previous weight, debut time of overweight, maximum weight, age at maximum weight, previous weight loss attempts, previous use of anti-obesity prescription medication, and other methods to lose weight must be documented at screening.

Other relevant concomitant illness/medical history (also including COVID-19 illness, and including malignant neoplasms not covered by the above categories).

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

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

8.2.1 Physical examinations

A physical examination will include assessments of the cardiovascular, respiratory, gastrointestinal, neurological system and skin.

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

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

8.2.2 Vital signs

Pulse rate, systolic and diastolic blood pressure will be assessed. 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 screening, randomisation, week 2, 4, 8, 12, 16, 20, 28 and 36, and end of study intervention.

The method for measuring systolic and diastolic blood pressure needs to follow the standard clinical practice at site.

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

8.2.3 Eye examination

Participants with T2D at screening only:

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

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

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

After randomisation, an eye examination must be performed according to above as per protocol flowchart (Section 1.2). 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 (Section 8.3).

8.2.4 Mental health assessment instruments

Two patient reported outcome questionnaires will be used. The paper-based questionnaires will be filled in at site. Participants should complete the questionnaires at site at screening (visit 1), visit 8 and end-of-treatment (visit 14)

Patient Health Questionnaire-9 (PHQ-9)[68]

PHQ-9 is a 9-item depression module of the patient health questionnaire, which is a self-administered diagnostic tool used for assessment of mental disorders. The questionnaire will be available in a linguistically validated translated version. The paper-based questionnaire will be filled in after instructions from site staff. Participants should be given the opportunity to complete the questionnaires by themselves without interruption. The questionnaire takes approximately 5 minutes to complete.

If a participant has a PHQ-9 score of 10-14 (both inclusive) the participant should be referred to a mental health professional (MHP) if judged relevant by the investigator. If referral is not deemed relevant this along with the reason why must be documented in the participant's medical records.

C-SSRS Baseline and C-SSRS Since Last Visit[69]

C-SSRS is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation. The questionnaire will be administered as an interview by the investigator or a qualified delegate. The questionnaire (C-SSRS Baseline and C-SSRS Since Last Visit) will be available in a linguistically validated translated version.

Prior to administering the C-SSRS questionnaire, the investigator or qualified delegate must complete sufficient training.

A participant must be referred to a MHP if:

- the participant has a PHQ-9 score ≥15 or
- the participant has any suicidal behaviour or
- the participant has any suicidal ideation of type 4 or type 5 on any C-SSRS assessment or
- in the opinion of the investigator, it is necessary for the safety of the participant

If one or more of the referral criteria are met, the investigator should explain to the participant why the referral and psychiatric evaluation by a MHP is needed. If the participant refuses to be referred to a MHP, the participant's decision should be documented in participant's medical record and the investigator must assess if it is safe for the participant to continue in the trial or if the participant should be discontinued from trial product.

Referral to an MHP should be performed if any of the above referral criteria are met at any time during the trial, including at the screening and end of trial visit. If one or more of the referral criteria are met, the investigator should explain to the participant why the referral and psychiatric evaluation by an MHP is needed. If the participant refuses to be referred to an MHP, the participants decision should be documented in the participants medical record and the investigator must assess if it is safe for the participant to continue in the study or if the participant should be discontinued from randomised treatment.

If a participant's psychiatric disorder can be adequately treated with psychotherapy and/or pharmacotherapeutic treatment, then the participant, at the discretion of the investigator (and in agreement with the MHP), may continue in the trial. Otherwise, the participant must be discontinued from trial product due to safety concern as judged by the investigator.

8.2.5 Clinical safety laboratory assessments

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

8.2.6 Pregnancy testing and contraceptive counselling

Urine pregnancy tests provided by central laboratory must be performed for women of childbearing potential (WOCBP) at screening and as specified in the flowchart.

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

Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.

Additional pregnancy testing should be performed during the treatment period, if required locally, refer to Appendix 4, Section 10.4.

WOCBP must receive contraceptive counselling, at each site visit, to ensure effective contraception. The content of the contraceptive counselling session is the responsibility of the investigator and per the investigator's discretion. The contraceptive counselling and the result of the pregnancy test must be documented in the eCRF.

8.2.7 Surgical procedures assessment

While enrolled in this study, participants are not encouraged to commence other anti-obesity medication or bariatric surgery. However, if due to clinical reasons a participant does undergo bariatric surgery, hip surgery or knee surgery while enrolled in this study, the investigator should record this in the Procedures Form described below.

During site and/or phone visits marked in the Flowchart, the investigator should ask the participant if they have undergone the surgical procedures listed below, since their previous assessment. If the participant has undergone the procedure(s), the investigator should fill out the Procedures Form. A separate form should be filled out for separate procedures.

Bariatric surgery – including bariatric gastric balloon insertion/removal, duodenal-jejunal bypass sleeve therapy, endoscopic sleeve gastroplasty, gastric binding (includes laparoscopic adjustable gastric band), gastric band repositioning, gastric band reversal, gastric bypass, gastric bypass reversal or duodenal switch.

Knee surgery – including partial knee replacement or total knee replacement.

Hip surgery – including partial hip replacement or total hip replacement.

8.3 Adverse events and other safety reporting

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

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

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

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

Event type	AE requiring additional data collection	Other event requiring collection of additional information
Medication error[a]	X	
Misuse and abuse[a]	X	
Acute pancreatitis	X	
Acute gallbladder disease	X	
Malignant neoplasms	X	
Hepatic event	X	
Elevated liver enzymes		X
Acute kidney injury[b]	X	
Diabetic retinopathy[b]	X	
Hypoglycaemic episodes[b]		X

[a]Additional data for Misuse or abuse of trial product is reported on the medication error event form.

[b]For participants with T2D at screening only

Definitions and reporting timelines for the events mentioned in the above table can be found in Appendix 3, Section 10.3 and Appendix 7, Section 10.7 for hypoglycaemic episodes.

8.3.1 Time period and frequency for collecting AE information

All AEs and SAEs must be collected from the first study-related activity after obtaining informed consent and until the end of study visit in accordance with the flowchart (Section 1.2) or whenever, within the above time period, the site becomes aware of an AE or SAE.

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

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

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

8.3.2 Method of detecting AEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3, Section 10.3.

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

8.3.3 Follow-up of AEs

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

8.3.4 Regulatory reporting requirements for SAEs

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

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR).

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

8.3.5 Pregnancy

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

8.3.6 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to AE/SAEs description in Section 10.3.

8.3.7 Hypoglycaemic episodes

For participants without T2D at screening:

All hypoglycaemic episodes must be reported as an AE in accordance with Section 8.3.1 and Appendix 3, Section 10.3.

For participants with T2D at screening:

All hypoglycaemic episodes must be recorded on a hypoglycaemic episode form in the eCRF. If the hypoglycaemic episode fulfils the criteria for an SAE, then, in addition to the hypoglycaemic episodes form, an AE form and a safety information form must be filled in, please refer to Appendix 3, Section 10.3. For more information on hypoglycaemic episodes, please refer to Appendix 7, Section 10.7.

8.3.8 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 6 (Section 10.6).

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

8.4 Pharmacokinetics and pharmacodynamics

8.4.1 Pharmacokinetics

Not applicable for this study.

8.4.2 Pharmacodynamics

Not applicable for this study.

8.5 Genetics

Not applicable for this study.

8.6 Biomarkers

Not applicable for this study.

8.7 Immunogenicity assessments

Not applicable for this study.

8.8 Health economics

Not applicable for this study.

9 Statistical considerations

The statistical analysis plan (SAP) will be finalised prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical hypotheses

For the co-primary estimands with co-primary endpoints, 1) change in body weight (%) from baseline to end of treatment (week 44) and 2) body weight reduction ≥ 5% (yes/no) at end of treatment (week 44), the following 1-sided hypotheses are planned to be tested for semaglutide 2.4 mg versus placebo. Let the mean treatment difference in 1) be defined as:

μ = ([semaglutide 2.4 mg] minus [placebo])

and let the odds ratio of 2) be defined as:

OR = (odds[semaglutide 2.4 mg] divided by odds[placebo]).

Superiority

1) $H0_1$: $\mu \geq 0.0$ percentage points against Ha_1: $\mu < 0.0$ percentage points

   and

2) $H0_2$: OR ≤ 1 against Ha_2: OR > 1

Operationally the hypotheses will be evaluated by 2-sided tests.

For the confirmatory secondary estimand with the endpoint body weight reduction ≥ 10 % (yes/no) at end of treatment (week 44) a hypothesis similar to 2) will be tested.

For the confirmatory secondary estimand with the endpoint change in waist circumference (cm) from baseline (week 0) to end of treatment (week 44) a hypothesis similar to 1) will be tested.

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 2-sided 95% confidence interval approach until an insignificant result appears. Consequently, the second null hypothesis will only be tested if the first null hypothesis has been rejected in favor of semaglutide 2.4 mg.

The steps in the hierarchical testing procedure are as follows:

- Step 1: Superiority of semaglutide 2.4 mg versus placebo with respect to both co-primary estimands.
- Step 2: Superiority of semaglutide 2.4 mg versus placebo with respect to secondary estimand with endpoint body weight reduction ≥ 10 % (yes/no) at end of treatment (week 44).
- Step 3: Superiority of semaglutide 2.4 mg versus placebo with respect to secondary estimand with the endpoint change in waist circumference from baseline (week 0) to end of treatment (week 44).

9.2 Analysis sets

The following participant analysis sets are defined:

Table 9-1 Analysis sets

Participant analysis set	Description
Full analysis set (FAS)	All randomised participants.
Safety analysis set (SAS)	All participants who are exposed to at least one dose of randomised IMP.

FAS participants will be included in the analyses according to the planned intervention. SAS participants will be included in the analyses according to the intervention they actually received.

The following data points sets are defined:

Table 9-2 Defined data point sets

Defined data points set (DPS)	Description
In-trial (DPS1)	The time period where the participant is assessed in the study. The in-trial observation period for a participant begins on the date of randomisation and ends at the first of the following dates (both inclusive): • 'End of study' visit • withdrawal of consent • last contact with participant (for participants lost to follow-up) Observations will be included in the in-trial observation period regardless of initiation of other anti-obesity therapies.
On-treatment (DPS2)	The time period where participants are treated with study product. A time-point is considered as "on-treatment" if any dose of study product has been administered within the prior 2 weeks (14 days). The participant is considered "on-treatment" regardless of dose reduction. The on-treatment period is defined as all times which are considered on-treatment. In general, the on-treatment period will therefore, be from the date of first study product administration to date of last study product administration (+14 days) excluding potential off-treatment time intervals triggered by at least two consecutive missed doses. For the evaluation of AEs, hypoglycaemic episodes and potential pregnancies, the lag time for each on-treatment time interval is 5 weeks (35 days). Observations will be included in the on-treatment observation period regardless of initiation of other anti-obesity therapies.
On-treatment until first discontinuation of study product or initiation of other anti-obesity therapies (DPS3)	The time period where participants are treated with study product. A time-point is considered as "on-treatment" if any dose of study product has been administered within the prior 2 weeks (14 days). The participant is considered "on-treatment" regardless of dose reduction. Observations after the first discontinuation of study product or initiation of other anti-obesity therapies will not be included.

FAS and DPS1 are used to estimate the co-primary estimands and the secondary estimands for the secondary objectives.

FAS and DPS3 are used to estimate the additional estimand for the primary objective and secondary objectives.

FAS and either DPS1 or DPS2(14 days) are used to present efficacy data.

SAS and either DPS1 or DPS2(35 days) are used to present safety data.

The in-trial (DPS1) and on-treatment (DPS2(35 days)) periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

Any observation excluded from the analysis database will be documented before database lock with the reason for exclusion provided.

9.3 Statistical analyses

9.3.1 General considerations

This section is a summary of the planned statistical estimation of the most important estimands including primary and confirmatory secondary estimands.

The last available observation at or before randomization is used as the baseline value. If no assessments are available, the mean value at randomization across all participants is used as the baseline value.

All tests are tests of superiority of semaglutide 2.4 mg once weekly versus placebo. All estimated treatment contrasts between semaglutide 2.4 mg and placebo will be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

The stratification factor is defined as T2D/non-T2D.

9.3.2 Primary estimands analysis

The co-primary endpoints are:

- Relative change in body weight (%) from baseline (week 0) to end of treatment (week 44)
- Body weight reduction ≥ 5% (yes/no) at end of treatment (week 44)

The two primary analyses are aligned with the two co-primary estimands defined in Section 3.

The analysis model for relative change in body weight (%) will be a linear regression (ANCOVA) with randomised treatment and stratification groups as factors and baseline body weight (kg) as covariate.

The analysis model for the body weight reduction ≥ 5% is a logistic regression using randomised treatment and stratification group as factors and baseline body weight (kg) as covariate.

All available data at week 44 are used and missing values at week 44 will be imputed and the endpoint will be derived from the imputed values. The imputation approach for the primary analysis

is wash-out multiple imputation (WO-MI), which utilizes different imputation models depending on randomised treatment group and end of treatment status. (1) For on-drug participants in the semaglutide 2.4 mg arm, missing week 44 values of body weight are imputed based on observed data from the on-drug participants in the semaglutide 2.4 mg arm using the retrieved participants multiple imputation approach (RD-MI) similar to the one described by McEvoy et al.[70] (2) For participants in semaglutide placebo arm, missing week 44 values of body weight are imputed based on all observed data at all time points in the semaglutide placebo arm using a MMRM model. (3) For off-drug participants in the semaglutide 2.4 mg arm, missing week 44 values of body weight are imputed from the semaglutide placebo arm assuming that all drug effect will be washed-out and gone before week 44 similar to jump to reference multiple imputation. Details of the multiple imputation approach will be provided in the SAP.

Sensitivity analyses

Jump to reference multiple imputation approach (J2R-MI): Missing values of body weight at week 44 for both the semaglutide 2.4 mg and placebo group are imputed by sampling among all available assessments at week 44 in the placebo group. This approach makes the assumption that participants instantly after discontinuation lose any effect of randomised treatment beyond what can be expected from placebo treatment as adjunct to reduced-calorie diet and increased physical activity. The J2R-MI analysis targets the robustness of the MAR assumption. Details of the multiple imputation approach are provided in the SAP.

Tipping-point multiple imputation analysis (TP-MI): For the semaglutide 2.4 mg treatment arm and placebo treatment arm, a penalty will be added to the imputed values at week 44 in the main analysis. The approach is to gradually increase this penalty until all confirmed conclusions from the primary analysis are reversed. The penalty that reverses the conclusion will be evaluated from a clinical perspective and if the value is deemed to be clinically implausible, this will support the conclusion from the primary analysis. The TP-MI analysis addresses the MAR assumption.

Non-retrieved participants as non-responders: For the analysis of body weight reduction ≥ 5% an analysis using non-retrieved participants as non-responders in the logistic regressions will be done. This analysis also targets the MAR assumption.

ANCOVA for unequal variances: The assumption of unequal variances is tested by repeating the primary analysis with the modification that variances in the ANCOVA model are allowed to differ across treatment groups.

Supplementary analyses

The following statistical analyses are designed to address the additional estimand for the primary objective.

The estimation of the estimand with the endpoint of relative change in body weight (%) will be a mixed model for repeated measurements (MMRM). The MMRM will be fitted using randomised treatment and stratification group as factors and baseline body weight (kg) as covariate all nested within visit as a factor. An unstructured covariance matrix for measurements within the same participant will be employed. Measurements for different participants are assumed to be independent.

The estimation of the estimand with the endpoint of body weight reduction ≥ 5% is a logistic regression where any missing values at week 44 will be predicted from the MMRM. The predicted values will be used to classify each participant as 5% responder or not. The logistic regression model will include randomised treatment and stratification groups as factors and baseline body weight (kg) as covariate.

9.3.3 Secondary estimands analysis

9.3.3.1 Confirmatory secondary estimands

The confirmatory secondary endpoints related to the secondary objective are:

- Body weight reduction ≥ 10% (yes/no) at end of treatment (week 44)
- Change in waist circumference (cm) from baseline (week 0) to end of treatment (week 44)

All confirmatory secondary endpoints will be analysed using the same analysis model and imputation approach as used to address the primary estimand for the primary endpoints.

The analysis model for change in waist circumference will be a linear regression (ANCOVA) with randomised treatment and stratification groups as factors and baseline value as covariate.

The analysis model for the responder endpoint is a logistic regression using randomised treatment and stratification groups as factors and baseline body weight (kg) as covariate.

Sensitivity analysis

For the change in waist circumference a sensitivity analysis using jump to reference as imputation approach will be carried out. For binary confirmatory secondary endpoints, a sensitivity analysis using non-retrieved participants as non-responders will be carried out.

Supplementary analysis

The estimation of the additional estimands for the secondary objectives will be similar to those described for the additional estimands for the primary objective.

The estimation of the estimand with the endpoint change in waist circumference will be a mixed model for repeated measurements (MMRM). The MMRM will be fitted using randomised treatment and stratification groups as factors and baseline value as covariate all nested within visit. An unstructured covariance matrix for measurements within the same participants will be employed, assuming that measurements for different participants are independent.

The estimation of the estimand with the endpoint body weight reduction ≥ 10% is a logistic regression where any missing values at week 44 will be predicted from the MMRM. The predicted values will be used to classify each participant as 10% responder or not. This classification will then be analysed using a logistic regression model with randomised treatment and stratification groups as factors and baseline body weight (kg) as covariate.

9.3.3.2 Supportive secondary estimands

Supportive secondary estimands with relative endpoints are described in Section 3, and the statistical analyses are detailed in the SAP.

Safety related supportive secondary estimands

The safety endpoint pulse will be analysed using an MMRM for efficacy as described in Section 9.3.2.

Adverse events will be defined as "treatment-emergent" (TEAE) if the onset of the event occurs in the on-treatment (DPS2 [35 days]). TEAEs and SAEs will be summarised by descriptive statistics, such as frequencies and rates. No formal statistical inference will be carried out based on the number of TEAEs and SAEs.

9.3.4 Exploratory endpoints analysis

[redacted]

9.3.5 Other safety analyses

Please refer to the SAP for details.

9.3.6 Other analyses

Please refer to the SAP for details.

9.4 Interim analysis

There is no interim analysis planned for this study.

9.5 Sample size determination

The sample size was calculated to achieve an effective power of approximately 90% to detect differences on the primary and secondary confirmatory endpoints for China mainland. The effective power was calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively which is a conservative approach. The power calculations for continuous endpoints are based on a t-test on the mean difference assuming equal variances, whereas those for the categorical endpoints are based on the Pearson chi-square test for two independent proportions.

Assumptions for the power calculations are presented in Table 9-3 and are based on findings from NN9536-4382 (STEP 6, East Asian study). In STEP 6 the study population is Japanese and South Korean participants with a BMI $\geq$ 27.0 kg/m^2 with $\geq$2 weight-related complications or BMI $\geq$ 35.0 kg/m^2 with $\geq$1 weight-related complications. In STEP 6, 25% of the participants had T2D which is comparable with this study. We expect a lower treatment effect in the current study compared with STEP 6 due to potential dose reduction when reaching a BMI in the normal range. In STEP 6 the in-trial mean relative weight loss (SD) was -11.8 (7.0)% and the change in waist circumference was -10.0 (6.5) cm in the semaglutide 2.4 mg arm at week 44. Adjusting for a lower baseline BMI, lower baseline waist circumference and potential dose reduction it is assumed the

relative weight loss (SD) will be -11.0 (8.0) % and the change in waist circumference (SD) -7.1 (7.0) cm in the semaglutide 2.4 mg arm in the current study. The standard deviation is chosen slightly higher than the observed standard deviation in STEP 6 as a conservative estimate.

Based on the multinational study STEP 1, where 18.9% permanently discontinued study product it is assumed that 20% of participants will discontinue study product permanently before week 44. It is assumed that approximately 60% will be retrieved at week 44. All participants in the placebo arm are assumed to have same effect as participants who complete the study on placebo. Retrieved participants in the semaglutide 2.4 mg arm are assumed to have an effect corresponding to half the treatment difference (compared to placebo) of participants who complete the study on semaglutide 2.4 mg. Non-retrieved participants in the semaglutide 2.4 mg arm are assumed to have an effect corresponding to placebo.

Based on data from the NN9536 global phase 3a studies, it is expected that <1% of participants will initiate other anti-obesity therapies, so the impact of this intercurrent event is expected to be negligible.

The impact of dose reduction is included in the assumed mean and proportions in Table 9-3. Similarly, the impact of T2D in the study population is also included. A comparison of power curves based on the assumptions in Table 9-3 and with the observed standard deviation from STEP 6 instead is shown in Figure 9-1.

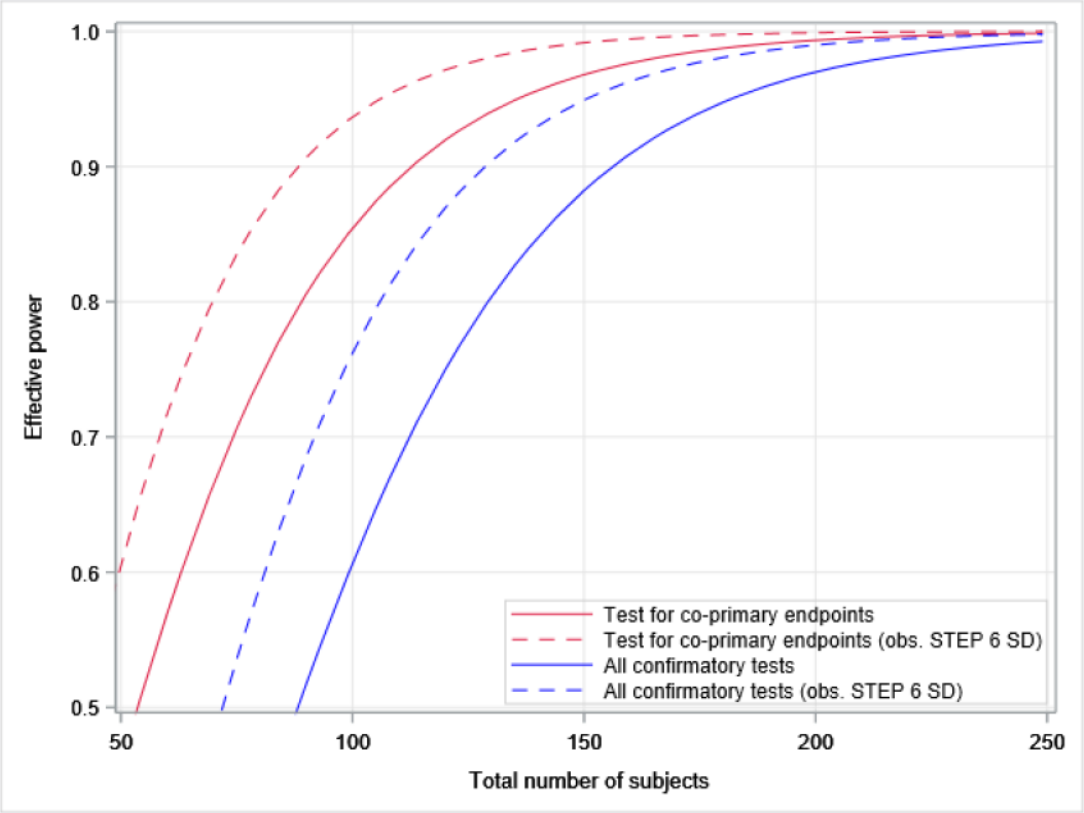
Under these assumptions and a 2:1 randomisation ratio, a sample size of 162 participants randomised to either receive semaglutide 2.4 mg (108 participants) or placebo (54 participants) yields an effective power of 92% for all confirmatory endpoints.

Table 9-3 Assumptions, marginal power, and effective power for each endpoint in the hierarchical testing procedure

Order	Endpoint	Assumed mean (SD) or proportion for completers		Expected mean (SD) or proportion	Expected difference or proportion ratio	Marginal power (%)	Effective power (%)
		Sema 2.4 mg	Placebo	Sema 2.4 mg			
162 participants / 242 participants							
1	Relative change in body weight (%)	11.0 (8.0)	3.0 (8.0)	9.9 (8.4)	6.9 %-points	99.8 / >99.9	99.8 / >99.9
2	Body weight reduction ≥ 5%	77.3%	40.1%	72.3%	1.8	98.0 / >99.9	97.8 / >99.9
3	Body weight reduction ≥ 10%	55.0%	19.1%	49.8%	2.6	98.0 / >99.9	95.8 / >99.9
4	Change in waist circumference (cm)	7.1 (7.0)	2.0 (7.0)	6.4 (7.2)	4.4 cm	95.5 / 99.8	91.5 / 99.8

For regulatory purposes and safety concern, the trial will include an additional 80 participants from Taiwan. Therefore, in total approximately 242 Chinese participants (162 participants from China mainland and 80 participants from Taiwan) will be randomized 2:1 to semaglutide 2.4 mg or placebo.

Figure 9-1 Power curves for co-primary endpoints and all confirmatory 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[71] and applicable ICH Good Clinical Practice (GCP) Guideline[72]
- Applicable laws and regulations

The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CSR according to national requirements. Any trial procedure conducted should comply with local guidelines. 'Regulations on management of Human Genetic Resources of People's Republic of China' and relative guidelines.

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

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.

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[72] guidelines, Declaration of Helsinki,[71] privacy and data protection requirements, where applicable, and the IRB/IEC or site.

The medical record must include a statement that written informed consent was obtained before any study-related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any study-related activity.

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

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

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

10.1.4 Information to participants during the study

The site may be offered a communication package for the participant during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the 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.

Different initiatives for participant retention will be implemented throughout this trial. Site retention activities may include cooking classes, group meetings and others. Materials and items will be supplied if locally acceptable. The retention items will be relevant for the participants' participation in the trial and/or their obesity and will not exceed local fair market value.

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

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

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

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

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee. The safety committee may recommend unblinding of any data for further analysis, and in this case an independent *ad hoc* group may be established in order to maintain the blinding of the study personnel.

10.1.6.2 Study safety group

Not applicable for this study.

10.1.6.3 Data monitoring committee

Not applicable for this study.

10.1.6.4 Event adjudication committee

Not applicable for this study.

10.1.7 Dissemination of clinical study data

Study information will be disclosed at clinicaltrials.gov, chinadrugtrials.org.cn 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,[71] the International Committee of Medical Journal Editors (ICMJE),[73] the Food and Drug Administration Amendment Act (FDAAA),[74] European Commission Requirements[75-77] and in accordance with Novo Nordisk commitment to clinical transparency. If a participant requests to be included in the study via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the participant. As a result of

increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

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

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

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

The following will be provided as paper CRFs:

- Pregnancy forms

The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF 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 CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

10.1.8.2 Monitoring

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the study. If the electronic source data does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone).

Study monitors will perform ongoing source data verification of critical data points to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents. Study monitors will perform ongoing source data review to ensure that the study is being conducted in accordance with the current approved protocol and any other study agreements, ICH GCP[72], 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 CRF or via listings from the study database.

10.1.9 Source documents

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

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

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

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the site. Any source data generated by investigator's subcontractors must be archived and accessible by the site.
Data that is transcribed into the CRF from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

It must be possible to verify participant's medical history in source documents, such as participant's medical record.

The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.

Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical study documentation

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

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

Participant's medical records must be kept for the maximum period permitted by the hospital, institution or private practice. About site specific data storage, sites have the equal right with sponsor. Long term preservation of Patients Trial Data is prohibited in any other entities.

10.1.11 Study and site closure

Novo Nordisk reserves the right to close the site or terminate the study at any time for any reason at the sole discretion of Novo Nordisk. If the study is suspended or terminated, the investigator must inform the participants promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

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

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a site by Novo Nordisk or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines
- inadequate recruitment of participants by the investigator
- discontinuation of further study intervention development.

10.1.12 Responsibilities

The investigator is accountable for the conduct of the study at his/her site and must ensure adequate supervision of the conduct of the study at the site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified study-related duties. The investigator must ensure that there is adequate and documented training for all

staff participating in the conduct of the study. It is the investigator's responsibility to supervise the conduct of the study and to protect the rights, safety, and well-being of the participants.

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

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

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

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

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

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

10.1.13 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with regional laws, acts and local guidelines.

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 participant 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.[78]

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned publication.

Where required by the journal, the investigator from each site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

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

For a multicentre clinical study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or participants, and therefore may not be supported by Novo Nordisk. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the study.

10.1.14.4 Investigator access to data and review of results

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

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

10.2 Appendix 2: Clinical laboratory tests

The tests detailed in Table 10-1 will be performed by a central laboratory.

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

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

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

The laboratory samples will be destroyed no later than at the finalisation of the CSR. All laboratory samples will be destroyed according to local regulatory requirement.

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

Table 10-1 Protocol-required efficacy and safety laboratory assessments

Laboratory assessments	Parameters	
Glucose metabolism	• HbA_{1c} • Fasting plasma glucose (mg/dL)[a] • Self measured plasma glucose	
Lipids	• Total cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Very low-density lipoprotein (VLDL) cholesterol • Free fatty acids • Triglycerides	
Haematology	• Basophils • Eosinophils • Haemoglobin • Leucocytes	• Lymphocytes • Monocytes • Neutrophils • Thrombocytes

Laboratory assessments	Parameters	
Biochemistry[b]	• Alanine Aminotransferase (ALT)[c] • Aspartate Aminotransferase (AST)[c] • Alkaline phosphatase • Albumin • Albumin corrected calcuim • Bilirubin[d] • Creatinine • Creatinine kinase	• Gamma Glutamyl Transferase • Potassium • Sodium • High-sensitivity C-Reactive Protein (hsCRP)
Pregnancy Testing[e]	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test	
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation	

Notes:

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

[b]See Section 10.3 (Hy's Law) and Appendix 5 (Section 10.5) for details of required actions and follow-up assessments for increased liver parameters. Discontinuation and/or stopping criteria are given in Section 7.1.

[c]If ALT or AST > 3 upper normal limit (UNL), additional blood sample should be taken from the participant to analyse international normalised ratio (INR) by central laboratory (except at screening visit). Repeat testing of the abnormal laboratory assessments should be performed via central laboratory for the participant until abnormalities return to normal or baseline state.

[d]Details on hepatic safety, suggested actions and follow-up assessment are given in Appendix 5 (Section 10.5).

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

Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes

Table 10-2 Criteria for laboratory outliers

	Cut-off
Leucocytes	< 1 x 10^9/L
Lymphocytes	< 0.2 x 10^9/L
Thrombocytes	< 25 x 10^9/L
Albumin corrected calcium	< 1.5 mmol/L > 3.4 mmol/L
Alkaline phosphatase	> 20 x UNL
Alanine Aminotransferase	>5 x UNL
Aspartate Aminotransferase	>5 x UNL
Bilirubin, total	>10 x UNL
Creatinine	> 6 x UNL
Creatine kinase	> 10 x UNL
Potassium	< 2.5 mmol/L > 7 mmol/L
Sodium	< 120 mmol/L > 160 mmol/L

Abbreviations: UNL = upper normal limit

All study-required laboratory assessments will be performed by a central laboratory.

Hepatic laboratory outliers

If the hepatic laboratory parameters of alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and total bilirubin are above the cut-off values in Table 10-2, it is considered hepatic laboratory outliers and should be reported by completing a hepatic event form in the eCRF. It is at the investigator's discretion to determine whether it should be reported as an adverse event (see Appendix 3, Section 10.3).

In case of hepatic events, see Appendix 5, Section 10.5 for definition, suggested actions and follow-up assessments.

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
- Obesity-related surgical procedures where both the event leading up to the AE and the procedure (e.g., knee surgery, bariatric and metabolic surgery) should be reported as an AE.

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.

- In general, medical or surgical procedures (e.g., endoscopy, appendectomy) should not be reported as AEs. The condition (new or worsening) that leads to the procedure is the AE. Exceptions include obesity-related surgical procedures where both the surgical procedure and the condition (new or worsening) that leads to the procedure should be reported as AEs.

10.3.2 Definition of an SAE

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

- Results in death
- Is life-threatening
    - The term 'life-threatening' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
    - Hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.
    - Hospitalisation for elective treatment (e.g., elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE.

Note: Hospitalisations for administrative, study-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for medical or surgical procedures, planned before study inclusion, are not considered AEs or SAEs

- Results in persistent or significant disability/incapacity
    - The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Important medical event:
    - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
    - The following must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:
        - Suspicion of transmission of infectious agents via IMP
        - Risk of liver injury defined as alanine aminotransferase (ALT) or asparate aminotransferase (AST) >3x UNL and total bilirubin >2x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of AEs requiring additional data collection

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

Acute gallbladder disease

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

Hepatic event

- Any disorders of the liver including cholestatic conditions and liver related signs and symptoms.
- If a liver related AE is reported, the Hepatic Event form must be filled out.

Malignant neoplasms

Malignant neoplasm by histopathology or other substantial clinical evidence.

Acute pancreatitis

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

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

Acute kidney injury (for participants with T2D at screening only)

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

Diabetic retinopathy (for participants with T2D at screening only)

New onset or worsening of diabetic retinopathy.

Medication error:

- A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to harm to the participant, such as:
    - administration of wrong drug
      Note: Use of wrong 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.

Other events requiring collection of additional information

Hypoglycaemic episodes (for participants with T2D at screening only):

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

Definitions, classification, and reporting requirements are described in Appendix 6, Section 10.7.

Please note, that for participants without T2D at screening all hypoglycaemic episodes must be reported as an AE.

Elevated liver enzymes
In all cases where one or more results from liver laboratory parameters (ALT, AST or ALP) measured in a blood sample at the central laboratory are increased above the limits defined below, the Elevated Liver Enzymes form must be completed. Criteria for discontinuation of study intervention may also apply; see Section 7.1.1.1.

- Alanine aminotransferase (ALT): >3.0 x ULN if baseline was normal; >3.0 x above baseline if baseline was abnormal.
- Aspartate aminotransferase (AST): >3.0 x ULN if baseline was normal; >3.0 x above baseline if baseline was abnormal.
- Alkaline phosphatase (ALP): >2.5 x ULN if baseline was normal; >2.5 x above baseline if baseline was abnormal.

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

10.3.4.1 AE and SAE recording

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

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

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

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

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

Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the study, it is important that the suspected relationship is reported to Novo Nordisk, e.g., in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

10.3.4.2 Assessment of severity

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

- **Mild**: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: An AE that is assessed as severe should not be confused with an SAE. Both AEs and SAEs can be assessed as severe.

10.3.4.3 Assessment of causality

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

Relationship between an AE/SAE and the relevant IMP should be assessed as:

- **Probable** - Good reason and sufficient documentation to assume a causal relationship.
- **Possible** - A causal relationship is conceivable and cannot be dismissed.
- **Unlikely** - The event is most likely related to aetiology other than the IMP.

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

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

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

The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.4.4 Final outcome

The investigator will select the most appropriate outcome:

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

10.3.4.5 Follow-up of AE and SAE

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

New or updated information should be recorded in the CRF.

10.3.5 Reporting of SAEs

AE and SAE reporting via CRF

Relevant forms must be completed in the CRF.

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

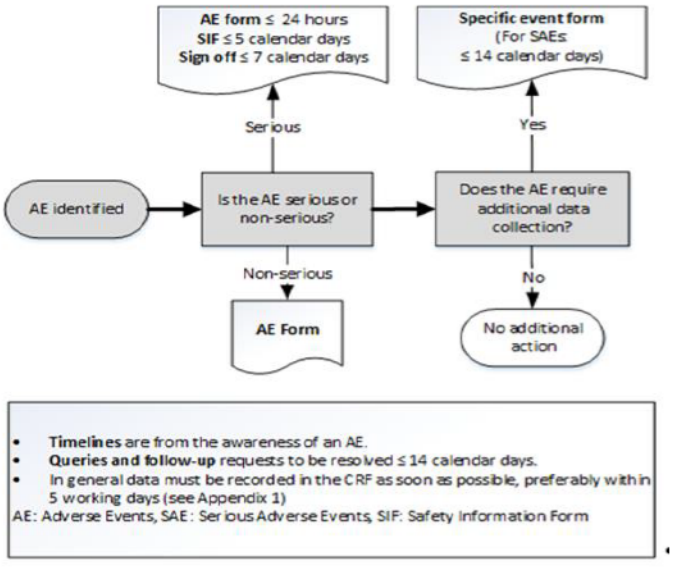
- AE form within 24 hours
- Safety information form within 5 calendar days
- Both forms must be signed within 7 calendar days after first knowledge by the investigator
- Specific event form within 14 calendar days

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

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

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

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



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

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

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
3. 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.
4. 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 (HRT) and whose menopausal status is in doubt are considered of childbearing potential and will be required to use one of the highly effective/acceptable 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.

Female participants

Female participants of childbearing potential are eligible to participate if they are using highly effective contraceptive method prior to randomisation and agree to use consistently and correctly until end of study with accordance to exclusion criteria. Table 10-3 lists the highly effective and acceptable methods of contraception allowed.

Highly effective or acceptable contraception should be utilised until the end of study.

Table 10-3 Highly effective contraceptive methods allowed[79]

Highly effective methods[a] (Failure rate of <1% per year when used consistently and correctly):

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  • oral
  • intravaginal
  • transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation
  • oral
  • injectable
  • implantable
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner
Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
• Sexual abstinence
Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

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

In addition, a combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered as highly effective methods of contraception.

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 10-1).

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

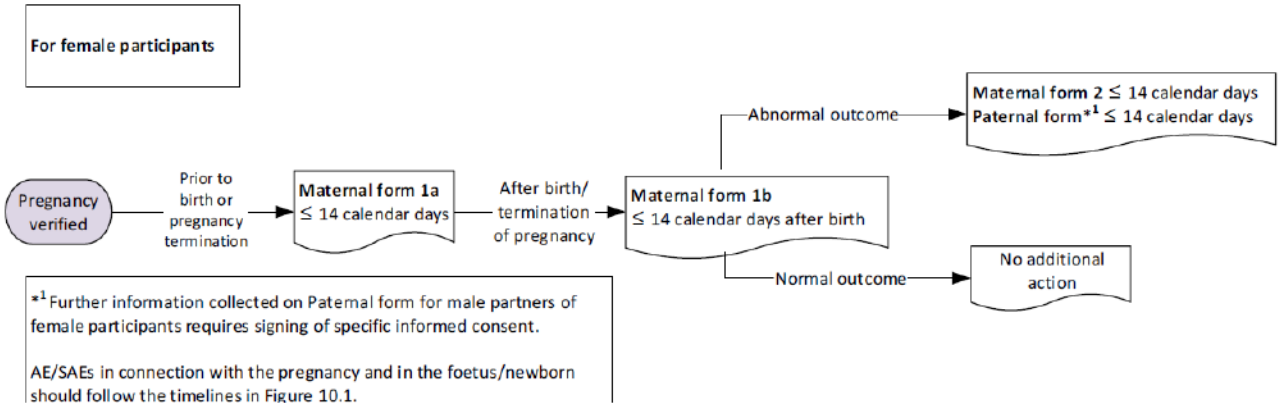
Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

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

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

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

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



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

10.5 Appendix 5: Hepatic Safety: Suggested actions and follow-up assessments

For all events defined as:

- ALT or AST > 8 x upper limit of normal (ULN)
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN (> 35% direct bilirubin) or ALT or AST > 3 x ULN and international normalised ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, anorexia, abdominal pain or tenderness, fever, rash and/or eosinophilia (>5%),

the following must be performed:

- repeat testing within 48 to 72 hours at central laboratory
- follow-up assessments
- work-up for alternative aetiology

If no alternative or competing aetiology is identified:

- Complete liver profile including ALT, AST, ALP, total bilirubin, liver function tests (INR/coagulation factors, albumin, PT), performed at the central laboratory. Repeat testing and frequency of retesting should be determined at the discretion of the investigator.
- Detailed clinical information, such as related symptoms, risk factors, medical history, family history, including contributing conditions (e.g., viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, hypoxic/ischemic hepatopathy, hepatobiliary or pancreatic disorders, exposure to environmental chemical agents) should be gathered to seek a possible alternative aetiology of the observed laboratory test abnormalities.
- Evaluation of the need for imaging and other examinations and procedures such as liver biopsy, ultrasonography, computerised tomography (CT) scan, magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), echocardiography.
- History of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, special diets, recent events of food poisoning or excessive physical activity should also be evaluated.
- Referral to hepatologist/gastroenterologist should be considered.

10.6 Appendix 6: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

10.6.1 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.

10.6.2 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.
3. One technical complaint form must be completed for each onset.

Timelines for reporting technical complaints to Novo Nordisk

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

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

If the CRF 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 CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

Follow-up of technical complaints

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

Collection, storage and shipment of technical complaint samples

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

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

10.7 Appendix 7: 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, ADA, ISPAD,[80] type 1 diabetes outcomes program,[81] ATTD.[82] Severe hypoglycaemia as defined by Seaquist and ISPAD.		

Severe hypoglycaemia

Severe hypoglycaemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[83]

Nocturnal hypoglycaemia

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

Reporting of hypoglycaemic episodes

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

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

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

Upon onset of a hypoglycaemic episode the participant is recommended to measure PG every 15 minutes until the PG value is ≥3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines.[83]

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

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

Regarding the question: "To feel better, did you need help to get a sugary drink, food, or medicine?" the investigator must instruct the participants to answer "Yes", if the episode was an event that required assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.[83]

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

Diary review

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

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

1. If a hypoglycaemic episode form in the diary is not completed by the participant within 7 calendar days of the PG measurement, the episode should be described in the source documents and reported by the investigator on a hypoglycaemic episode (e)CRF with as much information as possible. If the participant did not need help to get a sugary drink, food, or medicine, Novo Nordisk will only ask for start date due to recall bias.[84, 85]

Re-training of participants

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

10.8 Appendix 8: Abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	aspartate aminotransferase
ATTD	Advanced Technologies & Treatments for Diabetes
BG	blood glucose
BMI	body mass index
BMR	basal metabolic rate
CDE	Certified Diabetes Educators
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	coronavirus disease-19
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTFG	clinical trial facilitation group
DFU	directions for use
DMC	Data Monitoring Committee
DPP4	dipeptidyl peptidase 4
DPS	data points set
DUN	dispensing unit number
[redacted]	[redacted]
EASD	European Association for the Study of Diabetes
eCRF	electronic case report form
FAS	full analysis set
FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
$HbA1_c$	glycated haemoglobin
HRT	hormone replacement therapy
IB	investigator's brochure

ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IHSG	The International Hypoglycaemia Study Group
IMP	investigational medicinal product
INR	international normalised ratio
IRB	Institutional Review Board
ISPAD	International Society for Pediatric and Adolescent Diabetes
KDIGO	Kidney Disease Improving Global Outcomes
LDL	low-density lipoprotein glucose
MAR	missing at random
MMRM	model for repeated measurements
NIMP	non-investigational medicinal product
OAD	oral antidiabetic drugs
PCD	primary completion date
PG	plasma glucose
PHQ	Patient Health Questionnaire
PRO	Patient Reported Outcome
RTSM	Randomisation Trial Supplies Management
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	safety analysis set
SGLT	sodium-glucose co-transporter
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TEE	total daily energy expenditure
TFDA	Taiwan Food and Drug Administration
TMM	Trial Materials Manual
UNL	upper normal limit
USA	United States of America
WHO	World Health Organisation
WOCBP	woman of childbearing potential

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