Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
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Protocol

Protocol Title: Effect and safety of semaglutide 7.2 mg once-weekly in participants with obesity

Substance name: semaglutide

Universal Trial Number: U1111-1274-4259

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Redacted protocol
Includes redaction of company confidential information only.

Study phase: 3b

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

Protocol amendment summary of change table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
Protocol Version 5.0	22 June 2023	Global
Protocol Version 4.0	20 January 2023	Global
Protocol version 3.0	28 September 2022	Global
Protocol version 2.0	30 June 2022	Global
Original protocol version 1.0	18 May 2022	Internal

Protocol version 5.0 (22 June 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.[1]

Overall rationale for preparing protocol, version 5.0

The primary reason for this protocol amendment was to include information about the new drug-device combination product, allowing for a single injection instead of 3 consecutive injections during the maintenance phase.

Section # and name	Description of change	Brief rationale
Throughout the document	Editorial changes e.g. spelling errors, punctuation or updates to more exact wording.	To improve readability.
[redacted]		
Section 2.3.1, Table 2-1	Removal of the potential risk of 'Neoplasms' (malignant and non-malignant) from Table 2-1	Risk removed in alignment with update of the investigator's brochure (DLP 31 May 2023).
Sections 4.1 and 8.1.2	The number of randomised participants in the MRI subgroup changed from approximately 210 to 50 participants	To adjust the number of participants in the MRI subgroup based on the enrolled number of participants
Table 6-1 and 6-2 and Sections 6.1 and 6.5	Update of the dosage and administration of, and transition to, the new drug-device combination product during the maintenance phase.	To update information about the introduction of the new drug-device combination product
[redacted]		

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1 Protocol summary

1.1 Synopsis

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

Rationale:

Semaglutide s.c. 2.4 mg once-weekly (Wegovy®) has been approved for weight management in adults with obesity or overweight and the presence of at least one weight-related comorbidity. Some individuals may not reach their goals in terms of weight loss and cardiovascular benefits on 2.4 mg and may benefit from a higher dose of semaglutide. Modelling of data suggest that this can be achieved with an increased dose of semaglutide without jeopardising the safety of the individuals (Section 4.3).

The present study is designed to evaluate the efficacy and safety of semaglutide s.c. 7.2 mg once-weekly versus placebo and semaglutide s.c. 2.4 mg once-weekly as an adjunct to reduced-calorie diet and increased physical activity in adults with obesity (BMI ≥ 30.0 kg/m^2).

Objectives, endpoints and estimand(s):

Table 1-1 Key objectives and endpoints

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to relative change in body weight after 72 weeks, in adults with obesity.	**Co-primary:**		
	Relative change in body weight	From baseline (week 0) to end of treatment (week 72)	%
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 5% after 72 weeks, in adults with obesity.	≥5% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant
Secondary	**Title**	**Time frame**	**Unit**
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 10% after 72 weeks, in adults with obesity.	**Confirmatory secondary:**		
	≥10% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 15% after 72 weeks, in adults with obesity.	≥15% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 20% after 72 weeks, in adults with obesity.	≥20% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant

Objectives	Endpoints		
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 25% after 72 weeks, in adults with obesity.	≥25% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to change in waist circumference after 72 weeks, in adults with obesity.	Change in waist circumference	From baseline (week 0) to end of treatment (week 72)	Cm
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus semaglutide s.c. 2.4 mg as an adjunct to a reduced-calorie diet and increased physical activity, with respect to relative change in body weight after 72 weeks, in adults with obesity.	Relative change in body weight	From baseline (week 0) to end of treatment (week 72)	%
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus semaglutide s.c. 2.4 mg as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 20% after 72 weeks, in adults with obesity.	≥20% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus semaglutide s.c. 2.4 mg as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 25% after 72 weeks, in adults with obesity.	≥25% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant
Supportive secondary			
To compare the safety and tolerability of semaglutide s.c. 7.2 mg versus placebo, as an adjunct to reduced-calorie diet and increased physical activity in adults with obesity, after 81 weeks.	Safety parameters		
	Number of Adverse Events (AEs)	From baseline (week 0) to end of study (week 81)	Count of events
	Number of Serious Adverse Events (SAEs)	From baseline (week 0) to end of study (week 81)	Count of events
To compare the safety of semaglutide s.c. 7.2 mg versus placebo, as an adjunct to reduced-calorie diet and increased physical activity, with respect to pulse after 72 weeks, in adults with obesity.	Change in pulse	From baseline (week 0) to end of treatment (week 72)	Bpm
To compare the safety and tolerability of semaglutide s.c. 7.2 mg versus semaglutide s.c. 2.4 mg, as an adjunct to reduced-calorie diet and increased physical activity in adults with obesity, after 81 weeks.	Number of Adverse Events (AEs)	From baseline (week 0) to end of study (week 81)	Count of events
	Number of Serious Adverse Events (SAEs)	From baseline (week 0) to end of study (week 81)	Count of events
Abbreviations: AEs = adverse events; SAEs = serious adverse events; s.c. = subcutaneous.			

Co-primary estimands

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 obesity (defined as BMI ≥ 30 kg/m^2), with or without weight-related comorbidities.
- **Endpoint:** 1) relative change from baseline to week 72 in body weight and 2) ≥ 5% body weight reduction (yes/no) at week 72.
- **Treatment condition:** Semaglutide s.c. 7.2 mg once-weekly versus placebo regardless of discontinuation or dose reduction of randomised treatment, and regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery).
- **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 for both the confirmatory secondary and supportive secondary objectives are similar to the co-primary estimands except for the endpoint attribute and/or comparator.

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 obesity (defined as BMI ≥ 30 kg/m^2), with or without weight-related comorbidities.
- **Endpoint:** 1) relative change from baseline to week 72 in body weight and 2) ≥ 5% body weight reduction at week 72.
- **Treatment condition:** Semaglutide s.c. 7.2 mg once-weekly versus placebo both as an adjunct to a reduced-calorie 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, as well as safety endpoints, in the population.

Overall design:

The study consists of:

- a 1-week screening period
- a 20-week dose escalation period
- a 52-week maintenance period
- a 9-week follow-up period

Study intervention groups and duration:

Following a screening period of up to 1 week, the participants will be randomised 5:1:1 at the randomisation visit to semaglutide s.c. 7.2 mg once-weekly, semaglutide s.c. 2.4 mg once-weekly or placebo once-weekly as an adjunct to reduced-calorie diet and increased physical activity.

The maximum duration of the study intervention for each participant is 72 weeks and the duration of the study for each participant is 81 weeks.

The following trial products will be supplied by Novo Nordisk A/S:

- Semaglutide [redacted] mg/mL, solution for injection, DV3396 [redacted] mL single-dose pen-injector
- Semaglutide [redacted] mg/mL, solution for injection, DV3396 [redacted] mL single-dose pen-injector
- Semaglutide [redacted] mg/mL, solution for injection, DV3396 [redacted] mL single-dose pen-injector
- Semaglutide [redacted] mg/mL, solution for injection, DV3396 [redacted] mL single-dose pen-injector
- Semaglutide [redacted] mg/mL, solution for injection, DV3396 [redacted] mL single-dose pen-injector
- Semaglutide [redacted] mg/mL, solution for injection, DV3396 [redacted] mL single-dose pen-injector*
- Semaglutide placebo Ia, solution for injection, [redacted] mL single-dose pen-injector
- Semaglutide placebo Ib, solution for injection, [redacted] mL single-dose pen-injector

*The new drug-device combination product, which can administer 7.2 mg of the IMPs in a single s.c. injection will be introduced to all participants during the maintenance phase.

Number of participants:

Approximately 1610 participants will be screened to achieve 1400 participants randomly assigned to study intervention in a 5:1:1 ratio.

Participant characteristics:

The participants will be adult males and females who meet the following key inclusion criteria and none of the following key exclusion criteria:

Key inclusion criteria

- Male or female.
- Age above or equal to 18 years at the time of signing informed consent.
- BMI $\geq$ 30.0 kg/m^2.
- History of at least one self-reported unsuccessful dietary effort to lose body weight.

Key exclusion criteria

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

- History of type 1 or type 2 diabetes.
- Treatment with glucose-lowering agent(s) within 90 days before screening.
- A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records.
- Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.

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

Data monitoring committee: No

1.2 Flowchart

Procedures	Protocol section	Screening	Randomisation	Dose escalation period						Maintenance period												End of treatment[a]	End of study
Visit		V1	V2	V3	V4	V5	V6	V7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	V23
Timing of Visit (Weeks)		-1	0	2	4	8	12	16	20	21	24	28	32	36	40	44	48	52	56	60	64	68	72	81
Visit Window (Days)		-7	0	±3	±3	±3	±3	±3	±3	-4[b]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
SUBJECT RELATED INFORMATION AND ASSESSMENTS																								
Informed Consent and Demography[c]	10.1.3	X																						
Medical History/Concomitant Illness	8.2.1	X																					X	
Weight History	8.2.1	X																						
Eligibility Criteria	5.1 and 5.2	X	X																					
Risk Factors	8.2.1	X																						
Randomisation	6.3		X																					
Childbearing potential[d]	10.4	X																						
Discontinuation Criteria	7.1.1			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test[e]	8.2.7	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X	X
Contraceptive Counselling	8.2.7	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X	
Concomitant medication	6.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Surgery Procedures Form	8.2.8			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation of glycaemic status	8		X								X												X	
Evaluation of Antihypertensive Treatment	8										X												X	
Evaluation of Lipid-lowering Treatment	8										X												X	

Procedures	Protocol section	Screening	Randomisation	Dose escalation period						Maintenance period												End of treatment[a]	End of study
Visit		V1	V2	V3	V4	V5	V6	V7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	V23
Timing of Visit (Weeks)		-1	0	2	4	8	12	16	20	21	24	28	32	36	40	44	48	52	56	60	64	68	72	81
Visit Window (Days)		-7	0	±3	±3	±3	±3	±3	±3	-4[b]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
EFFICACY																								
Body measurements	8.1.1	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X	X
HbA1c	10.2	X	X						X		X		X						X				X	
High sensitive C-reactive Protein (hsCRP)	10.2		X						X		X												X	
MR scan[f]	8.1.2		X																				X	
Fasting plasma glucose	10.2		X				X		X		X		X						X				X	
Fasting serum insulin	10.2		X						X		X		X						X				X	
Lipids	10.2		X						X		X												X	
PK Sampling	8.4.1				X		X		X		X		X		X		X		X		X		X	X
SAFETY																								
Physical Examination	8.2.3	X																					X	
Vital Signs	8.2.4	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X	X
ECG	8.2.5	X									X												X	
Adverse Event	8.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Breast Neoplasms Follow-up	8.2																						X	X
Colon Neoplasm Follow-up	8.2																						X	X
Haematology	10.2		X						X		X						X						X	
Biochemistry	10.2	X	X						X		X						X						X	

Procedures	Protocol section	Screening	Randomisation	Dose escalation period						Maintenance period													End of treatment[a]	End of study
Visit		V1	V2	V3	V4	V5	V6	V7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	V23
Timing of Visit (Weeks)		-1	0	2	4	8	12	16	20	21	24	28	32	36	40	44	48	52	56	60	64	68	72	81
Visit Window (Days)		-7	0	±3	±3	±3	±3	±3	±3	-4[b]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
Attend Visit Fasting	5.3.1		X			X	X		X		X		X				X		X				X	X
Technical Complaint	8.3.7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Requiring Additional Data	8.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication Error, Misuse and Abuse	8.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]																								
Anti semaglutide antibodies	8.7		X		X		X		X		X				X				X				X	X
OTHER ASSESSMENTS																								
[redacted]																								
Clinical Outcome Assessments	8.1.5 and 8.2.2	X	X						X		X				X				X				X	X
C-SSRS Baseline		X																						
C-SSRS Since Last Visit									X		X				X				X				X	
Patient Health Questionnaire - 9		X							X		X				X				X				X	
[redacted]																								
[redacted]																								
TRIAL MATERIAL																								
Drug Dispensing	6.2		X		X	X	X	X	X		X		X		X		X		X		X			
Administration of Trial Product	6.5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Procedures	Protocol section	Screening	Randomisation	Dose escalation period						Maintenance period												End of treatment[a]	End of study
Visit		V1	V2	V3	V4	V5	V6	V7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	V23
Timing of Visit (Weeks)		-1	0	2	4	8	12	16	20	21	24	28	32	36	40	44	48	52	56	60	64	68	72	81
Visit Window (Days)		-7	0	±3	±3	±3	±3	±3	±3	-4[b]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
REMINDERS																								
Barriers and motivation interview	8	X																						
Hand out ID card	8	X																						
Hand out direction for use	6.1		X																					
Hand out dose reminder card	6.5		X		X	X	X	X	X		X		X		X		X		X		X			
Hand out and instruct in PK diary	8			X		X		X	X		X		X		X		X		X		X			
Training in trial product, pen-handling	6.1		X	X	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	X	X	X	X	X	X	
Collect, review and transcribe diaries	8				X		X		X		X		X		X		X		X		X		X	X
HIDDEN																								
IWRS/RTSM	6.2	X	X		X	X	X	X	X		X		X		X		X		X		X		X	
End of Study	4.4																							X
End of Treatment	6.1																						X	

[a]End of treatment includes both end of IMP treatment and end of lifestyle intervention. [b]Participants shall be called 3 days after administration of the first 7.2 mg dose. If this day falls on a weekend or bank holiday, the call shall be made on the first coming weekday. [c]Demography consists of date of birth, sex, ethnicity, and race (according to local regulation). Race and ethnicity must be self-reported by the participant. [d]For all female participants. [e]Only in women of childbearing potential. [f]MRI is performed in a subset of participants.

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; [redacted]; ECG = electrocardiogram; HbA1c = glycated haemoglobin; [redacted]; ID = identification; IWRS = interactive web response system; MR = magnetic resonance; [redacted] PK = pharmacokinetics; RTSM = randomisation and trial supplies management system; [redacted]

2 Introduction

2.1 Study rationale

The prevalence of obesity has reached epidemic proportions in most countries around the world and the prevalence is still increasing at an alarming rate.[2-8] The medical and societal impacts are considerable and obesity is one of the most significant public health challenges worldwide.[2-8] Obesity is associated with increased risk of a variety of comorbidities including hyperglycaemia, type 2 diabetes (T2D), hypertension, dyslipidaemia, obstructive sleep apnoea, atherosclerosis, osteoarthritis, urinary incontinence, non-alcoholic steatohepatitis, cardiovascular disease, certain types of cancer, and risk of early death.[9-23] Moreover, obesity adversely affects physical and mental health and reduces health related quality of life.[24, 25] Obesity is also associated with decreased cardiorespiratory fitness, which also increases the risk of cardiovascular diseases and all-cause mortality.[26]

The risk of obesity-related complications increases with increasing BMI, and a weight loss of 5-10 % has significant health benefits in terms of slowing progression of T2D.[27-30] Furthermore, a weight loss of up to 15% improves many other obesity related complications as well as physical symptoms and quality of life.[31-39] Finally, studies suggest a beneficial impact of weight loss on cardiovascular risk and mortality in both people with diabetes and obesity.[40-42] Pharmacotherapy providing high weight loss results will allow a higher proportion of people to achieve these benefits.

Lifestyle interventions in the form of diet and exercise is first line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss.[43-52] Surgical treatments offer an effective alternative for some people with severe obesity, but surgery carries a risk in connection with the procedure and is not without complications. Furthermore, surgery requires close follow-up of the individual which can be cumbersome and costly.[43-48, 53, 54] Pharmacotherapy may therefore serve as a valuable adjunct to lifestyle intervention for individuals with obesity in order to achieve and sustain a clinically relevant weight loss, to improve obesity related complications and to facilitate a healthier lifestyle. Few anti-obesity medications are currently available and there is a need for more safe and effective therapeutic options for treatment of obesity, especially treatments that also target weight maintenance, prevention, and treatment of complications.[43-47, 55, 56]

The glucagon-like peptide-1 receptor agonist (GLP-1 RA) drug class is associated with multiple benefits; they have a well-documented safety profile, reduce body weight, improve blood pressure, lipid profile and other cardiovascular risk factors as well as glucose metabolism. Semaglutide is one of these GLP-1 RAs.

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

as high blood pressure, T2D, or high cholesterol). Modelling of data based on exposure levels of what is to be expected suggest that a dose of 7.2 mg semaglutide could be an effective treatment option without jeopardising the safety of the individuals (Section 4.3).

The present study is designed to evaluate the efficacy and safety of semaglutide s.c. 7.2 mg once-weekly versus placebo and semaglutide s.c. 2.4 mg once-weekly as an adjunct to reduced-calorie diet and increased physical activity in adults with obesity (BMI ≥ 30.0 kg/m^2).

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®) and in lower doses for treatment of T2D in adults (Ozempic®). Semaglutide has a half-life of approximately 160 hours, making it suitable for once-weekly dosing.[57]

GLP-1 is a physiological regulator of appetite and postprandial GLP-1 response is present in several areas of the brain involved in appetite regulation.[58] In line with this, clinical and non-clinical data indicate that the body weight-reducing effect of semaglutide is mainly mediated by a reduced energy intake.[59-65]

[redacted]

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)[66] and any updates hereof.

2.2.2 Study population

The study population will consist of participants with obesity (BMI ≥ 30.0 kg/m^2). These participants represent a clinically relevant population for pharmacotherapeutic weight management as they are at significant risk of weight-related comorbidities and mortality, and are likely to benefit from weight reduction. Information about weight-related comorbidities, including hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease, will be collected systematically at screening by the investigator as part of the medical history.

First line treatment in weight management should 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 guidelines.[67, 68]

2.3 Benefit-risk assessment

The main benefits and risks related to participation in the study are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of semaglutide may be found in the IB[66] and any updates hereof. The risks are based on findings in non-clinical studies and clinical trials with semaglutide (both s.c. and oral) as well as other GLP-1 RAs. For each of these risks, mitigating actions have been implemented to minimise the risks for participants enrolled in this trial.

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		
Identified risks		
Gastrointestinal adverse events	Consistent with findings with other GLP-1 RAs, the most frequently reported AEs in clinical studies with semaglutide were gastrointestinal (GI) AEs (such as nausea, vomiting and diarrhoea). 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 participants with impaired renal function as it may cause a deterioration of renal function.	Clinical studies have shown that a low starting dose and gradual dose escalation mitigates the risk of developing GI symptoms. 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. Adults with renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR <15 mL/min/1.73 m^2 will not be enrolled in the study (see Section 5.2).
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.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 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 (see 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.
Potential risks		
Medullary thyroid cancer (*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[69], 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 clinical studies with semaglutide (see Section 5.2).
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 a history of malignant neoplasms within the past 5 years prior to screening will be excluded from the study (see Section 5.2).
Allergic reactions	As is the case with all protein-based pharmaceuticals, treatment 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.
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.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Discomfort related to multiple consecutive injections	Administration of the 7.2 mg semaglutide/semaglutide placebo maintenance dose requires 3 consecutive injections (3 x 2.4 mg, 2.4 mg + 2 x placebo, or 3 x placebo) which may be associated with slight discomfort.	The participants will be recommended to rotate injection site with each consecutive injection. The 2nd and 3rd injection should be administered immediately after the 1st injection using a different site of injection, either within the same or a new body region, but at least 5 cm from the first injection site. Injections may be administered in the thigh, abdomen, or upper arm. (see Section 6.5).
Risk of COVID-19 infection in relation to study participation	Participants may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country at the time of study conduct.	The risk of COVID-19 transmission in relation to site visits is overall considered to be low, however this may vary between geographical area. To minimize the risk as much as possible, local guidelines must be followed.
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 Appendix 8 (Section 10.8).
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. 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.	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, Table 10-4). 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.

Risk assessment has been conducted for DV3396 single-dose pen-injector for semaglutide and placebo in accordance with ISO 14971:2019. A general device risk assessment has been performed to ensure safe and accurate handling and dosing of semaglutide and placebo when using DV3396 in participants with obesity.

In addition to the general device risk assessment, all new identified risks associated with using DV3396 for semaglutide and placebo according to the clinical procedures specified in this protocol have been reduced as far as possible and are acceptable, based on the current state of the art. The use of DV3396 for semaglutide and placebo in this study it therefore considered to be of non-significant risk.

2.3.2 Benefit assessment

Participants will be treated with a regimen anticipated to be better than or equal to the weight management they receive at the time of entry into the study. The phase 3a programme has demonstrated clinically significant weight loss with semaglutide s.c. 2.4 mg once-weekly and a safe and well-tolerated profile, consistent with previous findings. Semaglutide s.c. 7.2 mg once-weekly is expected to provide substantial weight loss benefits without jeopardising the safety of the participants (Section 4.3).

In addition, it is expected that all participants will benefit from participation through close contact with the study site and counselling by a dietician or a similar qualified healthcare professional, all of which will most 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 (7.2 mg or 2.4 mg) 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 of participation in the study.

The potential risks identified in association with participation in the present study 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[66] and any updates hereof.

3 Objectives, endpoints and estimands

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to relative change in body weight after 72 weeks, in adults with obesity.	**Co-primary:**		
	Relative change in body weight	From baseline (week 0) to end of treatment (week 72)	%
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 5% after 72 weeks, in adults with obesity.	≥5% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant
Secondary	**Title**	**Time frame**	**Unit**
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 10% after 72 weeks, in adults with obesity.	**Confirmatory secondary:**		
	≥10% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 15% after 72 weeks, in adults with obesity.	≥15% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 20% after 72 weeks, in adults with obesity.	≥20% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 25% after 72 weeks, in adults with obesity.	≥25% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo as an adjunct to a reduced calorie diet and increased physical activity, with respect to change in waist circumference after 72 weeks, in adults with obesity.	Change in waist circumference	From baseline (week 0) to end of treatment (week 72)	cm

Objectives	**Endpoints**		
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus semaglutide s.c. 2.4 mg as an adjunct to a reduced-calorie diet and increased physical activity, with respect to relative change in body weight after 72 weeks, in adults with obesity.	Relative change in body weight	From baseline (week 0) to end of treatment (week 72)	%
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus semaglutide s.c. 2.4 mg as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 20% after 72 weeks, in adults with obesity.	≥20% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant
To demonstrate the superiority of semaglutide s.c. 7.2 mg once-weekly versus semaglutide s.c. 2.4 mg as an adjunct to a reduced-calorie diet and increased physical activity, with respect to achieving body weight reduction ≥ 25% after 72 weeks, in adults with obesity.	≥25% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 72)	Count of participant
Supportive secondary:			
To compare the efficacy of semaglutide s.c. 7.2 mg once-weekly versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity in adults with obesity, on other factors related to body weight after 72 weeks.	***Body weight parameters***		
	Change in body weight	From baseline (week 0) to end of treatment (week 72)	kg
	Change in BMI	From baseline (week 0) to end of treatment (week 72)	kg/m^2
To compare the efficacy of semaglutide s.c. 7.2 mg once-weekly versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity in adults with obesity, on body composition after 72 weeks (for the MRI subgroup).	Change in total fat mass	From baseline (week 0) to end of treatment (week 72)	%, L
	Change in lean body mass	From baseline (week 0) to end of treatment (week 72)	%, L
	Change in visceral fat mass	From baseline (week 0) to end of treatment (week 72)	%, L
To compare the efficacy of semaglutide s.c. 7.2 mg once-weekly versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity in adults with obesity, on cardiovascular risk factors after 72 weeks.	***Cardiovascular parameters***		
	Change in systolic blood pressure	From baseline (week 0) to end of treatment (week 72)	mmHg
	Change in diastolic blood pressure	From baseline (week 0) to end of treatment (week 72)	mmHg
	Change in total cholesterol	From baseline (week 0) to end of treatment (week 72)	Ratio to baseline
	Change in high-density lipoprotein (HDL) cholesterol	From baseline (week 0) to end of treatment (week 72)	Ratio to baseline
	Change in low-density lipoprotein (LDL) cholesterol	From baseline (week 0) to end of treatment (week 72)	Ratio to baseline
	Change in very low-density lipoprotein (VLDL) cholesterol	From baseline (week 0) to end of treatment (week 72)	Ratio to baseline
	Change in triglycerides	From baseline (week 0) to end of treatment (week 72)	Ratio to baseline

Objectives	Endpoints		
	Change in free fatty acids	From baseline (week 0) to end of treatment (week 72)	Ratio to baseline
	Change in high-sensitivity c-reactive protein (hsCRP)	From baseline (week 0) to end of treatment (week 72)	Ratio to baseline
	Change in lipid-lowering treatment (decrease, no change, increase)	From baseline (week 0) to end of treatment (week 72)	Count of participant
	Change in antihypertensive treatment (decrease, no change, increase)	From baseline (week 0) to end of treatment (week 72)	Count of participant
To compare the efficacy of semaglutide s.c. 7.2 mg once-weekly versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity in adults with obesity, on glucose metabolism after 72 weeks.	***Glucose metabolism parameters***		
	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 72)	%
	Change in fasting plasma glucose	From baseline (week 0) to end of treatment (week 72)	mg/dL
	Change in fasting serum insulin	From baseline (week 0) to end of treatment (week 72)	Ratio to baseline
	Change in glycaemic category (Normo-glycaemia, pre-diabetes, T2D)	From baseline (week 0) to end of treatment (week 72)	Count of participant
To compare the safety and tolerability of semaglutide s.c. 7.2 mg versus placebo, as an adjunct to reduced-calorie diet and increased physical activity in adults with obesity, after 81 weeks.	***Safety parameters***		
	Number of Adverse Events (AEs)	From baseline (week 0) to end of study (week 81)	Count of events
	Number of Serious Adverse Events (SAEs)	From baseline (week 0) to end of study (week 81)	Count of events
To compare the safety of semaglutide s.c. 7.2 mg versus placebo, as an adjunct to reduced-calorie diet and increased physical activity, with respect to pulse after 72 weeks, in adults with obesity.	Change in pulse	From baseline (week 0) to end of treatment (week 72)	bpm
To compare the safety and tolerability of semaglutide s.c. 7.2 mg versus semaglutide s.c. 2.4 mg, as an adjunct to reduced-calorie diet and increased physical activity in adults with obesity, after 81 weeks.	Number of Adverse Events (AEs)	From baseline (week 0) to end of study (week 81)	Count of events
	Number of Serious Adverse Events (SAEs)	From baseline (week 0) to end of study (week 81)	Count of events
Exploratory	**Title**	**Time frame**	**Unit**
[redacted]			

Objectives	Endpoints
[redacted]	

Abbreviations: AEs = adverse events; BMI = body mass index; [redacted]; HbA_{1c} = glycated haemoglobin; HDL = high-density lipoprotein; hsCRP = high-sensitivity c-reactive protein; LDL = low-density lipoprotein; MRI = magnetic resonance imaging; SAEs = serious adverse events; s.c. = subcutaneous; T2D = type 2 diabetes; [redacted]; VLDL = very low-density lipoprotein.

Co-primary estimands

The primary clinical question of interest is: What is the treatment effect of semaglutide s.c. 7.2 mg once-weekly versus placebo, as an adjunct to reduced-calorie diet and increased physical activity in adults with obesity, measured by relative change from baseline (week 0) to week 72 in body weight and ≥ 5% body weight reduction at week 72, regardless of discontinuation or dose reduction of randomised trial 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 obesity (defined as BMI ≥ 30.0 kg/m^2), with or without weight-related comorbidities.
- **Endpoint:** 1) relative change from baseline to week 72 in body weight and 2) ≥ 5% body weight reduction (yes/no) at week 72.
- **Treatment condition:** Semaglutide s.c. 7.2 mg once-weekly versus placebo regardless of discontinuation or dose reduction of randomised treatment, and regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery).
- **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 for both the confirmatory secondary and supportive secondary objectives related to efficacy are similar to the co-primary estimands except for the endpoint attribute and/or comparator. The secondary estimands with continuous endpoints for secondary objectives are similar to the co-primary estimand 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 ≥ 5% body weight reduction.

Additional estimands

An additional clinical question of interest for the primary objective is: What is the treatment effect of semaglutide s.c. 7.2 mg once-weekly versus placebo, as an adjunct to reduced-calorie diet and increased physical activity in adults with obesity, measured by relative change from baseline (week 0) to week 72 in body weight and ≥ 5% body weight reduction at week 72, had they remained on their randomised trial product 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 obesity (defined as BMI ≥ 30 kg/m^2), with or without weight-related comorbidities.
- **Endpoint:** 1) relative change from baseline to week 72 in body weight and 2) ≥ 5% body weight reduction at week 72.
- **Treatment condition:** Semaglutide s.c. 7.2 mg once-weekly versus placebo both as an adjunct to a reduced-calorie 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 trial product discontinuation.

A similar additional estimand also applies to all confirmatory and supportive secondary objectives in the population.

4 Study design

4.1 Overall design

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

Approximately 1400 participants will be randomised 5:1:1 to receive either semaglutide s.c. 7.2 mg, semaglutide s.c. 2.4 mg or placebo once-weekly, as an adjunct to reduced-calorie diet and increased physical activity. The study population consists of adults with obesity.

A sub-population of approximately 50 randomised participants will have their body composition assessed by MRI at the beginning and at the end of the treatment to investigate the degree to which weight loss is caused by reduction in fat mass, in accordance with the EMA and FDA guidelines.[67, 68]

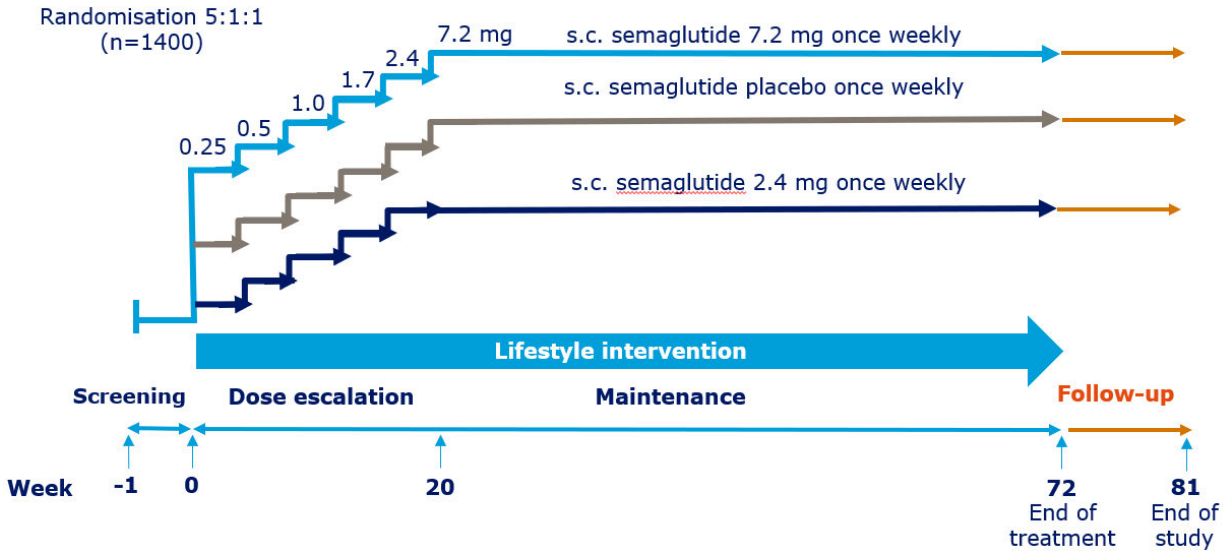
The study consists of:

- a 1-week screening period
- a 20-week dose escalation period
- a 52-week maintenance period
- a 9-week follow-up period

The duration of the study intervention (trial product and lifestyle intervention) is 72 weeks followed by a 9-week follow-up period without study interventions (Figure 4-1).

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

Figure 4-1 Study design



Note: 'end of study intervention' (week 72) corresponds to both end of IMP treatment and end of lifestyle intervention.

4.2 Scientific rationale for study design

A 72-week treatment duration (20 week of dose escalation and 52 weeks on maintenance dose) is considered sufficient to assess weight loss, safety and tolerability of semaglutide s.c. 7.2 mg versus

semaglutide s.c. 2.4 mg once-weekly and placebo in accordance with regulatory guidelines.[67, 68] The 9 weeks follow-up period is included to account for the exposure and long half-life of semaglutide.

A randomised, double-blind, placebo-controlled, multi-national, multi-centre, three-armed, parallel trial design is chosen to minimise bias in the assessment of the efficacy and safety of semaglutide s.c. 7.2 mg once-weekly versus semaglutide s.c. 2.4 mg once-weekly and placebo, as an adjunct to reduced-calorie diet and increased physical activity.

The study population is chosen in accordance with regulatory guidelines[67, 68] to consist of adults with BMI $\geq$ 30.0 kg/m^2 with or without weight-related comorbidities.

4.3 Justification for dose

In the phase 2 dose-finding trial (NN9536-4153), 5 once-daily doses of semaglutide were explored. Study results showed a monotone dose-response relation within the investigated dose interval from 0.05 to 0.4 mg once-daily with a steadily increasing effect with increasing dose. Hence, from the dose-finding study the effect of semaglutide did not seem to plateau within the investigated dose interval from 0.05 to 0.4 mg once-daily, indicating the effect on weight change of semaglutide might not yet have reached a saturation point at the highest investigated dose level. Exposure-response relationships have characterised the relative weight loss from baseline to week 52, following administration of once-daily s.c. semaglutide doses. This analysis supported the selection of 2.4 mg once-weekly semaglutide for phase 3 development in weight management.

The phase 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 was anticipated to ease the burden of drug administration in clinical practice.

To fully utilize data from the semaglutide weight management development programme (NN9536-4153 and STEP), a *post-hoc* longitudinal exposure-response analysis was undertaken, developing a model that is suited for simulation of the time-course weight loss across different dose regimens and time points. The simulations show that substantial weight loss benefits may be realised with the 7.2 mg once-weekly.

The predicted exposure range following s.c. 7.2 mg semaglutide is within the exposure range observed for the once-daily oral dose of [redacted] mg in the clinical pharmacology study [redacted]. The safety and tolerability profile of the participants in study [redacted] with exposure levels within the predicted exposure range of 7.2 mg was in line with the expected safety profile of semaglutide and did not indicate any unexpected safety findings. Thus, an increase of dose to 7.2 mg is expected to be possible without jeopardising the safety of the participants.

Safety of semaglutide s.c. 7.2 mg once-weekly versus semaglutide s.c. 2.4 mg will be evaluated in this study to support bridging of the safety profile to previous studies.

A low starting dose and fixed-dose escalation regimen is expected to mitigate the risk of developing gastrointestinal (GI) 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 increases the dose every 4 weeks (to 0.5, 1.0, 1.7, 2.4 mg/week). After 20 weeks participants will start on their respective maintenance doses of 7.2 mg/week, 2.4 mg/week or placebo. To increase GI tolerability, dose level reductions and extensions of dose-escalation periods will be allowed based on clinical evaluation made by the investigator.

Please refer to Section 6.1 for more details on trial product doses and Section 6.5 for dose modification and mitigation of GI symptoms.

4.4 End of study definition

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

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

The primary endpoint is evaluated at visit 22 (week 72). The primary completion date (PCD) is defined as the date of visit 22 (week 72) on which the last participant in the clinical study has an assessment for the primary endpoint. If the last participant is withdrawn early, the PCD is considered the date when the last participant would have completed visit 22.

5 Study population

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

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

5.1 Inclusion criteria

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

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Male or female.
3. Age above or equal to 18 years at the time of signing informed consent.
4. Body mass index (BMI)[a] ≥ 30.0 kg/m^2.
5. History of at least one self-reported unsuccessful dietary effort to lose body weight.

[a]BMI as calculated in the eCRF at screening (Section 8.1.1)

MRI sub-population

To be qualified for the MRI sub-population, the following criteria must be answered "yes". Participants who do not fulfil the below criteria can be randomised in the study outside the MRI sub-group.

1. Body weight < 149.0 kg at screening.
2. No metal implants e.g., pacemaker, intracranial clips, cochlear implant, infusion pump or neurostimulators
3. Suitable for MRI as per Investigator's discretion e.g., no claustrophobia.

All inclusion criteria will be assessed at the investigator's discretion unless otherwise stated. For country specific requirements, see Section 10.10.

5.2 Exclusion criteria

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

1. Known or suspected hypersensitivity to study intervention(s) or related products.
2. Previous participation in this study. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using highly effective contraceptive method, as defined in Appendix 4 (Section 10.4).
4. Participation (i.e., signed informed consent) in any interventional, clinical study within 90 days before screening.
5. HbA1c ≥ 48 mmol/mol (6.5%) as measured by the central laboratory at screening.
6. History of type 1 or type 2 diabetes.[a]
7. Treatment with glucose-lowering agent(s) within 90 days before screening.
8. Treatment with GLP-1 receptor agonist within 180 days prior to screening.

9. A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records.
10. Treatment with any medication for the indication of obesity within 90 days before screening.
11. Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following are allowed: 1) liposuction and/or abdominoplasty, if performed > 1 year before screening, 2) lap banding, if the band has been removed > 1 year before screening, 3) intragastric balloon, if the balloon has been removed > 1 year before screening, or 4) duodenal-jejunal bypass sleeve, if the sleeve has been removed > 1 year before screening.
12. Uncontrolled thyroid disease per investigator's discretion.
13. Active or unstable depression or other active or unstable psychiatric conditions[a] which in the investigator's opinion can jeopardize participant's safety or compliance with the protocol.
14. A Patient Health Questionaire-9 (PHQ-9) score of ≥ 15 at screening.
15. A lifetime history of suicidal attempt.[a]
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 30 days before screening.
18. Presence of acute pancreatitis within 180 days before screening.[a]
19. History or presence of chronic pancreatitis.[a]
20. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.[a]
21. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR < 15 mL/min/1.73 m^2 as defined by KDIGO 2012[70] by the central laboratory at screening.
22. Presence or history[a] of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in situ prostate cancer) within 5 years prior to the day of screenings.
23. Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina or transient ischaemic attack within 60 days before screening.
24. Participants presently classified as being in New York Heart Association (NYHA) class IV.
25. Surgery scheduled for the duration of the trial, expect for minor surgical procedures, in the opinion of the investigator.
26. Known or suspected abuse of alcohol or recreational drugs.
27. Other participant(s) from the same household participating in any semaglutide trial.
28. Any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the participant's safety or compliance with the protocol.

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

The criteria will be assessed at the investigator's discretion unless otherwise stated.

For country specific requirements, see Section 10.10.

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 no food or liquids, except for water, at least 8 hours overnight before the visit. Participants should be encouraged to stop drinking water 2 hours before the time they are scheduled to arrive for the visit. Trial 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 fasting plasma glucose (FPG), fasting serum insulin, lipids, [redacted].

[redacted]

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 must be made in the system (randomisation and trial suppliers management system [RTSM]/interactive web response system [IWRS]).

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

5.5 Run-in criteria and randomisation criteria and 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.

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

6.1 Study intervention(s) administered

Table 6-1 and Table 6-2 provides an overview of the study interventions. Participants will be transitioned to the single injection administration using the new drug-device combination product, during their next planned site visit from when the new drug-device combination product is available on site.

Table 6-1 Study interventions

Intervention/Arm name	Semaglutide 7.2 mg	Semaglutide 2.4 mg	Placebo	Any other interventions
Intervention name	Semaglutide [redacted] mg/mL DV3396 or Semaglutide [redacted] mg/mL DV3396	Semaglutide [redacted] mg/mL DV3396	Placebo	Diet and physical activity counselling
Intervention type	IMP	IMP	IMP, reference therapy	Background intervention
Pharmaceutical form	Solution for injection	Solution for injection	Solution for injection	
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous	
Trial product strength	See Table 6-2 for details	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	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. Injection(s) 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.	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.	Manufactured and supplied by Novo Nordisk A/S.	

Intervention/Arm name	Semaglutide 7.2 mg	Semaglutide 2.4 mg	Placebo	Any other interventions
Packaging and labelling	• Labelled and packaged by Novo Nordisk A/S. • Labelled in accordance with Annex 13,[71] local regulations and study requirements. • IMP is provided in a DV3396 single-dose pen-injector) (see Table 6-2).	• Labelled and packaged by Novo Nordisk A/S. • Labelled in accordance with Annex 13,[71] local regulations and study requirements. • IMP is provided in a DV3396 single-dose pen-injector (device constituent of approved drug-device combination product) (see Table 6-2).	• Labelled and packaged by Novo Nordisk A/S. • Labelled in accordance with Annex 13,[71] local regulations and study requirements. • IMP is provided in a DV3396 single-dose pen-injector (see Table 6-2).	
Abbreviations: IMP = investigational medicinal product.				

The investigator must document that directions for use was given to the participant verbally and in writing as a directions for use (DFU) document at the first dispensing visit (as specified in the flowchart).

Investigational medicinal products (IMP)

All trial products listed in Table 6-2 are considered IMPs.

See Section 6.5 for details on dose escalation, dose adjustment and missed doses.

Table 6-2 Investigational medicinal products

Arm	Trial product name	Dose	Delivery device	Injection volume	Duration
Dose escalation period					
Sema 7.2	Semaglutide [redacted] mg/mL DV3396	0.25 mg	[redacted] mL single-dose pen-injector	[redacted] mL	4 weeks
Sema 2.4	Semaglutide [redacted] mg/mL DV3396	0.25 mg	[redacted] mL single-dose pen-injector		
Placebo	Semaglutide placebo Ia[a]	N/A	[redacted] mL single-dose pen-injector		
Sema 7.2	Semaglutide [redacted] mg/mL DV3396	0.5 mg	[redacted] mL single-dose pen-injector	[redacted] mL	4 weeks
Sema 2.4	Semaglutide [redacted] mg/mL DV3396	0.5 mg	[redacted] mL single-dose pen-injector		
Placebo	Semaglutide placebo Ia[a]	N/A	[redacted] mL single-dose pen-injector		
Sema 7.2	Semaglutide [redacted] mg/mL DV3396	1.0 mg	[redacted] mL single-dose pen-injector	[redacted] mL	4 weeks
Sema 2.4	Semaglutide [redacted] mg/mL DV3396	1.0 mg	[redacted] mL single-dose pen-injector		
Placebo	Semaglutide placebo Ia[a]	N/A	[redacted] mL single-dose pen-injector		
Sema 7.2	Semaglutide [redacted] mg/mL DV3396	1.7 mg	[redacted] mL single-dose pen-injector	[redacted] mL	4 weeks
Sema 2.4	Semaglutide [redacted] mg/mL DV3396	1.7 mg	[redacted] mL single-dose pen-injector		
Placebo	Semaglutide placebo Ib[a]	N/A	[redacted] mL single-dose pen-injector		
Sema 7.2	Semaglutide [redacted] mg/mL DV3396	2.4 mg	[redacted] mL single-dose pen-injector	[redacted] mL	4 weeks
Sema 2.4	Semaglutide [redacted] mg/mL DV3396	2.4 mg	[redacted] mL single-dose pen-injector		
Placebo	Semaglutide placebo Ib[a]	N/A	[redacted] mL single-dose pen-injector		
Maintenance period[b]					
Before transition to single pen					
Sema 7.2	Semaglutide [redacted] mg/mL DV3396	7.2 mg	[redacted] mL single-dose pen-injector	[redacted] mL*	52 weeks
Sema 2.4	Semaglutide [redacted] mg/mL DV3396	2.4 mg	[redacted] mL single-dose pen-injector		
Placebo	Semaglutide placebo Ib[a]	N/A	[redacted] mL single-dose pen-injector		
After transition to single pen					
Sema 7.2	Semaglutide [redacted] mg/mL DV3396	7.2 mg	[redacted] mL single-dose pen-injector	[redacted] mL#	52 weeks
Sema 2.4	Semaglutide [redacted] mg/mL DV3396	2.4 mg	[redacted] mL single-dose pen-injector		
Placebo	Semaglutide placebo Ib[a]	N/A	[redacted] mL single-dose pen-injector		

[a]Semaglutide placebo Ia and Ib will be named "placebo" on label.

[b]The maintenance dose will be administered as either 3 consecutive injections* (3 x 2.4 mg, 2.4 mg + 2 x placebo, or 3 x placebo) or as a single injection# (1 x 7.2 mg, 1 x 2.4 mg or 1 x placebo) using the new drug-device combination product, when available. The duration of either of these regimens will be overall 52 weeks and depends on when the new drug-device combination product is introduced. For the 3 consecutive injections*, the 2nd and 3rd injection should be administered immediately after the 1st injection using a different site of injection, either within the same or a new body region, but at least 5 cm from the first injection site.

Abbreviations: N/A = not applicable; sema = semaglutide.

Other study intervention(s)

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 health care professional every 4th week 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.[72]

$$TEE = BMR \times 1.3$$

Table 6-3 Equation for estimated Basal Metabolic Rate (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

Auxiliary supplies including non-investigational medical device(s)

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

Auxilliary supply	Details
Direction for use (DFU)	DFU for DV3396 single-dose pen-injector. Not included in the dispensing unit and to be handed out separately.

The DV3396 pen-injector, is a single use, fixed dose disposable pen-injector for self-injection with a build-in needle. Information about the DV3396 single-dose pen-injector may be found in the IB[66] and any updates hereof. Information about the use of the DV3396 single-dose pen-injector can be found in the DFU.

6.2 Preparation, handling, storage and accountability

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

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

For selected countries and if permitted by local regulations, the investigator may offer to send study intervention from the study site or pharmacy to the participant's home by courier service. The process for sending study intervention from the study site or pharmacy to a participant's home is described in the "Study site/pharmacy instruction for shipment of trial product to 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 Trial Materials Manual (TMM).

The investigator or designee is responsible for trial product accountability and record maintenance (i.e., receipt, accountability and final disposition records). Drug accountability is performed on item level by using the RTSM/IWRS.

The investigator or designee must instruct the participant in what to return at next visit. The participant must return all used and unused trial product including empty packaging materials during the study as instructed by the investigator.

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, if not otherwise agreed at the site selection.

All returned, 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 the system (RTSM or IWRS) and assigned to the next available trial product according to the randomisation schedule. Trial product will be allocated by the system 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 system (RTSM/IWRS) is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's trial product is warranted. Participant safety must always be the first consideration in making such a determination.

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

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

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

6.4 Study intervention compliance

Drug treatment compliance

Throughout the study, the investigator will remind the participants to follow the study procedures and requirements to encourage participant compliance. Treatment compliance will be assessed by monitoring of drug accountability and by discussing treatment compliance and dosing conditions with the participant. If a participant is found to be non-compliant the investigator will remind the participant of the importance of following the instructions given, including taking the trial products as prescribed.

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. The participant will be asked about date of first dose at visit 3. Information about treatment compliance will be collected at every visit/phone contact from randomisation. Information on treatment dose start and stop dates will be recorded in the CRF. If any suspicion of non-compliance arises, the site must enter into a dialogue with the participant, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented.

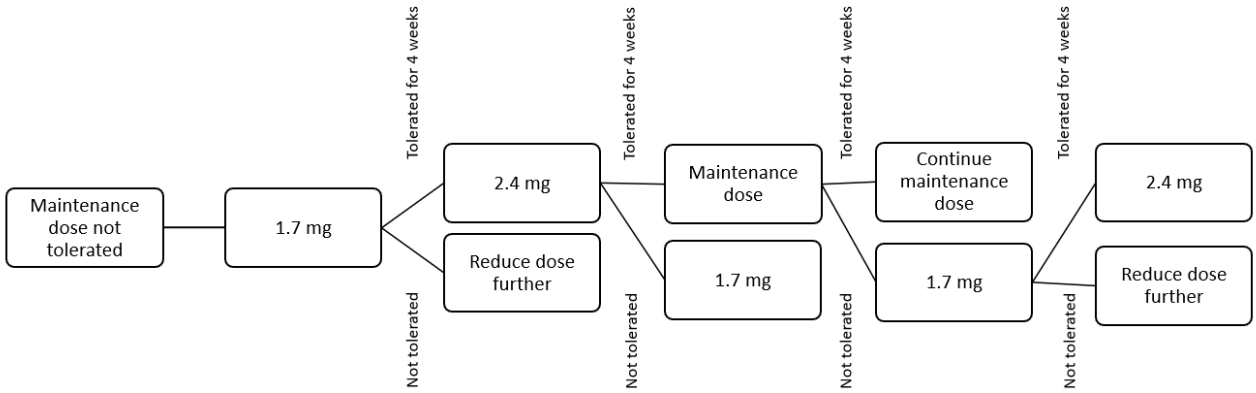
6.5 Dose modification

Dose escalation

- Participants will be initiated at a once-weekly dose of 0.25 mg and follow a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7, and 2.4 mg/week). After 20 weeks participants will start on their respective target dose of 7.2 mg/week, 2.4 mg/week or placebo. All participants should aim at reaching the recommended target dose.
- During escalation one injection should be administered per week. During the maintenance period 3 consecutive injections (3 x 2.4 mg, 2.4 mg + 2 x placebo, or 3 x placebo) should be administered per week to obtain the target dose of 7.2 mg semaglutide and maintain blinding. The 2nd and 3rd injection should be administered immediately after the 1st injection using a different site of injection, either within the same or a new body region, but at least 5 cm from the first injection site. A new drug-device combination product which can administer 7.2 mg semaglutide s.c. in a single injection, will be using the DV3396 single-dose pen-injector and will be introduced during this study . When the new drug-device combination product is introduced the maintenance dose will be administered as a single injection for all treatment arms.
- If a participant does not tolerate the current dose, consider delaying the dose escalation or reducing the dose. This should only be allowed if the participant would otherwise discontinue trial product completely and if considered safe to continue trial product, as per the investigator's discretion. It is recommended that the participant makes at least one attempt to re-escalate. If re-escalation is not tolerated participants should stay at a lower dose level.
- De-escalation should follow the regimen outlined in Figure 6-1. If the maintenance dose (all treatment arms) is not tolerated, the participant shall be de-escalated to 1.7 mg, to maintain blinding. If 1.7 mg is tolerated for 4 weeks, the participant can be re-escalated to 2.4 mg. If this dose is tolerated for 4 weeks, the participant can be re-escalated to maintenance dose. Re-escalation after < 4 weeks is allowed if feasible as per the investigator's discretion. It is recommended that the participant makes at least one attempt to re-escalate to maintenance dose.
- Participants will be contacted by phone within day 3-7 after escalation (phone visit 9) to the target dose, to ensure the dose is tolerated (see Section 1.2).
- It is recommended that the investigator consults with Novo Nordisk in case of persistent deviations from the planned escalation regimen.

- A dose reminder card will be handed out to the participants at dose escalation site visits and regularly during the maintenance period.

Figure 6-1 De-escalation guide



Note: Maintenance dose is referring to 7.2 mg/2.4 mg/placebo dose.

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 prescribed, at the investigator's discretion.

Dose adjustment

- If the participant with a BMI within the lower normal range continues to lose weight, and there is a health concern, the investigator must consider reducing the dose of the IMP. The investigator can 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 trial 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 trial product are missed, the participant should be encouraged to recommence the trial product if considered safe as per investigator's discretion and if the participant does not meet any of the discontinuation criteria (Section 7.1). The starting dose for re-initiation of trial product is at the investigator's discretion. In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk medical experts.

6.6 Continued access to study intervention after end of study

There is no treatment following the end of the study. When discontinuing study intervention, the participant should be transferred to a suitable marketed product at the discretion of the investigator.

6.7 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 AEs/SAEs 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, considering the long half-life of semaglutide of approximately one week.

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

For more information on overdose, also consult the current version of the investigator's brochure (IB).[66]

6.8 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 and dosing frequency for antihypertensive, lipid-lowering and antipsychotic medication, and anti-obesity preparations.
- Primary indication
- Dates of administration including start and stop dates

During the study, participants should not initiate any anti-obesity medication or treatment which is not part of the study procedures. If such treatment is initiated, the participants 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.

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.

The end-of-study visit (visit 23) is scheduled approximately 9 weeks after end of study intervention to account for the exposure and long half-life of semaglutide and to ensure the safety of the participant. If the participant has discontinued trial product > 9 weeks prior to the 'end of treatment' visit, and the requirements for the follow-up period prior to the end-of-study visit are fulfilled, then the end-of-study visit can be omitted.

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 concerns as judged by the investigator
2. Suspicion of acute pancreatitis
3. Pregnancy
4. Intention of becoming pregnant
5. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study
6. Suspicion of drug induced liver injury
7. Calcitonin ≥ 100 ng/L (see Appendix 9, Section 10.9)

If acute pancreatitis is suspected appropriate actions should be initiated, including local measurement of amylase and lipase (see Appendix 3, Section 10.3 for reporting).

Participants meeting discontinuation of trial product criteria no. 1, 2, 3, 4 and 6 are allowed to resume trial product, 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 the RTSM/IWRS.

Pregnancy testing is advised 9 weeks after premature discontinuation of study intervention (see 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. Similarly, a participant who discontinues trial product on their own initiative should be encouraged to resume trial product (Section 6.5).

In such cases a treatment discontinuation should not be made in the RTSM/IWRS.

If a treatment discontinuation previously has been made in RTSM/IWRS to indicate discontinuation of trial product, a 'resume treatment' must be made to resume trial product. Information on treatment dose start and stop dates will be recorded in the CRF.

In case of suspicion of acute pancreatitis, the randomised treatment should promptly be interrupted (discontinuation of randomised treatment should not be made in RTSM/IWRS before diagnosis of acute pancreatitis is confirmed). Appropriate actions should be initiated, including local measurements of amylase and lipase (see Appendix 3 [Section 10.3] for reporting).

Participants with suspected acute pancreatitis are allowed to resume trial product at the investigator's discretion if the Atlanta criteria[73] are not fulfilled and thus, the suspicion of acute pancreatitis is not confirmed. Trial product may be resumed for participants with a gallstone-induced pancreatitis in case of cholecystectomy.

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

7.1.1.1 Hepatic events requiring temporary discontinuation of study intervention

Temporary discontinuation of study intervention is required for hepatic events, defined as

- ALT (or AST) ≥ 3 x upper limit of normal (ULN) and total bilirubin ≥ 2 x ULN or ALT (or AST) ≥ 3 x ULN and international normalised ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (potential Hy's law)[a]
- ALT (or AST) ≥ 3 x ULN with the appearance of fatigue, nausea, vomiting, anorexia, abdominal pain or tenderness, fever, rash, and/or eosinophilia (>5%).

[a]Please note that such an event must be reported as a SAE using the important medical event criterion if no other seriousness criteria are applicable (as described in Appendix 3, Section 10.3).

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 6 (Section 10.6) 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).

7.2 Participant discontinuation/withdrawal from the study

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

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

If a participant withdraws consent or is withdrawn by the investigator after randomisation, the investigator must ask the participant if he/she is willing, as soon as possible, to have assessments performed according to visit 22 (end of treatment) and have a blood sample taken for immunogenicity assessment > 9 weeks after last treatment dose. See the flowchart (Section 1.2) for data to be collected.

Final trial product accountability must be performed even if the participant is not able to come to the site. Treatment discontinuation must be made in the RTSM/IWRS.

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

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

Although a participant is not obliged to give his/her reason(s) for withdrawing, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the 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/she repeatedly fails to return for scheduled visits and is unable to be contacted by the site. The final classification of the participant as lost to follow-up will not be until the initial date for the end of treatment visit.

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

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

8 Study assessments and procedures

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

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. Additional, participants should be evaluated for participation in the MRI subgroup (Section 5.1).

The investigator will maintain a screening log to record details of all participants screened 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, clinical outcome assessment, mental health assessment, ECG, and laboratory reports must be documented in the source documents or the participant's medical record. If clarification of entries or discrepancies is needed, the participant must be questioned, and a conclusion made in the participant's source documents. Care must be taken not to bias the participant.

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

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

1. Electrocardiogram (ECG, see Section 8.2.5), vital signs (see Section 8.2.4) and body measurements (see Section 8.1.1)
2. Blood samples (see Appendix 2 [Section 10.2])
3. Clinical outcome assessment (see Section 8.1.5) and Mental health assessment instruments (see Section 8.2.2)
4. Other assessments

Results of pregnancy testing must be documented in the participant's medical records.

For participants receiving antihypertensive or lipid-lowering treatment, the investigator should evaluate changes in the participants' treatment intensity within each therapeutic area. The evaluation should be based on whether an overall change in treatment intensity from randomisation until the time of the evaluation has occurred (i.e., either increase, decrease or no change) after

reviewing all available relevant information e.g., changes in drug dose, drug class, number of drugs or a combination of these.

Participants must receive training in how to collect dosing information prior to PK sampling in a designated paper diary (PK diary) to be handed out as outlined in the flowchart. See Section 8.4 for a description of the data to be entered in the PK diary.

The barriers and motivation interview identifies barriers to and motivation for lifestyle change and compliance with the protocol. The interview will be conducted at screening to assist in identifying participants who are unable or unwilling to comply with protocol procedures as per the exclusion criteria. In addition, the interview will ensure that any minor barriers are addressed during lifestyle counselling. The results of the interview will not be entered into the CRF. It will be at the investigator's discretion to evaluate the motivation of the participant and related eligibility.

The investigator will evaluate the participant's glycaemic status periodically during the trial as detailed in the flowchart based on all available relevant information e.g., medical records, concomitant medication, blood glucose parameters (HbA1c, FPG) and AEs. The participant's glycaemic status will be categorised as normo-glycaemia, prediabetes or diagnosed with type 2 diabetes according to the American Diabetes Association's definitions.

For participants in the MRI sub-population, MRI must be performed according to the manual from the supplier (see Section 8.1.2).

8.1 Efficacy assessments

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

8.1.1 Body measurements

Body weight must be measured at all site visits without shoes, with an empty bladder and only wearing light clothing. Body weight must be measured on a digital scale and recorded in kilograms or pounds (one decimal i.e., X.2 or X.7) using the same scale throughout the study. The scale must be calibrated according to manufacturer's recommendation or local requirements.

Height is measured without shoes in centimetres or inches (one decimal i.e., 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. 4 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.

8.1.2 Magnetic resonance Imaging

The 2 MRI scans will only be performed on a subgroup of approximately 50 randomised participants. The subgroup will consist of participants who fulfil the MRI inclusion criteria (Section 5.1). The first MRI scan should be performed between screening (V1) and randomisation (V2). The second MRI scan should be performed up to 7 days before end-of-treatment visit (V22) or at the time of end of treatment visit (V22).

The results of the MRI scan and the MRI scan image will be transferred from the central imaging laboratory to the Novo Nordisk database.

MRI scan must be performed according to the supplier's manual.

[redacted]

8.1.4 Clinical efficacy laboratory assessments

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

8.1.5 Clinical outcome assessment

The questionnaires will be filled in electronically at site. Participants should be given the opportunity to complete the questionnaires by themselves without interruption. The questionnaires take approximately 15 minutes to complete.

The following patient reported outcome questionnaire will be used:

[redacted]

8.2 Safety assessments

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

8.2.1 Medical history/concomitant illness

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.

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.

Medical history/concomitant illness includes but is not limited to the below list of pre-specified disease classes in the eCRF.

- Allergies, symptoms and predisposing conditions
- Breast neoplasm
- 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

Information on weight related co-morbidities will be collected as part of medical history/concomitant illness at screening (visit 1) and an evaluation will be done at the end of treatment (visit 22).

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, other methods to lose weight, and considerations regarding bariatric surgery) must be documented at screening.

To be used in the overall safety evaluation of the IMP, the following must be documented at screening: Risk factors for breast cancer (for female participants only), skin cancer and colon neoplasm, including both 1) family history of breast cancer, colon neoplasm and/or skin cancer in first-degree relatives, age at time of diagnosis for relevant family members and 2) predisposing factors for breast and skin cancer, such as menarche/menopause, alcohol intake above guidelines, hormone replacement therapy (HRT), sun exposure, light skin colour. Follow-up questions related to breast neoplasm (for female participants only) and colon neoplasm, will be asked at end of treatment and end of study.

In case of an abnormal and clinically significant finding, the investigator must record the finding on the Medical History/Concomitant Illness form if it is present at screening. Any new finding fulfilling the AE definition (see Appendix 3, Section 10.3) during the study and any clinically significant worsening from baseline must be reported as an AE (see Section 8.3).

8.2.2 Mental health assessment instruments

Two patient reported outcome questionnaires will be used. The questionnaires will be filled in electronically at site. Participants should complete the questionnaires at site at screening (visit 1), visit 8, visit 10, visit 14, visit 18, and end-of-treatment (visit 22).

PHQ-9[75] 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 questionnaire shall be filled in electronically after instructions from site staff. Participants should be given the opportunity to complete the questionnaires by themselves without interruption.

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[76] 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.

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.

8.2.3 Physical examinations

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

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

8.2.4 Vital signs

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

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

However, as a minimum:

- Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., no use of television, cell phones).
- Blood pressure and pulse rate measurements will be assessed sitting with a completely automated device. Manual techniques must be used only if an automated device is not available.

Blood pressure and pulse rate are collected at all physical visits (including screening, randomisation, end of treatment and end of study).

8.2.5 Electrocardiograms

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

QTc will also be estimated at a central ECG supplier, but local review for clinical significant abnormal findings must be performed by the investigator.

ECG must be performed according to the manual from supplier if the devices is provided by a vendor.

8.2.6 Clinical safety laboratory assessments

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

8.2.7 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.

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.

Pregnancy testing is advised 9 weeks after premature discontinuation of randomised study intervention, see Appendix 4 (Section 10.4).

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

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.

8.2.8 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 banding (includes laparoscopic adjustable gastric band), gastric band repositioning, gastric banding reversal, gastric bypass (roux-en-y), 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 event(s) are listed below in Table 8-1.

Table 8-1 AEs requiring additional data collection

Event type	AE requiring additional data collection
Medication error[a]	X
Misuse and abuse of trial product[a]	X
Acute pancreatitis	X
Acute gallbladder disease	X
Hepatic event[b]	X
Malignant neoplasm	X
Acute kidney injury	X
[a]Additional data for Misuse and abuse of trial product is reported on the medication error event form. [b]See further guidance in Section 10.3.3.	

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

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 within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

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

8.3.2 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 obtaining informed consent and until the end-of-study. For details regarding collection and reporting of pregnancy information, please refer to Appendix 4 (Section 10.4).

If a female participant becomes pregnant, the participant must discontinue randomised trial product as described in Section 7.1.

8.3.6 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to Section 8.3 and Appendix 3 (Section 10.3).

8.3.7 Technical complaints

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

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

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

8.4 Pharmacokinetics and pharmacodynamics

8.4.1 Pharmacokinetics

Single blood samples for measuring plasma concentration of semaglutide will be drawn for both semaglutide and placebo participants on visits specified in the flowchart (Section 1.2).

The purpose of measuring plasma semaglutide levels is to perform population pharmacokinetic (Pop-PK) analyses. Having Pop-PK in this study will further support bridging of Pop-PK from studies conducted in other populations.

Samples will be used to evaluate the pharmacokinetics of semaglutide. Each plasma sample will be divided into 2 aliquots (e.g., one for PK and a backup) and may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the study. Residual PK samples may be used for exploratory metabolite analysis. Potential metabolite analysis will be reported separately from the CSR. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Participants must receive training in how to collect dosing information prior to PK sampling in the designated PK diary. Only participants must make entries and corrections in the diaries, unless the section is specified for site staff.

The PK dosing information from the PK diary (i.e., the actual dose of trial product (mg), the date and time of administration) should be transcribed into the CRF for the last 2 doses of trial product prior to the PK assessment as outlined in the flowchart.

The exact timing of obtaining the PK sample must be recorded on the laboratory form.

8.4.2 Pharmacodynamics

Not applicable for this study.

8.5 Genetics

Refer to Section 8.8 and Appendix 7 (Section 10.7) for further details.

[redacted]

[redacted]

[redacted]

[redacted]

8.9 Health economics

Not applicable for this study.

9 Statistical considerations

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

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 72) and 2) body weight reduction ≥ 5% (yes/no) at end of treatment (week 72) the following 1-sided hypotheses are planned to be tested for semaglutide s.c. 7.2 mg versus placebo. Let the mean treatment difference in 1) be defined as:

μ = ([semaglutide 7.2 mg] minus [placebo])

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

OR = (odds[semaglutide 7.2 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 with significance level of $\alpha = 0.05$.

For each of the confirmatory secondary estimands with the endpoints body weight reduction ≥ 10 %, ≥ 15 %, ≥ 20 %, and ≥ 25 % (yes/no) at end of treatment (week 72) a hypothesis similar to 2) will be tested.

For the confirmatory secondary estimand with the endpoint change in waist circumference (cm) and relative change in body weight (%) (semaglutide s.c. 7.2 mg versus semaglutide s.c. 2.4 mg) from baseline (week 0) to end of treatment (week 72) 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 favour of semaglutide s.c. 7.2 mg.

The steps in the hierarchical testing procedure are as follows:

- Step 1: Superiority of semaglutide s.c. 7.2 mg versus placebo with respect to both co-primary estimands.

- Step 2: Superiority of semaglutide s.c. 7.2 mg versus placebo with respect to secondary estimand with endpoint body weight reduction ≥ 10 % (yes/no) at end of treatment (week 72).
- Step 3: Superiority of semaglutide s.c. 7.2 mg versus placebo with respect to secondary estimand with endpoint body weight reduction ≥ 15 % (yes/no) at end of treatment (week 72).
- Step 4: Superiority of semaglutide s.c. 7.2 mg versus placebo with respect to secondary estimand with endpoint body weight reduction ≥ 20 % (yes/no) at end of treatment (week 72).
- Step 5: Superiority of semaglutide s.c. 7.2 mg versus placebo with respect to secondary estimand with endpoint body weight reduction ≥ 25 % (yes/no) at end of treatment (week 72).
- Step 6: Superiority of semaglutide s.c. 7.2 mg versus placebo with respect to secondary estimand with the endpoint change in waist circumference from baseline (week 0) to end of treatment (week 72).
- Step 7: Superiority of semaglutide s.c. 7.2 mg versus semaglutide s.c. 2.4 mg with respect to secondary estimand with the endpoint relative change in body weight (%) from baseline (week 0) to end of treatment (week 72).
- Step 8: Superiority of semaglutide s.c. 7.2 mg versus semaglutide s.c. 2.4 mg with respect to secondary estimand with endpoint body weight reduction ≥ 20 % (yes/no) at end of treatment (week 72).
- Step 9: Superiority of semaglutide s.c. 7.2 mg versus semaglutide s.c. 2.4 mg with respect to secondary estimand with endpoint body weight reduction ≥ 25 % (yes/no) at end of treatment (week 72).

9.2 Analysis sets

The following participant analysis sets are defined:

Table 9-1 Participant analysis sets

Participant Analysis Set	Description
Full analysis set	All randomised participants.
Safety analysis set	All participants who are exposed to at least one dose of randomised IMP.

For the full analysis set (FAS) participants will be included in the analyses according to the planned intervention. For the safety analysis set (SAS) participants will be included in the analyses according to the intervention they actually received.

The following data points sets are defined:

[redacted]

[redacted]

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 randomisation is used as the baseline value. If no assessments are available, the mean value at randomisation across all participants is used as the baseline value.

All randomised participants in all treatment arms contribute to the analysis. All tests are tests of superiority of semaglutide s.c. 7.2 mg once-weekly versus placebo unless stated otherwise. All estimand treatment contrasts between semaglutide s.c. 7.2 mg versus placebo (or semaglutide s.c.

2.4 mg) will be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

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 72)
- Body weight reduction ≥ 5 % (yes/no) at end of treatment (week 72)

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

The analysis model for relative change in body weight (%) will be a linear regression (ANCOVA) with randomised treatment as factor and baseline body weight (kg) as covariate. The model will allow the variances to differ across treatment groups.

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

All available data at week 72 are used and missing values at week 72 will be imputed and the endpoints will be derived from the imputed continuous values. It is assumed that values are missing at random (MAR) conditional on factors and covariates in the imputation model. The imputation approach for the primary analysis is a multiple imputation similar to the one described by McEvoy et al.[77] For participants in the semaglutide s.c. 7.2 mg once-weekly, the semaglutide s.c. 2.4 mg once-weekly and the placebo groups, missing measurements at week 72 for non-retrieved participants are imputed using assessments from retrieved participants in each treatment group, missing measurements at week 72 for participants on randomised treatment are imputed by sampling from available measurements at week 72 from participants on randomised treatment in each intervention group. The imputation model will be a linear regression of gender (male/female) as factor and baseline body weight (kg), timing of last available observation during the on-treatment period (LAO-OT) and LAO-OT as covariates. 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 72 for both active treatment groups and placebo group are imputed by sampling among all available assessments at week 72 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 in the main analysis. Details of the multiple imputation approach are provided in the SAP.

Tipping-point multiple imputation analysis (TP-MI): This analysis will be performed only if superiority of semaglutide 7.2 mg is concluded with respect to the co-primary estimands. First, missing data are imputed according to the primary multiple imputation approach. Then, a penalty is added to the imputed values at week 68. The approach is to explore a range of penalties for both treatment groups, and the impact these would have on the study conclusions. The 2-dimensional

space of penalties covering the range from -30% to 30% will be explored for both treatment groups. The TP-MI analysis addresses the MAR assumption in the main analysis.

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.

Supplementary analyses

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

The estimation of the additional estimand with the endpoint relative change in body weight (%) will be a mixed model for repeated measurements (MMRM). The MMRM will be fitted using randomised treatment as factor 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 additional estimand with the endpoint body weight reduction ≥ 5% is a logistic regression where any missing values at week 72 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 as factor and baseline body weight (kg) as covariate.

All subjects contribute to the analysis, however, data points collected after treatment discontinuation and initiation of anti-obesity medication, as detailed in Section 9.2, will not be included in the analyses addressing the additional estimand.

9.3.3 Secondary estimands analysis

9.3.3.1 Confirmatory secondary estimands

All tests are tests of superiority of semaglutide s.c. 7.2 mg to placebo unless stated otherwise. The confirmatory secondary endpoints related to the secondary objective are:

- Body weight reduction ≥ 10% (yes/no) at end of treatment (week 72)
- Body weight reduction ≥ 15% (yes/no) at end of treatment (week 72)
- Body weight reduction ≥ 20% (yes/no) at end of treatment (week 72)
- Body weight reduction ≥ 25% (yes/no) at end of treatment (week 72)
- Change in waist circumference (cm) from baseline (week 0) to end of treatment (week 72)
- Relative change in body weight (%) (semaglutide s.c. 7.2 mg versus semaglutide s.c. 2.4 mg) from baseline (week 0) to end of treatment (week 72)
- Body weight reduction ≥ 20% (yes/no) (semaglutide s.c. 7.2 mg versus semaglutide s.c. 2.4 mg) at end of treatment (week 72)
- Body weight reduction ≥ 25% (yes/no) (semaglutide s.c. 7.2 mg versus semaglutide s.c. 2.4 mg) at end of treatment (week 72)

All confirmatory secondary estimands will be analysed using the same analysis model and imputation approach as used to address the co-primary estimand for the co-primary objectives. For

the estimands with binary endpoints, in any cases where response rates close to 0% or 100% in any treatment group lead to non-convergence, Firth's maximum-likelihood estimation will be used when performing the logistic regression.

Sensitivity analysis

For the change in waist circumference and relative change in body weight (%) (semaglutide s.c. 7.2 mg versus semaglutide s.c. 2.4 mg) 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.

9.3.3.2 Supportive secondary endpoints

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

Safety related supportive secondary endpoints

The estimation of the estimand with the safety endpoint change in pulse will be an MMRM as described in Section 9.3.2.

Adverse events will be summarised by descriptive statistics, such as frequencies and rates. No formal statistical inference will be carried out based on the number of AEs.

9.3.4 Exploratory endpoint(s)/estimand(s) analysis

Exploratory endpoints are listed in Section 3 and the statistical analyses are detailed in the SAP.

9.3.5 Other safety analyses

Please refer to the SAP for details.

9.3.6 Other analyses

9.3.6.1 Pharmacokinetic and pharmacodynamic modelling

Population PK and exposure-response analyses will be used as supportive evidence for the evaluation of efficacy and safety and further to support the 7.2 mg s.c. dose of semaglutide in participants with obesity. First, plasma semaglutide concentrations will be analysed using a population pharmacokinetic model, quantifying covariates (such as baseline body weight, age, gender, race, ethnicity and device) effects on semaglutide exposure. Second, model-based estimates of steady-state average concentrations will be derived for each participant, in order to facilitate subsequent exposure-response analyses. Relevant efficacy and safety endpoints will be related to steady-state average concentrations and subjected to model-based analysis. Data from historical weight management trials may be included to support the model-based analyses.

A modelling analysis plan will be prepared prior to first database lock and the results will be reported separately from the clinical study report.

9.4 Interim analysis

There is no interim analysis planned for this study.

9.5 Sample size determination

The sample size for this study was determined primarily to ensure adequate exposure to semaglutide s.c. 7.2 mg. It is considered sufficient if 1000 participants are randomised to the 7.2 mg dose. With a 5:1:1 randomisation, this results in a total sample size of 1400 randomised participants. In STEP phase 3a program, among participants with BMI ≥30 kg/m^2, approximately 70% in the semaglutide s.c. 2.4 mg treatment group were exposed to the 2.4 mg dose for at least 1 year. Based on this, it is assumed in this study that at least 65% of participants (n = 650) randomised to the semaglutide s.c. 7.2 mg treatment group will be exposed to the 7.2 mg dose for at least 1 year.

Given the study sample size, the effective power of statistical tests for the primary and confirmatory secondary estimands is >84%. 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 unequal 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 [redacted], which had similar eligibility criteria to this study. Exposure-response modeling was performed in order to simulate the change (%) in body weight expected among participants completing treatment with semaglutide s.c. 7.2 mg. This predicted mean change was assumed to be normally distributed, and thereby used to derive expected proportions of participants achieving body weight reduction ≥ 5%, ≥ 10%, ≥ 15%, ≥ 20%, and ≥ 25%. The amount by which this predicted mean change exceeds the change (%) in body weight observed among treatment completers in STEP 1, combined with the change in waist circumference observed in STEP 1, was also used to derive the predicted change in waist circumference among participants completing treatment with semaglutide s.c. 7.2 mg.

Based on STEP 1, where 18.9% permanently discontinued trial product it is assumed that 20% of participants will discontinue trial product permanently before week 72. It is assumed that approximately 60% of these will be retrieved at week 72. It is further assumed that, beyond the dose reductions observed in STEP 1 (in which 10.4% of treatment completers were on a reduced dose at end of treatment), an additional 5% of participants in the semaglutide 7.2 mg group will complete treatment at a lower dose. 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 s.c. 7.2 mg group are assumed to have the same effect to half the treatment difference (compared to placebo) of participants who complete the study on semaglutide s.c. 7.2 mg. Non-retrieved participants in the semaglutide s.c. 7.2 mg once-weekly arm are assumed to have an effect corresponding to placebo. The expected mean effect on relative change in body weight in semaglutide 2.4 mg group is assumed to be equal to the one estimated in STEP 1 for the treatment policy estimand (similar to primary estimand defined in this study). The expected proportions of

participants achieving body weight reduction ≥ 20%, and ≥ 25% in the semaglutide 2.4 mg group are assumed to be equal to observed proportions from the in-trial period in STEP 1.

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. Under these assumptions and a 5:1:1 randomisation ratio, a sample size of 1400 participants randomised to either receive semaglutide s.c. 7.2 mg once-weekly (1000 participants), semaglutide s.c. 2.4 mg once-weekly (200 participants) or placebo (200 participants) yields an effective power of >84% for all confirmatory endpoints.

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

Step	Endpoint	Assumed mean (SD) or proportion for completers		Expected mean (SD) or proportion		Expected difference or proportion ratio	Marginal power (%)	Effective power (%)
		Sema 7.2 mg	Placebo (or Sema 2.4 mg)	Sema 7.2 mg	Sema 2.4 mg			
Population of 1400 participants randomised (5:1:1) to either semaglutide 7.2 mg, semaglutide 2.4 mg or placebo								
1	Relative change in body weight (%)	21.3 (10)	3.1 (6.5)	18.4 (10)	-	15.3 %-points	> 99	> 99
1	Body weight reduction ≥5%	94.8%	31.5%	83.8%	-	2.7	> 99	> 99
2	Body weight reduction ≥10%	87.0%	12.0%	74.2%	-	6.2	> 99	> 99
3	Body weight reduction ≥15%	73.5%	4.9%	62.5%	-	12.7	> 99	> 99
4	Body weight reduction ≥20%	55.1%	1.7%	45.9%	-	27.0	> 99	> 99
5	Body weight reduction ≥25%	35.5%	0.4%	29.1%	-	72.7	> 99	> 99
6	Change in waist circumference (cm)	18.9 (10)	5.0 (7.5)	16.4 (10)	-	11.4 cm	> 99	> 99
7	Relative change in body weight (%)[a]	21.3 (10)	16.9 (10)	18.4 (10)	14.9 (10)	3.5 %-point	> 99	> 99
8	Body weight reduction ≥20%[a]	55.1%	34.8%	45.9%	32.0%	1.4	>95	>95
9	Body weight reduction ≥25% [a]	35.5%	20.0%	29.1%	18.6%	1.5	>88	>84

[a]semaglutide s.c. 7.2 mg versus semaglutide s.c. 2.4 mg
Abbreviations: SD = standard deviation.

9.6 Reporting of the study

A database lock is planned shortly after last participant last visit (week 81) of the study. The results will thereafter be reported in a CSR. A partial DBL may be performed at the end of the treatment period for all participants, i.e., after the date of the last patient last treatment (LPLT) visit (week

72). The database will be updated after the partial DBL to include remaining data. A detailed plan for data handling, blinding, data analysis, and operational aspects of the DBLs and the database update will be finalised before the partial DBL

Novo Nordisk may decide to opt out of the partial DBL.

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[78] and applicable ICH Good Clinical Practice (GCP) Guideline[79]
- Applicable laws and regulations

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

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

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

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

The investigator will be responsible for:

- providing written summaries of the status of the study annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- ensuring submission of the CSR synopsis to the IRB/IEC
- reporting any potential serious breaches to the sponsor immediately after discovery

10.1.2 Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and one year after completion of the study.
For US sites: Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

10.1.3 Informed consent process

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

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

Participants must be informed that their participation is voluntary. Participants will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH GCP[79] guidelines, Declaration of Helsinki,[78] 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 will be offered a communication package for the participant during the conduct of the study. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the participants. The written information will be translated and adjusted to local requirements and distributed to the participant at the discretion of the investigator. The participant may receive a “thank you for your participation letter” after completion of the study. Further, the participant may receive other written information during the study.

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

10.1.5 Data protection

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

The participant and any biological material obtained from the participant will be identified by subject ID, visit number and study ID. Appropriate measures such as encryption or leaving out

certain identifiers will be enforced to protect the identity of participants as required by local, regional and national requirements.

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

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

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

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

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

10.1.7 Dissemination of clinical study data

Study information will be disclosed at clinicaltrials.gov and novonordisk-trials.com and, if applicable, also on other national or regional study registries. It will be disclosed according to applicable requirements, relevant recommendations or regulations, such as the Declaration of Helsinki,[78] the International Committee of Medical Journal Editors (ICMJE),[80] the Food and Drug Administration Amendment Act (FDAAA),[81] European Commission Requirements[1, 82, 83] and in accordance with Novo Nordisk commitment to clinical transparency. If a participant requests to be included in the study via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the participant. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

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

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

All participant data relating to the study will be recorded on CRFs unless transmitted electronically to Novo Nordisk or designee (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the 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[79], 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. For clinical outcome and mental health assessment questionnaires the service providers' database is considered source data.

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. BMI is calculated in the eCRF based on entries of height and weight. Thus, the eCRF will be the source for BMI.

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

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the site. Any source data generated by investigator's subcontractors must be archived and accessible by the site.
Data that is transcribed into the 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 supplied by Novo Nordisk. Site-specific CRFs and other participant data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.

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

10.1.11 Study and site closure

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

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

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

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

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

10.1.12 Responsibilities

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

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

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

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

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

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

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

10.1.13 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with country-specific laws, acts and 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 subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CSR is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire study.

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

In all cases, the study results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

10.1.14.2 Authorship

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

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[84]

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 and Table 10-2 will be performed by the local laboratory, the central laboratory or by the special 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 lab will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their laboratory SOPs. These data will not be transferred to the study database. The investigator should review such values for AEs and report these according to this protocol.

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

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

[redacted]

For haematology samples (differential count) where the test result is not normal, then a part of the sample may be kept for up to two years or according to local regulations.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• Fasting plasma glucose • HbA_{1c} • Fasting serum insulin
Lipids	• Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides • Very low-density lipoprotein (VLDL) • Free fatty acids
[redacted]	
[redacted]	
Abbreviations: HbA_{1c} = glycated haemoglobin; [redacted]	

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	• Basophils • Eosinophils • Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Lymphocytes • Thrombocytes • Monocytes • Neutrophils • Platelets
Biochemistry[a]	• Alanine Aminotransferase (ALT)[b] • Albumin • Albumin corrected calcium • Alkaline phosphatase • Amylase[f] • Aspartate Aminotransferase (AST)[b] • Calcitonin[g] • Creatine kinase • Creatinine • Gamma Glutamyl Transferase • Lipase[f] • Potassium • Sodium • Thyroid stimulating hormone (TSH)[c] • Total bilirubin • Direct bilirubin • Urea • Cystatin c • Calcium
Pregnancy Testing	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test[d]
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation • Semaglutide plasma concentration • [redacted]

[a]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 3 (Section 10.3) (Hy's Law). [b]Details on hepatic safety, suggested actions and follow-up assessment are given in Section 7.1.1.1, Table 10-3, and Appendix 6 (Section 10.6). [c]If TSH level is out of normal range, additional testing will be performed by central laboratory: total and free T3 and T4 except at screening visit. [d]Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC, see Appendix 4 (Section 10.4). [redacted]. In case of suspicion of drug induced severe acute systemic hypersensitivity, samples will be collected for the measurement of tryptase and drug specific IgE. [f]Not collected at V1 or V2. [g]Not collected at V1, V2 or V10.

Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate.

[redacted]

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

Hepatic laboratory outlier: If the following hepatic laboratory parameters are above the cut-off values in Table 10-3, 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 AE (see Appendix 3, Section 10.3).

Table 10-3 Criteria for hepatic laboratory outliers

	Cut-off
Alkaline phosphatase	> 10 × UNL
ALT	> 5 × UNL
AST	> 5 × UNL
Total bilirubin	> 3 × UNL

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

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

10.3.1 Definition of AE

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

Events to be reported as AEs:

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

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

Events NOT to be reported as AEs:

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

10.3.2 Definition of an SAE

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

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

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

- Hospitalisation for elective treatment (e.g., elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE.

  Note: Hospitalisations for administrative, study-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for medical or surgical procedures, planned before study inclusion, are not considered AEs or SAEs
- **Results in persistent or significant disability/incapacity**
- The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Important medical event:**
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
- The following must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:
  - Suspicion of transmission of infectious agents via IMP
  - Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x ULN and total bilirubin >2x ULN 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. The selection of these events is based on the non-clinical and clinical data with semaglutide, knowledge from the GLP-1 RA drug class as well as regulatory requirements.

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

- Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)

- Serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal
- Characteristic findings of acute pancreatitis on imaging

Acute kidney injury

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

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

Hepatic event:

Hepatic event defined as:

- Disorders of the liver including cholestatic conditions and liver related signs and symptoms
- ALT or AST > 3x ULN and total bilirubin > 2x ULN or INR > 1.5[a]
- ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

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

Malignant neoplasm:
Malignant neoplasm by histopathology or other substantial clinical evidence.

Medication error:

- A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the participant, such as:
- administration of wrong drug
  Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in administration of wrong drug.
- wrong route of administration, such as intramuscular instead of subcutaneous
- accidental administration of a 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.
- Missed doses should not be reported as a medication error

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.

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 subject ID, must be redacted on the copies of the source documents before submission to Novo Nordisk.

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

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

10.3.4.2 Assessment of severity

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

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

10.3.4.3 Assessment of causality

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

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

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

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

The investigator should use the investigator's brochure[66] and any updates hereof 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.

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

New or updated information should be recorded in the 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 Table 10-1):

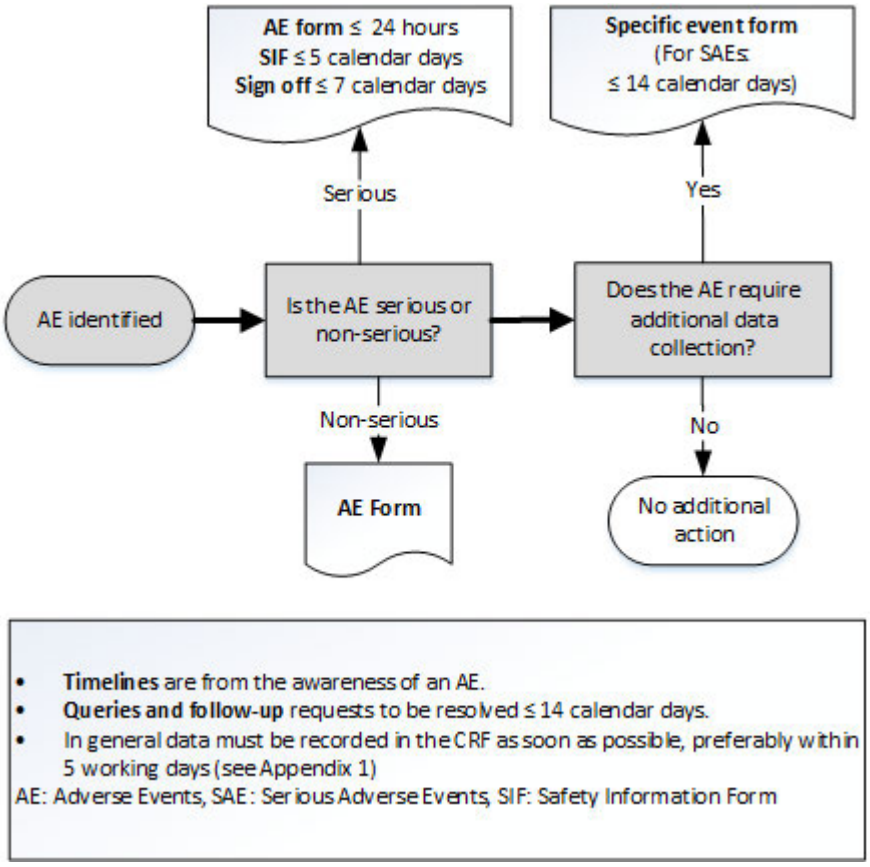
- AE form within 24 hours
- Safety information form within 5 calendar days
- Both forms must be signed within 7 calendar days after first knowledge by the investigator.
- Specific event form within 14 calendar days.

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

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

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

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

10.4.2 Contraceptive guidance

Male participants

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

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly. Table 10-4 lists the highly effective methods of contraception allowed. Local regulations may apply, see Appendix 10 (Section 10.10).

Highly effective contraception should be utilised for a least 9 weeks (63 days) after last dose of IMP (corresponding to time during treatment and until the end of relevant systemic exposure).

Table 10-4 Highly effective contraceptive methods allowed[85]

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, contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

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

In addition, a combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered 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 10-2).

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

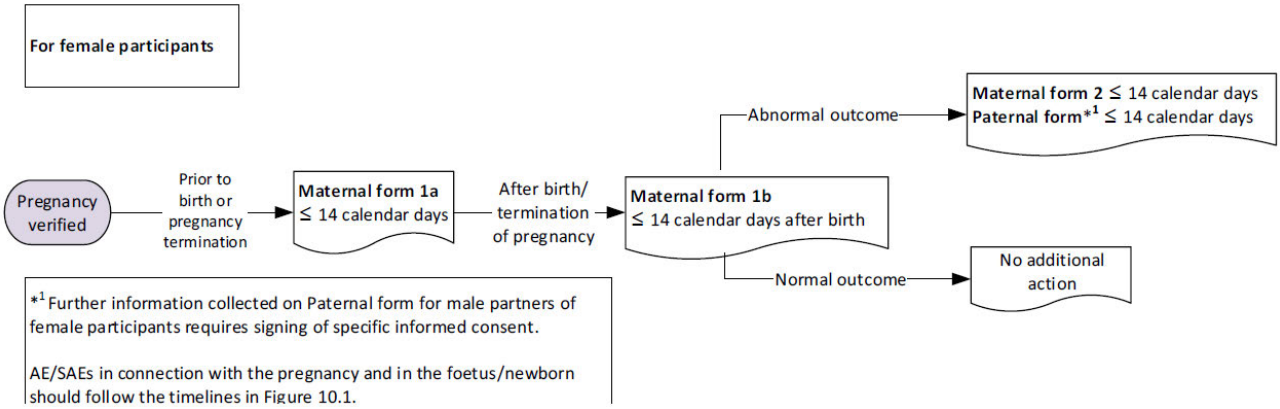
Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

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

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

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

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



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

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

10.5.1 Definition of technical complaint

A technical complaint is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself.

Examples of technical complaints:

- Problems with the physical or chemical appearance of study interventions (e.g., discoloration, particles or contamination)
- Problems with packaging material including labelling
- Problems related to devices

Time period for detecting technical complaints

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

10.5.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk

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

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

1. For products with DUN: One technical complaint form must be completed for each affected DUN.

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 calendar days 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.

10.6 Appendix 6: Hepatic Safety: Suggested actions and follow-up assessments

For all hepatic events, defined as:

- ALT (or AST) ⩾ 3 x upper limit of normal (ULN) and total bilirubin ⩾2 x ULN or ALT (or AST) ⩾ 3 x ULN and international normalised ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (potential Hy's law)
- ALT (or AST) ⩾ 3 x ULN with the appearance of fatigue, nausea, vomiting, anorexia, abdominal pain or tenderness, fever, rash, and/or eosinophilia (>5%),

where no alternative or competing aetiology exists, repeat testing within 48 to 72 hours, follow-up assessments and work-up for alternative aetiologies must be performed, including:

- 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.

[redacted]

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

10.8.1 Definition and scope of appendix

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

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

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

Section 10.8.2 indicates the minimum requirements for assessments that should be performed during a lock-down, but sites should always try to follow the assessments outlined in the original flowchart (Section 1.2) to the extent possible. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.

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

10.8.2 Visits

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

Visits 10, 22 and 23 should be performed as on-site visits, if in any way possible. If not, assessments can be conducted remotely (video, phone or similar) or as home or off-site visits.

On-site visits (Visits 3, 4, 5, 6, 7, 8, 12, 14, 16, 18, and 20) can be converted to remote visits (video, phone or similar) or home or off-site visits.

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

10.9 Appendix 9: Monitoring of calcitonin

Background

Two-year (104 weeks) carcinogenicity studies with semaglutide were completed with no adverse effects on tolerability and survival. The thyroid gland was the principal target organ in both species, with hyperplastic and neoplastic changes observed in the thyroid C-cells at all doses and in both sexes. No other treatment-related tumours were observed in the studies.

Proliferative C-cell changes in rodents are a known effect following GLP-1 receptor activation by GLP-1 RAs.[86] The findings in rodents are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive, and the effect is not related to the RET proto-oncogene activation as often seen in human medullary thyroid cancer.[87] The GLP-1 receptor is not expressed in the normal human thyroid,[69] and accordingly, the risk of GLP-1 receptor-mediated C-cell changes in humans is considered to be low.

No signs of C-cell activation (i.e., no increase in serum calcitonin) or C-cell proliferation were seen in cynomolgus monkey studies of up to 52 weeks' duration, applying doses up to 10-fold the human AUC exposure at 2.4 mg/week.

While there is general agreement on the clinical interpretation of substantially elevated calcitonin levels (greater than 100 ng/L) as likely indicative of C-cell neoplasia[88], the interpretation of values between the upper limit of normal and 100 ng/L can become problematic.

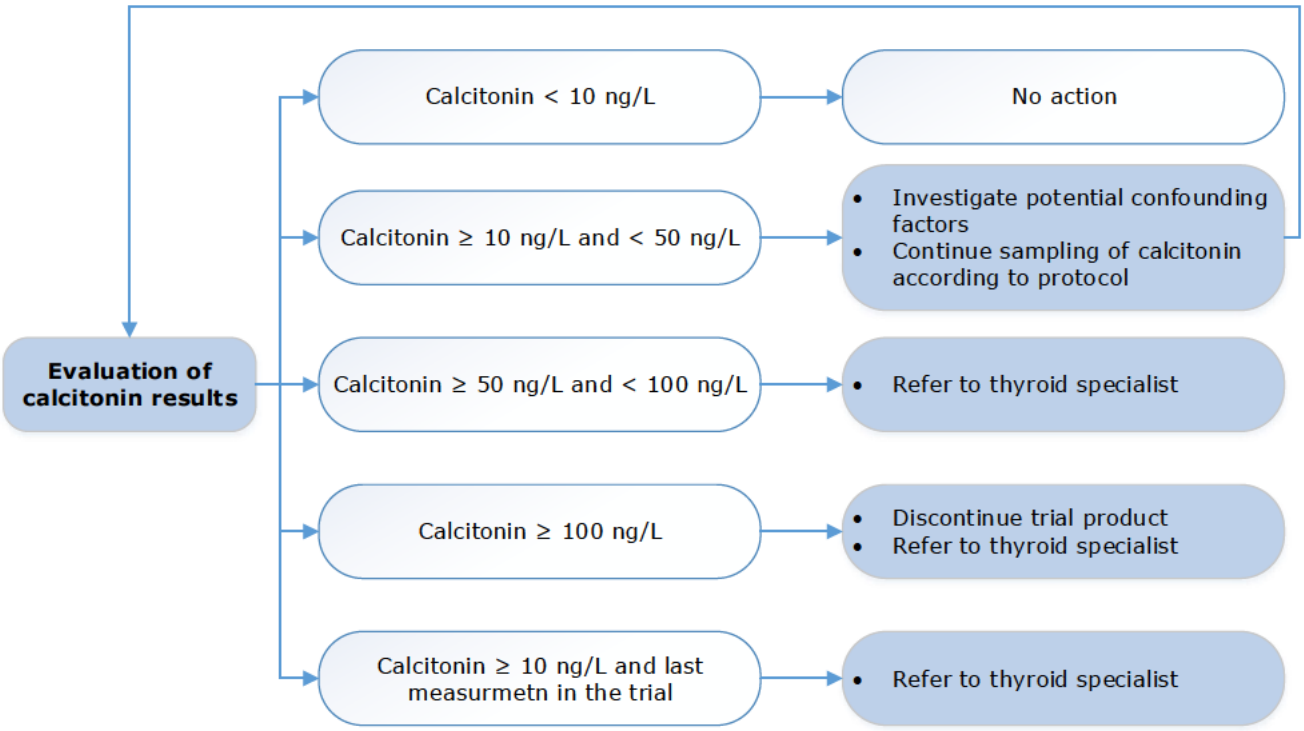
There are several known factors affecting calcitonin levels, namely renal dysfunction, smoking, several drug classes (proton pump inhibitors, beta-blockers, insulin secretagogues). Physiology of C-cell activation in various clinical conditions and in different patient populations (i.e., with various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

Calcitonin monitoring

Participants with a personal or family (family is defined as a first degree relative) history of MTC or multiple endocrine neoplasia syndrome type 2 (MEN2) must be excluded from the study (See Section **5.2**).

In case a participant has a calcitonin value ≥10 ng/L, the algorithm outlined in Figure 10-3 and described below should be followed. The algorithm applies for all calcitonin values in the study.

Figure 10-3 Flowchart of calcitonin monitoring



Calcitonin ≥ 100 ng/L

Action: The participant must immediately be referred to an endocrinologist or thyroid specialist for further evaluation and the study product must be discontinued (see Section 7.1). The participant should remain in the study; however, all medications suspected to relate to this condition must be discontinued until diagnosis has been established.

Background: These values were found in 9 (0.15%) of a population of 5817 patients with thyroid nodular disease[88]. All of these patients were diagnosed with MTC, resulting in a positive predictive value of 100%.

Diagnostic evaluation should include:

- thyroid ultrasound examination
- fine needle aspiration of any nodules >1 cm
- potentially, surgery with neck dissection

In case a participant is diagnosed with MTC, it is common clinical practice to explore the family history of MTC or MEN2 and perform a genetic test for RET proto-oncogene mutation.

Calcitonin ≥ 50 and < 100 ng/L

Action: The participant should be referred to a endocrinologist or thyroid specialist for further evaluation. The participant should remain in the study and can continue trial product.

Background: These values were found in 8 (0.14%) of the population of 5817 patients with thyroid nodular disease[88]. Two of these participants were diagnosed with MTC and two were diagnosed with C-cell hyperplasia, resulting in a positive predictive value of a C-cell anomaly of 50%.

Diagnostic evaluation should include:

- thyroid ultrasound examination
- if available, and if there are no contraindications, a pentagastrin stimulation test should be done. For participants with positive pentagastrin stimulation test, surgery should be considered
- if pentagastrin stimulation test is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information about the need for surgery

Calcitonin ≥ 10 and < 50 ng/L

Action: The participant can continue in the study, on study product. Continue sampling of calcitonin according to the protocol.
If the value is from the last sample taken in the study, the participant should be referred to a endocrinologist or thyroid specialist for further evaluation.

Background: Calcitonin values from 20-50 ng/L were found in up to 1% of participants of the population of 5817 patients with thyroid nodular disease[88]. The predictive value of a C-cell anomaly for this calcitonin level was 8.3%. However, the likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.

For calcitonin values between 10-20 ng/L, Costante et al.[88] identified 216 (3.7%) patients. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin value of 33 ng/L and had C-cell hyperplasia at surgery. Two other studies used a cut-off of calcitonin >10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT >10 and <20 ng/L to allow conclusions.[89, 90]

10.10 Appendix 10: Country-specific requirements

Czech Republic

- Section 1.2 Participant's full date of birth is not allowed to be collected and must be shortened to Year of Birth in CRF.
- Section 5.2 and Appendix 4 (Section 10.4): Monthly pregnancy test (urine) for female participant of childbearing potential is needed. The additional pregnancy testing will not be reported in the CRF. In case of pregnancy, trial product will be discontinued.

Germany

- Section 1.2 Participant's full date of birth is not allowed to be collected and must be shortened to Year of Birth in CRF.
- Section 8.3.1 Time period and frequency for collecting AE information: All SAEs must be recorded and reported to Novo Nordisk immediately, without undue delay, and the investigator must submit any updated SAE data to Novo Nordisk immediately, without undue delay.

Hungary

- Section 1.2 Participant's full date of birth is not allowed to be collected and must be shortened to Year of Birth in CRF.

South Africa

[redacted]

Slovakia

The investigator will be responsible for:

- notifying the IRB/IEC of SAEs – only death, as required by IRB/IEC procedures and local regulations
- providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- reporting any potential serious breaches to the sponsor immediately after discovery

The sponsor will be responsible for:

- providing written summaries of the status of the study annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- notifying the IRB/IEC of SAEs or other significant safety findings according to local regulations and procedures established by the IRB/IEC and/or regulatory authorities
- ensuring submission of protocol, protocol amendments, ICF, investigator brochure, CSR synopsis and other relevant documents to the IRB/IEC and/or regulatory authorities.

10.11 Appendix 11: Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BMR	basal metabolic rate
C-SSRS	Columbia-Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
[redacted]	
CRF	case report form
CRP	c-reactive protein
CSR	clinical study report
CT	(serum) calcitonin
CTFG	clinical trial facilitation group
DBL	database lock
DFU	directions for use
DPS	data points set
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European medicines agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HbA1c	glycated haemoglobin
HDL	High-density lipoprotein
HRT	hormone replacement therapy

hsCRP	High sensitive C-reactive Protein
IB	investigator's brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalised ratio
IRB	institutional review board
ISO	International Organization for Harmonization
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
J2R-MI	Jump to reference multiple imputation approach
KDIGO	Kidney Disease: Improving Global Outcomes
LAM	lactational amenorrhoea method
LAO-OT	last available observation during the on-treatment period
LDL	low-density lipoprotein
LPLT	last patient last treatment
MAR	missing at random
MEN2	multiple endocrine neoplasia type 2
MHP	mental health professional
MMRM	mixed model for repeated measurements
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NIMP	non-investigational medicinal product
NYHA	New York Heart Association
OR	odds ratio
PCD	primary completion date
PD	pharmacodynamics
PHQ-9	Patient Health Questionaire-9
PK	pharmacokinetics
Pop-PK	population pharmacokinetic
PYE	patient years of exposure
PYO	patient years of observation
QTLs	quality tolerance limits
RET	rearranged during transfection

RTSM/IWRS	Systems used for randomisation and trial supplies management (also Interactive Web Response System)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	safety analysis set
s.c.	subcutaneous(ly)
SD	standard deviation
SOP	standard operational procedures
SUSAR	suspected unexpected serious adverse reaction
T2D	Type 2 diabetes
TEE	total daily energy expenditure
[redacted]	
TMM	Trial Materials Manual
TP-MI	Tipping-point multiple imputation analysis
TSH	Thyroid stimulating hormone
ULN	upper limit of normal
US	United States of America
VLDL	very low-density lipoprotein
WOCBP	woman of childbearing potential

10.12 Appendix 12: Protocol amendment history

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

Protocol version 2.0: 30 June 2022, global

The amendment from version 1.0 of the protocol to version 2.0 was an administrative amendment as version 1.0 of the protocol was an internal version.

Protocol version 3.0: 28 September 2022, global

The amendment from version 2.0 of the protocol to version 3.0 is substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

Section # and name	Description of change	Brief rationale
Throughout the document	Editorial changes e.g. spelling errors, punctuation or updates to more exact wording.	To improve readability.
Section 1.1 Synopsis	Updated with the relevant changes described below.	For completeness of the document.
Section 1.2 Flowchart	Discontinuation criteria line added. Crosses corrected for contraceptive counselling, attend visit fasting, anti semaglutide antibodies and administration of trial product.	It shall be confirmed at all visits from visit 3 to visit 21 that the participant is still eligible to continue trial product. To align with treatment procedures and avoid unnecessary blood sampling.
Section 3 Objectives, endpoints and estimands	Two confirmatory secondary endpoints added.	To evaluate the difference in treatment effect between semaglutide 7.2 mg and 2.4 mg.
Section 4.1 Overall design	Number of participants increased to 1400 and randomisation changed to 5:1:1. Figure 4-1 updated accordingly. Number of participants in the MRI subpopulation increased to 210.	To increase the safety database for semaglutide 7.2 mg. To reflect the changes in number of participants and randomisation.
Section 5.2 Exclusion criteria	New criteria 8 added.	To avoid interference on endpoints from previous use of GLP-1 receptor agonists.

Section # and name	Description of change	Brief rationale
Section 7.1.1.1 Hepatic events requiring temporary discontinuation of study intervention Section 8.3 Adverse events and other safety reporting Section 10.2 Appendix 2: Clinical laboratory tests Section 10.6 Appendix 6: Hepatic Safety: Suggested actions and follow-up assessments.	New section added. New footnote added to Table 8-1 Hepatic event text deleted. New appendix added.	Collection of hepatic events has been updated.
[redacted]		
Section 9.1.1 Multiplicity adjustment Section 9.3.3.1 Confirmatory secondary estimands	Text added.	To align with the new endpoints added in Section 3.
Section 9.5 Sample size determination	Numbers updated	Updated to reflect the increased sample size.

Protocol version 4.0: 20 January 2023, global

The amendment from version 3.0 of the protocol to version 4.0 is substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union. The primary reason for this protocol amendment was to include additional safety and clinical outcome assessments.

Overall rationale for the amendment

Section # and name	Description of change	Brief rationale
Throughout the document	Editorial changes e.g. spelling errors, punctuation or updates to more exact wording.	To improve readability.

Section 1.2 Flowchart	Biochemistry and haematology assessments added at V16.	To add an additional assessments approximately half-way through the maintenance period.
Section 1.2 Flowchart	PHQ-9 and C-SSRS added to V8, V10, V14 and V18. Removed from V12.	To improve the evaluation of mental health for the participants on the 7.2 mg dose.
Section 1.2 Flowchart	Handout of PK diaries at V22 removed from flowchart.	Participants will not administer treatment after V22.
6.5 Dose modification	Added that delaying dose escalation is allowed.	This was previously only mentioned in the justification for dose section. Added in this section as well for clarity.
Section 7. 1 Discontinuation of study intervention	Calcitonin ≥ 100 ng/L added as a discontinuation criterion.	To evaluate safety for semaglutide 7.2 mg.
Section 8.2.2. Mental health assessment instruments	PHQ-9 and C-SSRS at V8, V10, V14 and V18 added to text. Removed from V12 from text.	To improve the evaluation of mental health for the participants on the 7.2 mg dose.
Section 8.3 Table 8-1	Added 'Acute kidney injury'.	Added based on feedback from FDA.
Section 10.2 Appendix 2 Table 10-2	Added direct bilirubin, amylase, calcitonin and lipase.	To evaluate safety for semaglutide 7.2 mg.
Section 10.2 Appendix 2 Table 10-3	Criteria for hepatic laboratory outliers added.	Added based on feedback from FDA.
Section 10.3.3	Added 'Acute kidney injury'.	Added based on feedback from FDA.
Section 10.9 Appendix 9: Monitoring of calcitonin.	Appendix added.	To evaluate safety for semaglutide 7.2 mg.
Section 10.10 Appendix 10 Country-specific requirements	Slovakia requirements added.	Added based on feedback from IRB/IEC.

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