Cover Page for SAP

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05649137
Sponsor trial ID:	NN9536-7545
Official title of study:	Effect and safety of semaglutide 7.2 mg once-weekly in participants with obesity and type 2 diabetes
Document date*	07-January-2025

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

Statistical Analysis Plan

Protocol Title: Effect and safety of semaglutide 7.2 mg once weekly in participants with obesity and type 2 diabetes

Substance: semaglutide

Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

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Version History

This Statistical Analysis Plan (SAP) for study NN9536-7545 is based on the protocol version 4.0 dated 22JUN2023.

SAP Version	Date	Change	Rationale
1.0	07-Jan-2025	-	-

List of abbreviations

AE	*adverse event*
ANCOVA	*analysis of covariance*
BMI	*body mass index*
BW	*body weight*
bpm	*beats per minute*
CI	*confidence interval*
cm	*centimetre*
COEQ	*control of eating questionnaire*
CSR	*clinical study report*
CVD	*cardiovascular disease*
DBL	*database lock*
FAS	*full analysis set*
FPG	*fasting plasma glucose*
HbA1c	*glycated haemoglobin*
HDL	*high-density lipoprotein*
hsCRP	*high sensitivity C-reactive protein*
ICH	*International Council on Harmonization*
IMP	*investigational medicinal product*
J2R-MI	*jump to reference multiple imputation*
kg	*kilogram*
LAO-OT	*last available observation during the on-treatment period*
LDL	*low-density lipoprotein*
LR	*logistic regression*
MedDRA	*medical dictionary for regulatory activities*
mg	*milligrams*
mg/dL	*milligrams per decilitre*
MI	*multiple imputation*
mmHg	*millimetre of mercury*
mmol/mol	*millimoles per mol*
MMRM	*mixed model for repeated measurements*
OAD	*oral antidiabetic drug*
OR	*odds ratio*
PEth	*Phosphatidylethanol*
PK	*pharmacokinetics*
POPEth	*1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanol*
PYE	*patient years of exposure*
PYO	*patient years of observation*
RD-MI	*multiple imputation using retrieved subjects*
SAP	*statistical analysis plan*
SAE	*serious adverse event*
SAS	*safety analysis set*
s.c.	*subcutaneous*
SD	*standard deviation*
TEAE	*treatment-emergent adverse event*

T2D	*type 2 diabetes*
TFEQ-R18V2	*three factor eating questionnaire revised 18-itmes version 2*
TFL	*tables, figures and listings*
TP-MI	*tipping-point multiple imputation*
VLDL	*very-low-density lipoprotein*

1 Introduction

This SAP is based on protocol version 4.0 dated 22Jun2023. Changes from the protocol are provided in section 4.8.

1.1 Objectives, Endpoints, and Estimands

Table 1-1 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 and T2D	**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 and T2D.	≥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 and T2D.	**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 and T2D.	≥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 and T2D.	≥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 change in waist circumference after 72 weeks, in adults with obesity and T2D.	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 placebo as an adjunct to a reduced-calorie diet and increased physical activity, with respect to change in HbA_{1c} after 72 weeks, in adults with obesity and T2D.	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 72)	%
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 and T2D, on other factors related to body weight after 72 weeks.	**Supportive secondary:**		
	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 and T2D, 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
	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

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 and T2D, on glucose metabolism after 72 weeks.	***Glucose metabolism parameters***		
	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
	HbA_{1c} < 7.0 % (53 mmol/mol)	From baseline (week 0) to end of treatment (week 72)	Count of participant
	HbA_{1c} ≤ 6.5 % (48 mmol/mol)	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 and T2D, 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 and T2D.	Change in pulse	From baseline (week 0) to end of treatment (week 72)	bpm
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 severe hypoglycaemic episodes after 81 weeks, in adults with obesity and T2D.	Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes	From baseline (week 0) to end of treatment (week 81)	Count of events
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 and T2D, 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
To compare the safety 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, with respect to severe hypoglycaemic episodes after 81 weeks, in adults with obesity and T2D.	Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes	From baseline (week 0) to end of treatment (week 81)	Count of events
Exploratory	Title	Time frame	Unit
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 and T2D, on change in concomitant treatment after 72 weeks.	***Concomitant treatment***		
	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
	Change in concomitant OAD medication (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 and T2D, on measures of physical strength after 72 weeks.	***Physical strength parameters***		
	Change in sit-to-stand test	From baseline (week 0) to end of treatment (week 72)	Repetitions
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 and T2D, on other clinical outcome assessments after 72 weeks.	***Clinical outcome assessments***		
	CoEQ: Change in scores from the 4 domains and 19 individual items	From baseline (week 0) to end of treatment (week 72)	Score points
	TFEQ-R18v2: Change in scores from the 18 items • Uncontrolled eating • Cognitive Restraint • Emotional Eating	From baseline (week 0) to end of treatment (week 72)	Score points
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 and T2D, on alcohol consumption after 72 weeks.	***Alcohol consumption***		
	Change in alcohol consumption category by phosphatidylethanol	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 and T2D, on usage of tobacco after 72 weeks.	***Tobacco usage***		
	Change in smoking status	From baseline (week 0) to end of treatment (week 72)	Count of participant
	Change in tobacco use	From baseline (week 0) to end of treatment (week 72)	Average number per day
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 and T2D, on other factors related to body weight after 72 weeks.	***Body weight parameters***		
	Change in waist to height ratio	From baseline (week 0) to end of treatment (week 72)	Change in ratio
	Achieving waist to height ratio < 0.53	From baseline (week 0) to end of treatment (week 72)	Count of participant
	Achieving BMI < 27 kg/m^2	From baseline (week 0) to end of treatment (week 72)	Count of participant

Abbreviations: AEs = adverse events; BMI = body mass index; CoEQ = Control of Eating Questionnaire; HbA_{1c} = glycated haemoglobin; HDL = high-density lipoprotein; hsCRP = high-sensitivity c-reactive protein; LDL = low-density lipoprotein; OAD = oral antidiabetic drug; SAEs = serious adverse events; s.c. = subcutaneous; T2D = type 2 diabetes; TFEQ-R18v2 = Three Factor Eating Questionnaire revised 18-items version 2; VLDL = very low-density lipoprotein.

1.1.1 Estimands

1.1.1.1 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 and T2D, 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) and T2D treated with either lifestyle intervention or treated with 1-3 marketed oral antidiabetic drugs according to local label.
- **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, 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 tolerability 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.

1.1.1.2 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. 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.

Note that in addition to the intercurrent events defined for the co-primary estimands, the initiation of anti-diabetic rescue medication will also be considered as an intercurrent event to estimate the secondary estimand for the secondary objectives addressing glucose metabolism.

1.1.1.3 Exploratory estimands

The exploratory estimands for exploratory endpoints related to clinical outcome assessments (CoEQ and TFEQ-R18v2) and exploratory endpoints related to body weight parameters are similar to the co-primary estimands except for the endpoint attribute. The exploratory estimands with continuous endpoints are similar to the co-primary estimand for relative weight change. The exploratory estimands with binary endpoints for secondary objectives are similar to the co-primary estimand for ≥ 5% body weight reduction.

1.1.1.4 Additional estimand

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 and T2D, 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) or initiated anti-diabetic rescue medication (only applicable to objectives addressing glucose metabolism).

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) and T2D treated with either lifestyle intervention or treated with 1-3 marketed oral antidiabetic drugs according to local label.
- **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 secondary, supportive secondary and exploratory objectives in the population.

Note that along with above defined intercurrent events, initiation of anti-diabetic rescue medication will also be considered as an intercurrent event to estimate the additional estimand for the primary objective and secondary objectives addressing glucose metabolism.

1.1.1.5 Supplementary estimand

Prompted by the occurrence of a supply issue during trial conduct, a supplementary 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 and T2D, 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) and had their treatment dosing not been impacted by the supply issue.

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

- **Population:** Adults with obesity (defined as BMI ≥ 30 kg/m^2) and T2D treated with either lifestyle intervention or treated with 1-3 marketed oral antidiabetic drugs according to local label.
- **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 except due to supply issue.
- **Remaining intercurrent events:** Treatment discontinuation and initiation of other anti-obesity therapies are both handled by the hypothetical strategy. Dose reduction of randomised treatment, in general, is handled by the treatment policy strategy except if due to the supply issue. Dose reduction due to supply issue will be identified as dose reduction (not related to any AE) by site and timing where supply issue was ongoing and will be handled by hypothetical strategy.
- **Population-level summary:** 1) difference in mean changes and 2) odds ratio between treatment conditions.

Rationale for estimand: The supplementary estimand aims at reflecting the treatment effect (including all doses of semaglutide) without the confounding effects of other anti-obesity therapies, trial product discontinuation or dose reduction (non-AE related) due to supply issue.

A similar supplementary estimand also applies to all confirmatory secondary objectives.

Note that along with above defined intercurrent events, initiation of anti-diabetic rescue medication will also be considered as an intercurrent event to estimate the supplementary estimand for the primary objective and secondary objectives addressing glucose metabolism.

1.2 Study Design

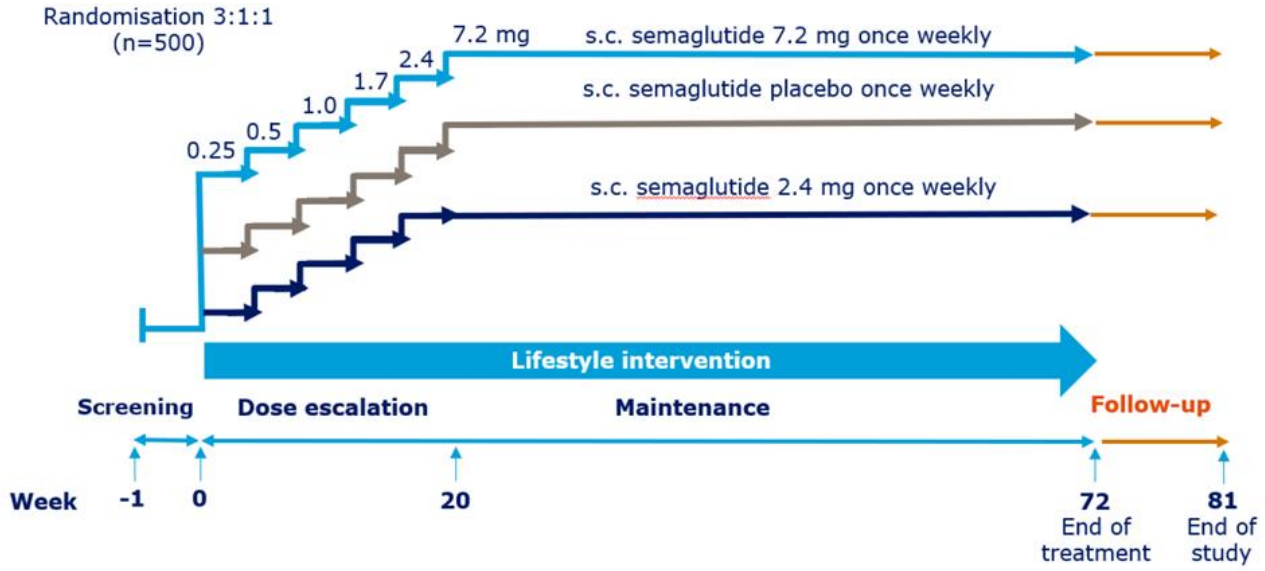
This is an interventional, multi-national, multi-centre, randomised, double-blind, placebo-controlled, three-armed, parallel group study.

Approximately 500 participants will be randomised 3:1:1 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 and T2D.

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 1-1**). The study design is provided in the protocol section 4.1.

Figure 1-1 Study design



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

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.

2 Statistical Hypothesis

For the below co-primary estimands with primary endpoints -

1) change in body weight (%) from baseline to end of treatment (week 72)
2) body weight reduction ≥ 5% (yes/no) at end of treatment (week 72)

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:

$$\mu = \text{semaglutide 7.2 mg} - \text{placebo}$$

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

$$\text{OR} = \frac{\text{odds[semaglutide 7.2 mg]}}{\text{odds[placebo]}}$$

Superiority

1) H_{01}: $\mu \geq 0.0$ percentage points against H_{a1}: $\mu < 0.0$ percentage points

and

2) H_{02}: OR ≤ 1 against H_{a2}: 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 %, and ≥ 20 % (yes/no) at end of treatment (week 72) a hypothesis similar to 2) will be tested.

For the confirmatory secondary estimands with the endpoints change in waist circumference (cm) and change in HbA_{1c} (%) from baseline (week 0) to end of treatment (week 72) a hypothesis similar to 1) will be tested.

2.1 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 with endpoints change in body weight (%) from baseline (week 0) to end of treatment (week 72) and body weight reduction ≥ 5 % (yes/no) at end of treatment (week 72).

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 the endpoint change in waist circumference (cm) from baseline (week 0) to 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 HbA_{1c} (%) from baseline (week 0) to end of treatment (week 72).

3 Analysis Sets

The following participant analysis sets are defined:

Table 3-1 Participant analysis sets

Participant Analysis Set	Description
Full analysis set	All randomised participants. Participants will be analysed according to the randomised treatment.
Safety analysis set	All participants who are exposed to at least one dose of randomised trial product. Participants are analysed according to the treatment they actually received.

The following data points sets are defined:

Table 3-2 Defined data point sets

Defined data points set (DPS)	Description
In-trial (DPS1)	All data points obtained at or after randomisation up to the end of study visit regardless of discontinuation, dose reduction or initiation of other anti-obesity therapies.
On-treatment (DPS2)	All data points where participants are treated with trial product. The participant is considered "on-treatment" regardless of dose reduction and initiation of other anti-obesity therapies. In general, a time point is considered as on-treatment if it falls in the period from the date of first trial product administration to date of last trial product administration (+14 days) excluding any off-treatment time intervals triggered by at least two consecutive missed doses. For the evaluation of AEs and potential pregnancies, the lag time for each on-treatment time interval is 9 weeks (63 days).
On-treatment until first discontinuation of trial product or initiation of other anti-obesity therapies (DPS3)	All data points obtained at or after randomisation until first discontinuation of trial product or initiation of other anti-obesity therapies, regardless of dose reduction.
On-treatment until first discontinuation of trial product or initiation of other anti-obesity therapies or initiation of anti-diabetic rescue medication (DPS4)	All data points obtained at or after randomisation until first discontinuation of trial product or initiation of other anti-obesity therapies or initiation of anti-diabetic rescue medication, regardless of dose reduction.
On-treatment until first discontinuation of trial product or initiation of anti-obesity rescue medication or dose reduction (non-AE related) due to supply issue (DPS5)	All data points obtained at or after randomisation until first discontinuation of trial product or initiation of anti-obesity therapies, regardless of dose reduction but with exception of dose reduction identified as potentially caused by supply issue (i.e. data collected for participants impacted during periods of supply issue with dose reductions not related to an AE are excluded from this data set).
On-treatment until first discontinuation of trial product or initiation of anti-obesity rescue medication or initiation of anti-diabetic rescue medication or dose reduction (non-AE related) due to supply issue (DPS6)	All data points obtained at or after randomisation until first discontinuation of trial product or initiation of anti-obesity therapies or initiation of anti-diabetic rescue medication regardless of dose reduction but with exception of dose reduction identified as potentially caused by supply issue (i.e. data collected for participants impacted during periods of supply issue with dose reductions not related to an AE are excluded from this data set).

- FAS and DPS1 are used to estimate the co-primary estimands and the secondary estimands for secondary objectives.
- FAS and DPS3 are used to estimate the additional estimand for the primary objective and secondary objectives except those addressing glucose metabolism.
- FAS and DPS4 are used to estimate the additional estimand for the primary objective and secondary objectives addressing glucose metabolism.
- FAS and DPS5 are used to estimate the supplementary estimand for the primary and secondary confirmatory endpoints except those addressing glucose metabolism.
- FAS and DPS6 are used to estimate the supplementary estimand for the primary and secondary confirmatory endpoints addressing glucose metabolism.
- FAS and both DPS1 and DPS2 (14 days) are used to present efficacy data.
- SAS and DPS3 are used to estimate the additional estimand for the safety objective related to pulse.
- SAS and either DPS2 (14 days) for e.g. lab data, pulse and ECG or DPS2 (63 days) for e.g. AEs are used to present on-treatment safety data. For e.g. deaths and AEs with a potential long latency to diagnosis, the evaluation will be based on the SAS and the in-trial period (DPS1).
- The in-trial (DPS1) and on-treatment (DPS2 [63 days]) periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

4 Statistical Analyses

4.1 General Considerations

All participants from all three arms will contribute to the analysis. All tests are tests of superiority of semaglutide s.c. 7.2 mg once weekly versus placebo. 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.

Handling of missing baseline data

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.

4.2 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 1.1.1.1.

4.2.1 Main Analysis

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.

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, the Firth's maximum-likelihood estimation will be used when performing the logistic regression.

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.

Average probabilities and treatment differences in probability with corresponding CIs will also be reported alongside the odds and odds ratios in the CSR.

Multiple imputation approach using retrieved subjects (RD-MI): The imputation approach for the primary analysis is a multiple imputation similar to the one described by McEvoy[6]. For participants in the semaglutide s.c. 7.2 mg once weekly, 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 multiple imputation approach is done in three steps:

- **Imputation**: Defines an imputation model using retrieved subjects from FAS and done within groups defined by randomised treatment and end of treatment status (on-drug/off-drug). 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. If no LAO-OT exists post-baseline then the LAO-OT will be the baseline body weight and the timing will be 0. No interactions will be included. If the imputation model cannot be fit the model will be reduced until the model can be fit. Reduction will be done in a fixed order by first removing gender and then removing baseline body weight (kg). If the imputation model with only LAO-OT of body weight (kg) cannot be fit, the imputation will be done regardless of the randomised treatment arm. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 72 body weight for each randomised treatment arm. This will be done 1,000 times and results in 1,000 complete data sets. The trial ID (95367545) will be used as seed number.

- **Analysis**: Analysis of each of the 1,000 complete data sets, using the analysis models (ANCOVA and logistic regression) results in 1,000 sets of estimates. For binary endpoints the results from the logistic regression model will be used to predict probabilities of achieving the response condition for all participants had they (counterfactually) been assigned to each specific treatment. Odds and treatment odds ratios will be estimated from the averaged predicted probabilities. Confidence intervals will be calculated using sandwich estimator. Average probabilities and treatment differences in probability with corresponding CIs will also be estimated.

- **Pooling**: Integrates the 1,000 times 2 estimation results into two final results using Rubin's formula.

4.2.2 Sensitivity Analysis

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 assumes 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. The multiple imputation approach is done as above with the first step replaced by

- **Imputation**: Defines an imputation model using semaglutide placebo subjects from FAS with a week 72 measurement. The model will be a linear regression of gender (male/female) as factor and baseline body weight (kg) as covariate. No interactions will be included. If the imputation model cannot be fit the model will be reduced until the model can be fit. Reduction will be done in a fixed order by first removing gender and then removing baseline body weight (kg). The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week

72 body weight values for each randomised treatment arm. This will be done 1,000 times and results in 1,000 complete data sets.

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 72. 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.

4.2.3 Supplementary Analysis

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

The estimation of the additional and supplementary estimands 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. If the model cannot be fit using an unstructured covariance matrix, alternate covariance matrix will be tried if considered appropriate. Measurements for different participants are assumed to be independent.

The estimation of the additional and supplementary 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. The results from the logistic regression model will be used to predict probabilities of achieving the response condition for all participants had they (counterfactually) been assigned to each specific treatment. Odds and treatment odds ratios will be estimated from the averaged predicted probabilities. Confidence intervals will be calculated using sandwich estimator. Average probabilities and treatment differences in probability with corresponding CIs will also be estimated and reported in the CSR.

All participants contribute to the analysis, however, data points collected after treatment discontinuation and initiation of anti-obesity medication or initiation of anti-diabetic rescue medication (only applicable to primary and secondary objectives addressing glucose metabolism), as detailed in 3, will not be included in the analyses addressing the additional estimand. Additionally, data points collected after relevant dose reductions during periods of supply issue will not be included in the analyses addressing the supplementary estimand.

Table 4-1 Analysis and imputation methods to address the primary and additional as well as supplementary estimands for primary endpoints

Endpoint title	Unit	Endpoint	Analysis Set	Estimand strategy	Statistical model	Imputation approach	Sensitivity Analysis
Relative change in body weight	%	Continuous	FAS	Treatment policy	ANCOVA	RD-MI	J2R-MI, TP-MI
			FAS	Hypothetical	MMRM		
≥5% body weight reduction (yes/no)	Count of participants	Binary	FAS	Treatment policy	LR	RD-MI	Non responders
			FAS	Hypothetical	LR	MMRM	

4.3 Secondary Estimands Analysis

4.3.1 Confirmatory Secondary Estimands

The confirmatory secondary endpoints are listed in Table 1-1. All tests are tests of superiority of semaglutide s.c. 7.2 mg once weekly versus placebo.

All confirmatory secondary endpoints will be analysed using the same analysis model and imputation approach as used to address the co-primary estimand for the primary objectives addressing weight management defined in 4.2.1. 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, the Firth's maximum-likelihood estimation will be used when performing the logistic regression.

4.3.1.1 Sensitivity Analysis

For the change in waist circumference and change in HbA_{1c} (%) 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 as defined in section 4.2.1.

4.3.1.2 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 in 4.2.3.

Table 4-2 Analysis and imputation methods to address the secondary and additional as well as supplementary estimands for confirmatory secondary endpoints

Endpoint title	Unit	Endpoint	Analysis set	Estimand strategy	Statistical model	Imputation approach	Sensitivity Analysis
≥10% body weight reduction (yes/no)	Count of participants	Binary	FAS	Treatment policy	LR	RD-MI	Non responders
			FAS	Hypothetical	LR	MMRM	
≥15% body weight reduction (yes/no)	Count of participants	Binary	FAS	Treatment policy	LR	RD-MI	Non responders
			FAS	Hypothetical	LR	MMRM	
≥20% body weight reduction (yes/no)	Count of participants	Binary	FAS	Treatment policy	LR	RD-MI	Non responders
			FAS	Hypothetical	LR	MMRM	
Change in waist circumference	cm	Continuous	FAS	Treatment policy	ANCOVA	RD-MI	J2R-MI
			FAS	Hypothetical	MMRM		
Change in HbA_{1c}	%	Continuous	FAS	Treatment policy	ANCOVA	RD-MI	J2R-MI
			FAS	Hypothetical	MMRM		

4.3.2 Supportive Secondary Estimands

The supportive secondary endpoints as listed in Table 1-1 will be analysed as explained below.

Analysis addressing the secondary estimand

The supportive secondary endpoints related to body weight, cardiovascular, glucose metabolism and safety will be analysed using the same imputation approach as used for the primary endpoint. The statistical model for continuous endpoints will be the same linear regression as for the primary endpoints (ANCOVA) with treatment as a factor and the baseline value of the endpoint as covariate. The statistical model for responder endpoints is a logistic regression using treatment as a factor and baseline value of the endpoint as covariate. An unstructured covariance matrix for measurements within the same participant will be employed. If the model cannot be fit using an unstructured covariance matrix, alternate covariance matrix will be tried if considered appropriate. Measurements for different participants are assumed to be independent.

Analysis addressing the additional estimand

The supportive secondary endpoints related to body weight, cardiovascular, glucose metabolism and safety addressing the additional estimand will be analysed using the same MMRM as described for the primary endpoints addressing the additional estimand with randomised treatment as a factor and the baseline value of the endpoint as covariate all nested within visit as a factor.

Responder endpoints addressing the additional estimand will be analysed using the same MMRM as described for the primary endpoint change in body weight (%) addressing the additional estimand except that the endpoint will be used as response variable in the model. For participants with missing assessments at week 72, individual values will be predicted from the MMRM and used to classify each participant as a responder or not. This classification will then be analysed using a logistic regression model with randomised treatment as a factor and baseline value of the endpoint as covariate.

Analysis of safety endpoints

The safety endpoint pulse will be analysed using an MMRM for efficacy as described in 4.2.3. These analyses will be based on the safety analysis set.

Table 4-3 Analysis and imputation methods to address the secondary and additional estimands for supportive secondary endpoints

Endpoint title	Unit	Endpoint	Estimand Strategy	Analysis set	Statistical model	Imputation approach
Change in body weight	kg	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	

Endpoint title	Unit	Endpoint	Estimand Strategy	Analysis set	Statistical model	Imputation approach
Change in BMI	kg/m^2	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in systolic blood pressure	mmHg	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in diastolic blood pressure	mmHg	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in lipids Total cholesterol High-density lipoprotein (HDL) cholesterol Low density lipoprotein (LDL) cholesterol Very-low-density lipoprotein (VLDL) cholesterol Triglycerides Free fatty acids	mg/dL mmol/L	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in high-sensitivity c-reactive protein (hsCRP)	mg/L	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in fasting plasma glucose	mmol/L mg/dL	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in fasting serum insulin	mIU/mL pmol/L	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
HbA_{1c} < 7.0 % (53 mmol/mol)	Count of participant	Binary	Treatment policy	FAS	LR	RD-MI

Endpoint title	Unit	Endpoint	Estimand Strategy	Analysis set	Statistical model	Imputation approach
			Hypothetical	FAS	LR	MMRM
$HbA_{1c} \leq 6.5$ % (48 mmol/mol)	Count of participant	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM
Number of Adverse Events (AEs)*	Count of events	Continuous		FAS	Descriptive Statistics	
Number of Serious Adverse Events (SAEs)*	Count of events	Continuous		SAS	Descriptive Statistics	
Change in pulse	bpm	Continuous	Hypothetical	SAS	MMRM	
Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes*	Count of events	Binary (only descriptive statistics)		SAS		

* Compare the safety of semaglutide s.c. 7.2 mg versus placebo and 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 and T2D, after 81 weeks.

4.4 Exploratory Estimands Analysis

Exploratory endpoints as listed in Table 1-1 will be analysed as explained below.

4.4.1 Control of Eating Questionnaire (CoEQ)

The CoEQ comprises 21-items designed to assess the intensity and type of food craving, as well as subjective sensations of appetite and mood. In STEP UP a version with 19 items has been used (see Table 4-4). One of the two excluded items is open-ended and addresses specific foods, and the other excluded item concerns how difficult it has been to resist this specific food; and the items are therefore not part of any of the four domains.

Table 4-4 Overview of items in CoEQ

Item No.	Item text	Response scale
1	How hungry have you felt?	10 = Extremely hungry, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all hungry
2	How full have you felt?	10 = Extremely full, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all full

3	How strong was your desire to eat sweet foods?	10 = Extremely strong, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all strong
4	How strong was your desire to eat salty and spicy foods (french fries, potato chips, burgers, pizza, etc.)?	10 = Extremely strong, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all strong
5	How happy have you felt?	10 = Extremely happy, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all happy
6	How anxious have you felt?	10 = Extremely anxious, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all anxious
7	How alert have you felt?	10 = Extremely alert, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all alert
8	How contented have you felt?	10 = Extremely contended, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all contended
9	During the last 7 days how often have you had food cravings?	10 = Very often, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all
10	How strong have any food cravings been?	10 = Extremely strong, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all strong
11	How difficult has it been to resist any food cravings?	10 = Extremely difficult, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all difficult
12	How often have you eaten in response to food cravings?	10 = After every one, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all
13	How often have you had cravings for chocolate and chocolate flavoured foods?	10 = Extremely often, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all
14	How often have you had cravings for other sweet foods (cakes, pastries, biscuits, etc)?	10 = Extremely often, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all
15	How often have you had cravings for fruit or fruit juice?	10 = Extremely often, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all
16	How often have you had cravings for dairy foods (cheese, yoghurt, milk, etc.)?	10 = Extremely often, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all
17	How often have you had cravings for starchy foods (bread, rice, pasta, etc.)?	10 = Extremely often, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all
18	How often have you had cravings for salty and spicy foods (french fries, potato chips, burgers, pizza, etc.)?	10 = Extremely often, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all
19	Generally, how difficult has it been to control your eating?	10 = Extremely difficult, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 = Not at all difficult

Item scores

The CoEQ item are scores on an 11-point graded response scale ranging from 10 to 0.

Domain scores

The sum of the items in each domain is calculated and divided by the number of items in the domain to obtain a domain score. Items 1 and 2 are not included in any domain score. Details are given in Table 4-5.

Table 4-5 Overview of domains for CoEQ

Domain	Items included in domain	Comment
Craving Control	Question 9, 10, 11, 12 and 19	The domain score is reversed such that a greater score represents a greater level of Craving Control (i.e. 10 to 0, 9 to 1, …, 0 to 10)
Positive Mood	Question 5, 6, 7 and 8	Scores from item 6 are reversed (i.e. 10 to 0, 9 to 1, …, 0 to 10)
Craving for Savoury	Question 4, 16, 17 and 18	
Craving for Sweet	Question 3, 13, 14, and 15	

Missing data at instrument level will be handled in the following way. To score a domain it is required that a least 50% of the items need to be answered. Then, the domain is scored based on the average of the items answered. If less than 50% of the items of a domain are answered no score will be derived.

4.4.2 Three Factor Eating Questionnaire (TFEQ-R18v2)

TFEQ-R18V2 comprises 18 items in a 4-point response format, which are aggregated to three separate scale scores:

- Uncontrolled eating - assesses the tendency to lose control overeating when feeling hungry or when exposed to external stimuli,
- Cognitive Restraint - assesses the tendency to control food intake in order to influence body weight and body shape,
- Emotional Eating – measures the propensity to overeat in relation to negative mood states, e.g., when feeling lonely, anxious, or depressed.

The recoding of questions and calculation of scores will be conducted according to Scoring Instruction document. Prior to analyses, all raw scores will be transformed to 0-100 scale.

4.4.3 PEth Test

Phosphatidylethanol (PEth) is a direct biomarker for alcohol (ethanol) intake. In presence of ethanol, phosphatidylcholine is converted to PEth on the red blood cell. Its levels correlate with the amount of alcohol consumed within the previous 2 weeks and may be detected in the blood up to 2 to 4 weeks after excessive alcohol consumption. For POPEth (1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanol), a PEth homolog, following clinical reference limits are defined in Table 4-6.

Table 4-6 Categorical interpretation of POPEth concentrations in blood.

Nr	Category (Interpretation)	POPEth concentration (ng/mL)
0	Not detected	< 10
1	Abstinence or light alcohol consumption (< 2 drinks per day for several days a week)	10 – 19
2	Moderate alcohol consumption (up to 4 drinks per day for several days a week)	20-200
3	Heavy alcohol consumption or chronic alcohol use (at least 4 drinks per day several days a week)	> 200

For analysis of the endpoint of change in alcohol consumption the two lowest categories will be combined into one, i.e.: 'Not detected or abstinence or light alcohol consumption (< 2 drinks per day for several days a week)'. Shift table will be presented in the CSR for the endpoint.

4.4.4 Analyses addressing the exploratory estimand

The endpoints related to CoEQ, TFEQ-R18v2, BMI and waist to height ratio will be analysed using the same imputation approach as used for the co-primary endpoints. The statistical model for continuous endpoints will be the same linear regression as for the co-primary endpoint of relative change in body weight (ANCOVA) with treatment as a factor and the baseline value of the endpoint as covariate. For binary endpoints, estimation will be done using logistic regression as described for co-primary endpoint of body weight reduction ≥ 5% with treatment as factor and baseline body weight (kg) as covariate.

Handling of missing week 72 values of CoEQ item scores for the exploratory estimand

The imputation method RD-MI will be modified for the CoEQ item scores as follows:

1. Imputed values will be rounded to whole numbers.
2. Imputed values outside the 0-10 scale will be truncated to the nearest extreme value.

4.4.5 Analyses addressing the additional estimand

The continuous endpoints related to CoEQ and TFEQ-R18v2 and waist to height ratio will be analysed using the same MMRM as described for the continuous co-primary endpoint addressing the additional estimand with randomised treatment as a factor and the baseline value of the endpoint as covariate. For binary endpoints, estimation will be done with the same imputation approach and a similar logistic regression model as described in 4.2.3 for the binary co-primary endpoint addressing additional estimand.

Table 4-7 Analysis and imputation methods to address the secondary and additional estimands for exploratory endpoints

Endpoint title	**Unit**	**Endpoint**	**Estimand strategy**	**Analysis set**	**Statistical model**	**Imputation approach**
Change in lipid-lowering treatment (decrease, no change, increase)	Count of participant	Categorical		FAS	Descriptive Statistics	
Change in antihypertensive treatment (decrease, no change, increase)	Count of participant	Categorical		FAS	Descriptive Statistics	
Change in concomitant OAD medication (decrease, no change, increase)	Count of participant	Categorical		FAS	Descriptive Statistics	
Change in sit-to-stand test	Repetitions	Continuous		FAS	Descriptive Statistics	
CoEQ: Change in scores from the 4 domains and 19 individual items	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
TFEQ-R18v2: Change in scores from the 18 items	Score points	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in alcohol consumption category by PEth*	Count of participant	Categorical		FAS	Descriptive Statistics	
Change in smoking status	Count of participant	Categorical		FAS	Descriptive Statistics	
Change in tobacco use	Average number per day	Continuous		FAS	Descriptive Statistics	
Change in waist to height ratio	cm/cm	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Achieving waist to height ratio < 0.53	Count of participants	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM
Achieving BMI < 27 kg/m^2	Count of participant	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM

*PEth: Phosphatidylethanol.

4.5 Other Safety Analysis

All other collected safety data (e.g. lab data) that were not defined as endpoints will be summarised by descriptive statistics.

4.5.1 Adverse Events

Adverse events will be defined as in-trial, if the onset of the event occurs in the in-trial period, and as "treatment-emergent" (TEAE), if the onset of the event occurs in the on-treatment period. AEs 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. All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA 27.1).

4.6 Other Analysis

4.6.1 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, 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 studies 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.

4.7 Interim Analysis

There is no interim analysis planned for this study.

4.8 Changes to Protocol-planned Analysis

- It has been clarified how the imputation model in the primary imputation approach for the treatment policy strategy will be reduced if the model cannot fit. It has also been clarified how the J2R-MI is reduced if the imputation model cannot fit.

- Addition of exploratory endpoints addressing new exploratory objective of comparing effect of semaglutide 7.2 mg vs placebo on factors related to body weight after 72 weeks:
    - Change in waist to height ratio
    - Achieving waist to height ratio <0.53
    - Achieving BMI < 27 kg/m^2

- Change in the exploratory endpoint addressing alcohol consumption from a continuous endpoint of "Change in phosphatidyloethanol" to a categorical endpoint of "Change in alcohol consumption category by phosphatidyloethanol".

- Addition of supplementary estimand addressing supply issue for primary and confirmatory secondary endpoints.

- Estimand section is updated to include initiation of anti-diabetic rescue medication as an intercurrent event for objectives addressing glucose metabolism.

- Defined data points set description is updated to include initiation of anti-obesity therapies along with anti-diabetic rescue medication for objectives addressing glucose metabolism.

5 Sample size determination

The study used a 3:1:1 randomization ratio and had a sample size of 500 participants. The participants were randomized to receive either semaglutide s.c. 7.2 mg once weekly (300 participants), semaglutide s.c. 2.4 mg once weekly (100 participants), or placebo (100 participants).

For more details on sample size determination, see protocol section 9.5.

6 References

1. McEvoy BW. Missing data in clinical trials for weight management. J Biopharm Stat. 2016;26(1):30-6.