Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05646706
Sponsor trial ID:	NN9536-4999
Official title of study:	Effect and safety of semaglutide 7.2 mg once-weekly in participants with obesity
Document date:	26 November 2024

Statistical Analysis Plan

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

Substance: semaglutide

Redacted statistical analysis plan
includes redaction of personal identifiable and company confidential information.

.

Author

[redacted]
Biostatistics

Table of contents

Page

Table of figures

Page

Table of tables

Page

Version History

This Statistical Analysis Plan (SAP) for study NN9536-4999 is based on the protocol version 5.0 dated 22Jun2023.

SAP Version	Date	Change	Rationale
1.0	03Jul2024	-	-
2.0	26Nov2024	Minor corrections and clarifications as well as editorial changes	

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*
[redacted]	
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*
[redacted]	
PK	*pharmacokinetics*
[redacted]	
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*
[redacted]	
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 5.0 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.	**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
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
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.	**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 semaglutide s.c. 2.4 mg, 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.	Change in body weight	From baseline (week 0) to end of treatment (week 72)	kg
To compare the efficacy of pooled semaglutide s.c. 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 volume	From baseline (week 0) to end of treatment (week 72)	%, L
	Change in lean body volume	From baseline (week 0) to end of treatment (week 72)	%, L
	Change in visceral fat volume	From baseline (week 0) to end of treatment (week 72)	%, L
	Change in body weight	From baseline (week 0) to end of treatment (week 72)	%, kg
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
	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]			

[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.

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, 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 consider 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 like the co-primary estimands except for the endpoint attribute and/or comparator. The secondary estimands with continuous endpoints for secondary objectives are like the co-primary estimand for relative weight change, except for 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 like the co-primary estimand for ≥ 5% body weight reduction.

[redacted]

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, 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% bodyweight reduction at week 72.
- **Treatment condition:** Semaglutide s.c. 7.2 mg once weekly versus placebo both as anadjunct 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 (includingall 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.

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, 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), with or without weight-related comorbidities.
- **Endpoint:** 1) relative change from baseline to week 72 in body weight and 2) ≥ 5% bodyweight reduction at week 72.
- **Treatment condition:** Semaglutide s.c. 7.2 mg once weekly versus placebo both as anadjunct 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 betweentreatment 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) during supply issue.

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

1.2 Study Design

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

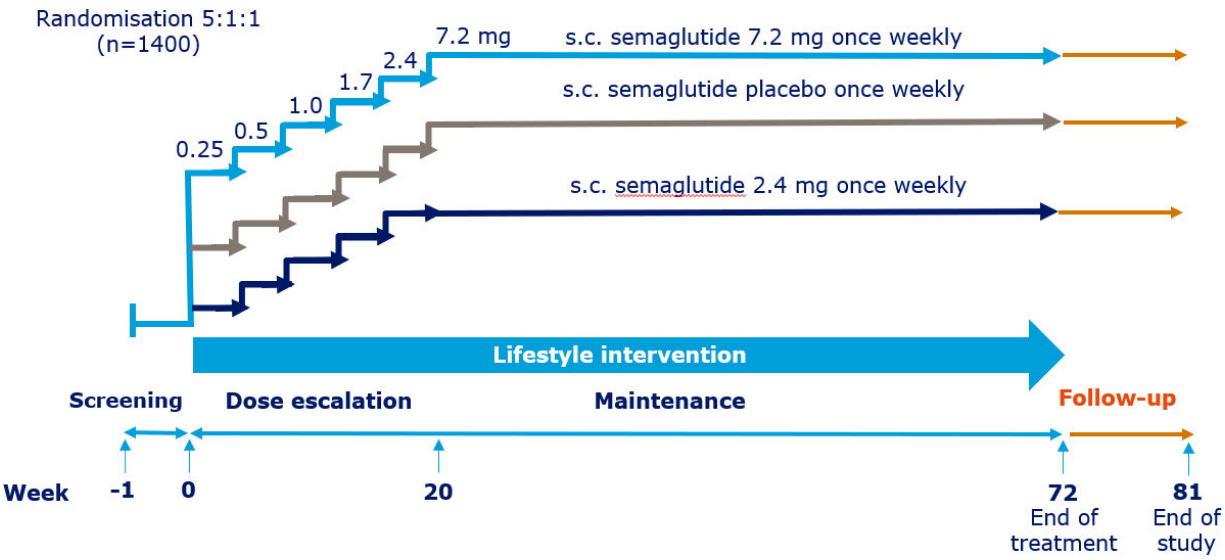
Approximately 1400 participants will be randomised 5:1:1 to receive either semaglutide s.c. 7.2 mg, semaglutide s.c. 2.4 mg or placebo once weekly, as an adjunct to reduced-calorie diet and increased physical activity. The study population consists of adults with obesity.

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.

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 detailed 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) H01: $\mu \geq 0.0$ percentage points against Ha1: $\mu < 0.0$ percentage points
and
2) H02: OR ≤ 1 against Ha2: 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 like 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 like 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 (week72).
- **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 (week72).
- **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 (week72).
- **Step 6:** Superiority of semaglutide s.c. 7.2 mg versus placebo with respect to secondary estimand with 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 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).

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.
MRI analysis set	All participants in the sub-population of FAS that have had a valid MRI scan performed at baseline.

The following data points sets are defined:

[redacted]

[redacted]

4 Statistical Analyses

4.1 General Considerations

All randomised 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 (or semaglutide s.c. 2.4 mg). All estimated 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 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.

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 McEvoy1. 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 sex (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 sex 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 (95364999) 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. 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.

- **Pooling**: Integrates the 1,000 sets of estimated results into a single set of 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 groups 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 sex (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 sex 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 estimands 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, as detailed in Section 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 test of superiority of semaglutide s.c. 7.2 mg once weekly versus placebo unless stated otherwise.

All confirmatory secondary endpoints will be analysed using the same analysis model and imputation approach as used to address the co-primary estimand as described in 4.2.1.

4.3.1.1 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 as defined in 4.2.2.

4.3.1.2 Supplementary Analysis

The estimation of the additional and supplementary estimands for the secondary objectives will be like those described for the additional and supplementary 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	Count of	Binary	FAS	Treatment	LR	RD-MI	Non

Endpoint title	Unit	Endpoint	Analysis set	Estimand strategy	Statistical model	Imputation approach	Sensitivity Analysis
weight reduction (yes/no)	participants			policy			responders
			FAS	Hypothetical	LR	MMRM	
≥25% 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 body weight*	%	Continuous	FAS	Treatment policy	ANCOVA	RD-MI	J2R-MI
			FAS	Hypothetical	MMRM		
≥20% body weight reduction (yes/no)*	Count of participants	Binary	FAS	Treatment policy	LR	RD-MI	Non responders
			FAS	Hypothetical	LR	MMRM	
≥25% body weight reduction (yes/no)*	Count of participants	Binary	FAS	Treatment policy	LR	RD-MI	Non responders
			FAS	Hypothetical	LR	MMRM	

* Comparison of semaglutide s.c. 7.2 mg versus semaglutide s.c. 2.4 mg.

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 parameter, cardiovascular parameter, glucose metabolism parameter and safety parameter 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 body weight parameter, cardiovascular parameter, glucose metabolism parameter and safety parameter 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.

MRI analysis

For analysing endpoints relating to body composition based on MRI scans and the endpoints of change in body weight (%, kg) for MRI sub-study population, the two active arms (semaglutide 7.2 mg and semaglutide 2.4 mg) will be pooled and compared against placebo. The analyses will be similar to those described above for other continuous supportive secondary endpoints, except that the jump to reference (J2R) approach (as described in 4.2.2) will be used to impute missing assessments at landmark for the treatment policy strategy.

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	
Change in BMI	kg/m^2	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in total fat mass*	%, L	Continuous	Treatment policy	MRI	ANCOVA	J2R-MI
			Hypothetical	MRI	MMRM	
Change in lean body mass*	%, L	Continuous	Treatment policy	MRI	ANCOVA	J2R-MI
			Hypothetical	MRI	MMRM	
Change in visceral fat mass*	%, L	Continuous	Treatment policy	MRI	ANCOVA	J2R-MI
			Hypothetical	MRI	MMRM	
Change in body weight*	%, kg	Continuous	Treatment policy	MRI	ANCOVA	J2R-MI
			Hypothetical	MRI	MMRM	
Change in systolic blood pressure	mmHg	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	

Endpoint title	Unit	Endpoint	Estimand Strategy	Analysis set	Statistical model	Imputation approach
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	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 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 HbA1c	%	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	
Change in glycemic Category (Normo-glycaemia, pre-diabetes, T2D)	Count of participant	Categorical		FAS	Descriptive statistics	

Endpoint title	Unit	Endpoint	Estimand Strategy	Analysis set	Statistical model	Imputation approach
Change in pulse	bpm	Continuous	Hypothetical	SAS	MMRM	
Number of Adverse Events (AEs)	Count of events	Continuous		SAS	Descriptive statistics	
Number of Serious Adverse Events (SAEs)	Count of events	Continuous		SAS	Descriptive statistics	

* Comparison for pooled semaglutide vs. placebo.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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, sex, 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 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 CSR.

4.7 Interim Analysis

There is no interim analysis planned for this study.

4.8 Changes to Protocol-planned Analysis

- Addition of supportive secondary objective on change in body weight in kg for comparison of semaglutide 7.2 mg vs semaglutide 2.4 mg
- Change in supportive secondary objective on body composition to address comparison for pooled semaglutide versus placebo instead of comparison of semaglutide 7.2 mg versus placebo.
- Addition of supportive secondary endpoint addressing objective on body composition:
    - Change in body weight (kg, %) for comparison of pooled semaglutide vs placebo in the MRI sub-study population.
- Secondary endpoint "Change in free fatty acids" was removed from supportive secondary endpoints due to lack of baseline data.

[redacted]

- Addition of supplementary estimand addressing supply issue for primary and confirmatory secondary endpoints.
- Correction of MRI endpoints naming according to unit from "mass" to "volume".

5 Sample size determination

The study used a 5:1:1 randomization ratio and had a sample size of 1400 participants. The participants were randomized to receive either semaglutide s.c. 7.2 mg once weekly (1000 participants), semaglutide s.c. 2.4 mg once weekly (200 participants), or placebo (200 participants).

For more details refer 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.