Cover Page for Statistical Analysis Plan

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Statistical Analysis Plan

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

Substance: semaglutide

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Biostatistics and Data Science, CMRQ

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Version History

This Statistical Analysis Plan (SAP) for trial NN9536-4706 is based on the protocol version 4.0 dated 05SEP2024.

SAP Version	Date	Change	Rationale
1.0	20 Sep 2024	Not Applicable	Original version
2.0	27 Mar 2025	[redacted]	[redacted]

List of abbreviations

AD	*available but discontinued*
AE	*adverse event*
ANCOVA	*analysis of covariance*
BMI	*body mass index*
bpm	*beats per minute*
CI	*confidence interval*
cm	*centimetre*
[redacted]	[redacted]
FAS	*full analysis set*
HbA1c	*glycated haemoglobin*
HDL	*high density lipoprotein*
hsCRP	*high-sensitivity C-reactive protein*
IMP	*investigational medicinal product*
J2R-MI	*jump to reference multiple imputation approach*
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*
OR	*odds ratio*
RD-MI	*multiple imputation using retrieved participants*
SAP	*statistical analysis plan*
s.c.	*subcutaneous*
TFL	*tables, figures and listings*
WO-MI	*wash-out multiple imputation*

1 Introduction

This SAP is based on protocol version 4.0 dated 05SEP2024.

1.1 Objectives, endpoints and estimands

Table 1 Objectives and endpoints

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

	Supportive secondary:		
	Body weight parameters		
To compare the efficacy of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to body weight parameters, after 44 weeks of treatment, in adults with overweight and obesity.	Change in body weight	From baseline (week 0) to end of treatment (week 44)	kg
	Change in body mass index	From baseline (week 0) to end of treatment (week 44)	kg/m^2
	Change in waist-height ratio (WtHR)	From baseline (week 0) to end of treatment (week 44)	Not applicable
	[redacted]		
	Cardiovascular parameters		
To compare the efficacy of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to cardiovascular parameters, after 44 weeks of treatment, in adults with overweight and obesity.	Change in systolic blood pressure	From baseline (week 0) to end of treatment (week 44)	mmHg
	Change in diastolic blood pressure	From baseline (week 0) to end of treatment (week 44)	mmHg
	Change in total cholesterol	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in high-density lipoprotein (HDL) cholesterol	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in low-density lipoprotein (LDL) cholesterol	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in very low-density lipoprotein (VLDL) cholesterol	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in triglycerides	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in free fatty acids	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Change in high-sensitivity c-reactive protein (hsCRP)	From baseline (week 0) to end of treatment (week 44)	Ratio to baseline
	Glucose metabolism parameters		
	Change in HbA1c	From baseline (week 0) to end of treatment (week 44)	%-point and mmol/mol

	Supportive secondary:		
To compare the efficacy of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, with respect to glycemic status, after 44 weeks of treatment, in adults with overweight and obesity.	Change in fasting plasma glucose	From baseline (week 0) to end of treatment (week 44)	mg/dL, mmol/L
Safety	**Title**	**Time frame**	**Unit**
To compare the safety and tolerability of semaglutide 2.4 mg versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, after 44 weeks of treatment, in adults with overweight and obesity.	***All participants***		
	Number of TEAEs	From baseline (week 0) to end of study (week 49)	count of events
	Number of SAEs	From baseline (week 0) to end of study (week 49)	count of events
	Pulse	From baseline (week 0) to end of treatment (week 44)	beats/min
	Participants with T2D		
	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L) confirmed by BG meter	From baseline (week 0) to end of study (week 49)	number of episodes

[redacted]

Co-primary estimands

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

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

- **Population:** Adults with overweight (defined as BMI ≥ 24 and < 28 kg/m^2), with at least one weight-related complication, or with obesity (defined as BMI ≥ 28 and < 30 kg/m^2), with or without weight-related complications.
- **Endpoint:** 1) relative change from baseline to week 44 in body weight and 2) body weight reduction ≥ 5% (yes/no) at week 44.
- **Treatment condition**: Semaglutide 2.4 mg vs. placebo regardless of discontinuation or dose reduction of randomised treatment, and regardless of initiating other anti-obesity therapies (as defined above).

- **Remaining intercurrent events**: None, all intercurrent events (discontinuation or dose reduction of randomised treatment and initiation of other anti-obesity therapies) are captured by the treatment condition attribute and handled by the treatment policy strategy.
- **Population-level summary**: 1) difference in mean changes and 2) odds ratio between treatment conditions.

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

Secondary estimand

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

Additional estimand

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

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

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

- **Population-level summary**: 1) difference in mean changes and 2) odds ratio between treatment conditions

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

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

1.2 Study Design

The study design is provided in the protocol section 4.1.

2 Statistical Hypotheses

2.1 Statistical hypotheses

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

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

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

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

Superiority

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

   and

2. $H0_2$: $OR \leq 1$ against Ha_2: $OR > 1$

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

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

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

2.2 Multiplicity Adjustment

The type I error will be controlled in the strong sense using a hierarchical (fixed sequence) testing procedure. This is based on priority ordering of the null hypotheses and testing them in this order using the 2-sided 95% confidence interval approach until an insignificant result appears. Consequently, the second null hypothesis will only be tested if the first null hypothesis has been rejected in favor of semaglutide 2.4 mg.

The steps in the hierarchical testing procedure are as follows:

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

- Step 3: Superiority of semaglutide 2.4 mg versus placebo with respect to secondary estimand with the endpoint change in waist circumference from baseline (week 0) to end of treatment (week 44).

3 Analysis Sets

The following participant analysis sets are defined:

Table 2 Analysis sets

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

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

The following data points sets are defined:

Table 3 Defined data point sets

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

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

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

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

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

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

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

4 Statistical analyses

4.1 General considerations

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

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

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

4.2 Primary estimands analysis

The co-primary endpoints are:

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

The two primary analyses are aligned with the two co-primary estimands defined in Section 1.1.

4.2.1 Main analyses

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

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

All available data at week 44 are used and missing values at week 44 will be imputed and the endpoint will be derived from the imputed values.

Wash-out multiple imputation approach (WO-MI): The primary imputation approach for the primary estimand is described as below:

1. Imputation: Defines an imputation step procedure utilizing different imputation models depending on randomised treatment group and end of treatment status as described in the following steps:

(1) For on-drug participants in the semaglutide 2.4 mg arm, missing week 44 values of body weight are imputed based on observed data from the on-drug participants in the semaglutide 2.4 mg arm. The *multiple imputation approach using retrieved participants* (RD-MI) similar to the one described by McEvoy[1] is used. The model will be a linear regression of body weight (kg) at week 44 with gender (male/female) and stratification groups as factors and baseline body weight (kg), timing of last available observation (LAO) and LAO of body weight (kg) as covariates. No

interactions will be included. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation model are then used to impute missing week 44 body weight values for on-drug participants in the semaglutide 2.4 mg arm. This will be done 1,000 times and results in 1,000 complete data sets for on-drug participants in the semaglutide 2.4 mg arm.

(2) For participants in placebo arm, missing week 44 values of body weight are imputed based on all observed data at all time points in the placebo arm, and using a MMRM model with gender (male/female) and stratification groups as factors and baseline body weight (kg) as a covariate – all nested within visit. 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. Each missing value of body weight at week 44 is imputed 1,000 times by random sampling from normal distribution with the MMRM-predicted value at week 44 as mean and variance as a sum of prediction variance and residual variance.

(3) For off-drug participants in the semaglutide 2.4 mg arm, missing week 44 values of body weight are imputed from the placebo arm assuming that all drug effect will be washed out and gone before the landmark visit. The imputation procedure will be similar to jump to reference multiple imputation as described in the sensitivity analyses section below. An imputation model will be fitted to each of 1,000 complete data sets resulting from MMRM imputation for the placebo arm in the previous step. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation model from each of 1,000 fits is then used to impute missing week 44 body weight values once, ultimately resulting in 1,000 complete data sets for off-drug participants in semaglutide 2.4 mg arm.

2. Analysis: Analysis of each of the 1,000 complete data sets, using the analysis models (ANCOVA) results in 1,000 estimations.

3. Pooling: The results obtained from analysing the datasets will be combined using Rubin's formula.

The multiple imputations will be generated using Novo Nordisk trial number 95364706 as seed number. The dataset will be sorted by participant ID.

4.2.2 Sensitivity analyses

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

1. Imputation: Defines an imputation model using placebo participants from FAS with a week 44

measurement. The model will be a linear regression of body weight (kg) at week 44 with gender (male/female) and stratification groups as factors and baseline body weight (kg) as covariate. No interactions will be included. If the imputation model cannot be fit, then the model will be reduced until the model can be fit. Reduction will be done in a fixed order by first removing gender, then removing stratification groups. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 44 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): First, missing data are imputed according to the primary multiple imputation approach. Second, for both treatment arms a penalty will be added to the imputed values at week 44. The approach is to explore a range of penalties for both treatment groups, and the impact these would have on the trial conclusions. The 2-dimensional space of penalties covering the range from -30% to 30% will be explored for both treatment groups. This sensitivity analysis evaluates the robustness of the superiority conclusions.

Non-retrieved participants as non-responders: For the analysis of body weight reduction ≥ 5% an analysis using participants with missing 44 assessments as non-responders in the logistic regressions will be done. This analysis also targets the MAR assumption.

ANCOVA for unequal variances: An alternative analysis model for the change in body weight (%) similar to the primary analysis model (ANCOVA), but assuming unequal variances instead of equal variances. The analysis model includes randomised treatment and stratification groups as factors and baseline body weight (kg) as covariate.

4.2.3 Supplementary analyses

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

The analysis model for change in body weight (%) will be a mixed model for repeated measurements (MMRM). The MMRM will use assessments only from participants who are taking the randomised treatment until end of treatment or until first discontinuation of randomised treatment. For participants who experience other intercurrent events (weight management drugs or bariatric surgery) before completion of treatment or first discontinuing of randomised treatment, the date of initiating other anti-obesity therapies will be used as latest date for using assessments in this MMRM. The MMRM will be fitted using randomised treatment and stratification groups as factors and baseline body weight (kg) as covariate all nested within visit. An unstructured covariance matrix for measurements within the same participant will be employed, assuming that measurements for different participants are independent. If the model cannot be fit using an unstructured covariance matrix, alternate covariance matrix will be tried if considered appropriate.

The analysis model for the 5% responder endpoint is a logistic regression where any missing values at week 44 will be predicted from the MMRM. The predicted values will be used to classify each participant as 5% responder or not. This classification will then be analysed using a logistic

regression model with randomised treatment and stratification groups as factors and baseline body weight (kg) as covariate.

Table 4 Analyses and imputation methods to address the efficacy estimands for the co-primary endpoints

Endpoint	Endpoint type	Analysis Set	Estimand	Statistical model	Imputation model	Sensitivity Analysis
Co-primary endpoints						
Change in body weight (%) from week 0 to week 44	Continuous	FAS	Treatment policy	ANCOVA	WO-MI	J2R-MI, TP-MI, ANCOVA for unequal variances
			Hypothetical	MMRM	-	-
body weight reduction ≥5% from week 0 to week 44	Binary	FAS	Treatment policy	LR	WO-MI	J2R-MI, TP-MI, Non-responders
			Hypothetical	LR	MMRM	-

4.3 Secondary estimands analysis

4.3.1 Confirmatory secondary estimands

The confirmatory secondary endpoints related to the secondary objective are:

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

4.3.1.1 Main analyses

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 endpoints.

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

The analysis model for body weight reduction ≥ 10% is a logistic regression using randomised treatment and stratification groups as factors and baseline body weight (kg) as covariate. In case no response occurred in certain group, the Firth approximation will be adopted in the logistic regression analysis to reduce bias.

4.3.1.2 Sensitivity analysis

For change in waist circumference, a sensitivity analysis using jump to reference as imputation approach will be carried out. For body weight reduction ≥ 10%, a sensitivity analysis using non-retrieved participants as non-responders will be carried out.

4.3.1.3 Supplementary analysis

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

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

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

Analyses addressing both primary and confirmatory secondary estimands for responder endpoints

For both analyses of responder endpoints (body weight reduction≥5% and ≥10% from week 0 to week 44), in addition to the estimated odds ratio, the estimated treatment differences (ETDs) will be provided by calculating the responder probabilities and treatment differences between responder probabilities based on the logistic regression model, with confidence intervals for treatment differences obtained using the delta method.

Table 5 Analyses and imputation methods to address the secondary estimands for the confirmatory secondary endpoints

Endpoint	Unit	Endpoint type	Strategy	Analysis set	Statistical model	Imputation approach	Sensitivity analysis
body weight reduction ≥10% from week 0 to week 44	Count of participant	Binary	Treatment policy	FAS	LR	WO-MI	non-responder
			Hypothetical	FAS	LR	MMRM	
Change in waist circumference from week 0 to week 44	cm	Continuous	Treatment policy	FAS	ANCOVA	WO-MI	J2R-MI
			Hypothetical	FAS	MMRM		

4.3.2 Supportive secondary estimands

Supportive secondary estimands with relative endpoints are described in Section 1.1.

Analyses addressing the supportive secondary estimand

The supportive secondary endpoints will be analysed using the same imputation approach as used for the primary endpoints to address the primary estimand. The statistical model for continuous endpoints will be the same linear regression as for the primary continuous endpoint (ANCOVA) with treatment and stratification groups as factors and baseline value of the endpoint as covariate. The statistical model for responder endpoints will be the same logistic regression as for the primary binary endpoint using treatment and stratification groups as factors and baseline value of the endpoint as covariate.

Analyses addressing the additional estimand

The supportive secondary endpoints will be analysed using the same approach as used for the primary endpoints to address the additional estimand.

Analyses of safety endpoints

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

Adverse events will be defined as "treatment-emergent" (TEAE), if the onset of the event occurs in the on-treatment period. TEAEs and SAEs will be summarised by descriptive statistics using the SAS, such as frequencies and rates. No formal statistical inference will be carried out. All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

Table 6 Analyses and imputation methods to address the secondary and additional estimands for the supportive secondary endpoints

Endpoint	Unit	Endpoint type	Strategy	Analysis set	Statistical model	Imputation approach
Change in body weight from week 0 to week 44	kg	Continuous	Treatment policy	FAS	ANCOVA	WO-MI
			Hypothetical	FAS	MMRM	
Change in body mass index from week 0 to week 44	kg/m^2	Continuous	Treatment policy	FAS	ANCOVA	WO-MI
			Hypothetical	FAS	MMRM	
Change in waist-height ratio (WtHR) from week 0 to week 44	NA	Continuous	Treatment policy	FAS	ANCOVA	WO-MI
			Hypothetical	FAS	MMRM	
Change in systolic blood pressure from week 0 to week 44	mmHg	Continuous	Treatment policy	FAS	ANCOVA	WO-MI
			Hypothetical	FAS	MMRM	
Change in diastolic blood pressure from week 0 to week 44	mmHg	Continuous	Treatment policy	FAS	ANCOVA	WO-MI
			Hypothetical	FAS	MMRM	
Change in lipids • Triglycerides • Total cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Very low-density lipoprotein (VLDL) cholesterol • free fatty acids from week 0 to week 44	Ratio to baseline	Continuous	Treatment policy	FAS	ANCOVA	WO-MI
			Hypothetical	FAS	MMRM	
Change in hsCRP from week 0 to week 44	Ratio to baseline	Continuous	Treatment policy	FAS	ANCOVA	WO-MI
			Hypothetical	FAS	MMRM	
Change in HbA_{1c} from week 0 to week 44	%-point mmol/mol	Continuous	Treatment policy	FAS	ANCOVA	WO-MI
			Hypothetical	FAS	MMRM	
Change in fasting plasma glucose from week 0 to week 44	mg/dL, mmol/L	Continuous	Treatment policy	FAS	ANCOVA	WO-MI
			Hypothetical	FAS	MMRM	
Change in pulse from week 0 to week 44	beats/min	Continuous	Hypothetical	SAS	MMRM	
Number of TEAEs	Count of events	Continuous		SAS	Descriptive statistics	
Number of SAEs	Count of events	Continuous		SAS	Descriptive statistics	
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L) confirmed by BG meter) *	Number of episodes	Continuous		SAS	Descriptive statistics	

*For participants with T2D only

4.4 Exploratory estimand analysis (not applicable to participants from China mainland)

4.4.1 Analyses addressing the exploratory estimand

[redacted]

4.4.2 Analyses addressing the additional estimand

[redacted]

4.5 Other analyses

All collected data that were not defined as endpoints will be summarised by descriptive statistics.

4.6 Interim analysis

There is no interim analysis planned for this study.

4.7 Changes to Protocol-planned Analysis

- In the J2R-MI imputation model, the model reduction steps have been pre-specified in case the model cannot run.
- It is clarified that, in addition to OR, ETD will be reported for logistic regression analyses.

5 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.