Cover Page for Statistical Analysis Plan

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Statistical Analysis Plan

Efficacy and safety of semaglutide 2.4 mg once-weekly in Asians with obesity diagnosed as BMI ≥ 25 kg/m^2 according to local guidelines.

Substance: semaglutide

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Version History

This Statistical Analysis Plan (SAP) for trial NN9536-4707 is based on the protocol version 6.0 dated 16DEC2022.

SAP Version	Date	Change	Rationale
1.0	28 Nov 2023	Not Applicable	Original version

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*
FAS	*full analysis set*
HbA1c	*glycated haemoglobin*
HDL	*high density lipoprotein*
hsCRP	*high-sensitivity C-reactive protein*
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 6.0 dated 16DEC2022.

1.1 Objectives, endpoints and estimands

The trial endpoints are listed in Table 1-1 by their association to the objectives.

Table 1-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
• To demonstrate the superiority of semaglutide s.c. 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity, classified as BMI ≥ 25 kg/m^2 according to local guidelines in Republic of Korea and Thailand on: • Body weight • ≥5% weight reduction	**Co-primary:**		
	Change in body weight	From baseline (week 0) to end of treatment (week 44)	%
	≥5% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 44)	Count of participant
	Confirmatory secondary:		
	≥10% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 44)	Count of participant
	≥15% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 44)	Count of participant
	Change in waist circumference	From baseline (week 0) to end of treatment (week 44)	cm
	Supportive secondary:		
	≥20% body weight reduction (yes/no)	From baseline (week 0) to end of treatment (week 44)	Count of participant
	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
Secondary	**Title**	**Time frame**	**Unit**
• To compare the efficacy of semaglutide s.c. 2.4 mg once weekly versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity, classified as BMI ≥ 25 kg/m^2 according to local guidelines in Republic of Korea and Thailand, on cardiovascular risk factors	**Supportive secondary:**		
	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)	mg/dL and mmol/L
	Change in high-density lipoprotein (HDL) cholesterol	From baseline (week 0) to end of treatment (week 44)	mg/dL and mmol/L
	Change in low-density lipoprotein (LDL) cholesterol	From baseline (week 0) to end of treatment (week 44)	mg/dL and mmol/L
	Change in triglycerides	From baseline (week 0) to end of treatment (week 44)	mg/dL and mmol/L
	Change in high-sensitivity c-reactive protein (hsCRP)	From baseline (week 0) to end of treatment (week 44)	mg/L

Objectives	Endpoints		
	Exploratory:		
	Change in use of antihypertensive medication (decrease/no change/increase)	From baseline (week 0) to end of treatment (week 44)	Count of participant
	Change in use of lipid-lowering medication (decrease/no change/increase)	From baseline (week 0) to end of treatment (week 44)	Count of participant
• To compare the efficacy of semaglutide s.c. 2.4 mg once weekly versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity, classified as BMI ≥ 25 kg/m^2 according to local guidelines in Republic of Korea and Thailand, on glucose metabolism	**Supportive:**		
	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 44)	% and mmol/mol
	Exploratory:		
	Shift in glycaemic status (normo-glycaemic/pre-diabetes/T2D)	From baseline (week 0) to end of treatment (week 44)	Count of participant

End of treatment (week 44) corresponds to end of trial intervention.

Co-primary estimands

The primary clinical question of interest is: What is the treatment effect of semaglutide s.c. 2.4 mg once weekly as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity defined according to local guidelines in Republic of Korea and Thailand, measured by relative change from baseline (week 0) to week 44 in body weight and ≥ 5% body weight reduction at week 44, 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**: People of Asian descent with obesity defined as BMI ≥ 25.0 kg/m^2.
- **Endpoint**: 1) relative change from baseline to week 44 in body weight and 2) ≥ 5% body weight reduction at week 44.
- **Treatment condition**: the randomised treatment regardless of discontinuation or dose reduction of randomised trial product, and regardless of initiating other anti-obesity therapies (as defined above)
- **Remaining intercurrent events**: none, all intercurrent events (discontinuation or dose reduction of randomised trial product 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 trial. The co-primary estimands are thus relevant to support regulatory decision-making.

Secondary estimand

The secondary estimands for both the confirmatory secondary and supportive secondary endpoints are similar to the co-primary estimands except for the endpoint attribute. For continuous endpoints, the secondary estimands for primary and secondary objectives are similar to the co-primary estimand for % weight change. For binary endpoints, the secondary estimands for primary and secondary objectives are similar to the co-primary estimand for ≥ 5% body weight reduction.

Additional estimand

An additional clinical question of interest for the primary objective is: what is the treatment effect of semaglutide s.c. 2.4 mg once weekly as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity defined according to local guidelines in Republic of Korea and Thailand, measured by relative change from baseline (week 0) to week 44 in body weight and ≥ 5% body weight reduction at week 44, had they remained on their randomised treatment for the entire planned duration of the trial 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**: People of Asian descent with obesity defined as BMI ≥ 25.0 kg/m^2
- **Endpoint**: 1) relative change from baseline to week 44 in body weight and 2) ≥ 5% body weight reduction at week 44.
- **Treatment condition**: the randomised treatment if participants had adhered to the randomised trial product (regardless of dose reduction) for the entire duration of the trial and not initiated any other anti-obesity therapies (as defined above).
- **Remaining intercurrent events**: none, all intercurrent events (discontinuation or initiation of other anti-obesity therapies and dose reduction) are captured by the treatment condition attribute. Discontinuation or initiation of other anti-obesity therapies are handled by the hypothetical strategy. Dose reduction of randomised trial product 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 without the confounding effects of other anti-obesity therapies or trial product discontinuation.

A similar additional estimand also applies to all confirmatory and supportive secondary endpoints addressing the primary and secondary objective in the population.

1.2 Study Design

The study design is provided in the protocol section 4.1.

2 Statistical Hypotheses

The tests of superiority of semaglutide s.c. 2.4 mg once weekly to placebo for the two primary and all confirmatory secondary endpoints are performed using a fixed-sequence statistical strategy and will be based only on analyses addressing the primary estimand. This strategy tests the endpoints using a predefined hierarchical order, all at the significance level of 5%, moving to test the next endpoint only after a statistically significant superiority result (p-value < 5%) on the previous endpoint.

For the co-primary estimands with the primary endpoints, 1) change in body weight (%) from baseline to end of treatment (week 44) and 2) ≥ 5% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44), the following confirmatory 1-sided hypotheses are planned to be tested for semaglutide s.c. 2.4 mg once weekly versus placebo. Let the mean difference in 1) be defined as:

μ_1 = ([semaglutide s.c. 2.4 mg] minus [placebo])

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

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

Superiority

1) $H0_1 : \mu_1 \geq 0.0$ percentage points against $Ha_1 : \mu_1 < 0.0$ percentage points.

   and

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

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

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. For example, the second null hypothesis will only be tested if the first null hypothesis has been rejected in favour of semaglutide s.c. 2.4 mg.

The steps in the hierarchical testing procedure are as follows:

- Step 1: change in body weight (%) from baseline (week 0) to end of treatment (week 44) superiority of semaglutide s.c. 2.4 mg versus placebo
  and
  ≥ 5% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44) superiority of semaglutide s.c. 2.4 mg versus placebo
- Step 2: ≥ 10% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44) superiority of semaglutide s.c. 2.4 mg versus placebo
- Step 3: ≥ 15% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44) superiority of semaglutide s.c. 2.4 mg versus placebo

- Step 4: Change in waist circumference from baseline (week 0) to end of treatment (week 44) superiority of semaglutide s.c. 2.4 mg versus placebo

3 Analysis Sets

For the purposes of analysis, the following analysis sets (Table 3-1) and observation periods (Table 3-2) are defined:

Table 3-1 Analysis sets

Participant Analysis Set	Description
Full analysis set (FAS)	All randomised participants. Participants will be included in the analyses according to the randomised intervention.
Safety analysis set (SAS)	All participants who are exposed to at least one dose of randomised IMP. Participants will be included in the analyses according to the intervention they actually received.

Table 3-2 Defined data point sets

Defined data point sets (DPS)	Description
In-trial (DPS1)	The time period where the participant is assessed in the trial. 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 trial' visit • withdrawal of consent • last contact with participant (for participants lost to follow-up) • death
On-treatment (DPS2)	The time period where participants are treated with trial product. A time-point is considered as "on-treatment" if any dose of trial 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 trial product administration to date of last trial product administration (+14 days) excluding potential 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 5 weeks (35 days).
On-treatment until first discontinuation of trial product or initiation of other anti-obesity therapies (DPS3)	The time period where participants are treated with trial product. A time-point is considered as "on-treatment" if any dose of trial 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 trial 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 primary and secondary objectives.

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

SAS and either DPS1 or DPS2 are used to present safety data.

The in-trial (DPS1) and on-treatment (DPS2) 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 and eligible observation at or before randomisation is used as the baseline value. If no assessments are available, the mean value at randomisation across all participants is used as the baseline value.

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

4.2 Co-primary estimands analyses

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

4.2.1 Definition of Endpoints

The co-primary endpoints are:

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

4.2.2 Main Analytical Approach

The analysis model for change in body weight (%) will be a linear regression (ANCOVA) with randomised trial intervention as factor and baseline body weight (kg) as covariate.

The analysis model for the 5% responder endpoint will be a logistic regression using randomised trial intervention as factor and baseline body weight (kg) as covariate.

Multiple imputation approach using retrieved subjects (RD-MI): All available data at week 44 are used and missing values at week 44 will be imputed and the endpoint will be derived from the imputed values. The imputation approach for the primary analysis is a multiple imputation similar to the one described by McEvoy et al.[1] For participants in the semaglutide s.c. 2.4 mg once weekly and the placebo groups, missing measurements at week 44 for non-retrieved participants are imputed using assessments from retrieved participants in each intervention group. The timing of last available observation during the on-treatment period (LAO-OT) will be included in the imputation model as a continuous covariate. Missing measurements at week 44 for participants on randomised trial intervention (at week 44) are imputed by sampling from available measurements at week 44 from participants on randomised trial intervention in the relevant randomised intervention group.

1. **Imputation:** Defines an imputation model using retrieved participants from FAS and done within groups defined by randomised treatment. The model will be a linear regression of body weight at week 44 with gender (male/female) and baseline BMI (kg/m^2) (in categories <35, 35-<40, ≥40) as factors and baseline body weight (kg), timing of the LAO-OT and LAO-OT of body weight (kg) as covariates. No interactions will be included. If no LAO-OT exists post-baseline then the LAO-OT will be the baseline value of body weight and the timing will be 0. If any participants are on-treatment with missing values at week 44, an imputation model for missing body weight at week 44 will be defined using participants on-treatment and with available observations at week 44 in a

similar way. 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. If the imputation model cannot be fit due to small group size, the wash-out multiple imputation approach (WO-MI) will be used instead as described below.

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

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

Wash-out multiple imputation approach (WO-MI): Missing values of body weight at week 44 are imputed using the same framework (Imputation, Analysis, Pooling) as described above with the first step replaced by:

- **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 s.c. 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 and according to the RD-MI procedure described above. This will result in 1,000 complete data sets for on-drug participants in the semaglutide s.c. 2.4 mg arm.

    2. For the participants in semaglutide placebo arm, missing week 44 values of body weight are imputed based on all observed data at all time points in the semaglutide placebo arm, and using an MMRM model with gender (male/female), baseline BMI (kg/m^2) (in categories <35, 35-<40, ≥40) as factors and baseline body weight (kg) as a covariate – all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed. 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 s.c. 2.4 mg arm, missing week 44 values of body weight are imputed from the semaglutide placebo arm assuming that all drug effect will be washed out and gone before 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 semaglutide 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 s.c. 2.4 mg arm.

Data sets obtained in steps 1-3 are combined resulting in 1,000 complete data sets for all randomised participants.

Based on NN9536-4153 phase 2 results 1,000 copies should be sufficient to establish stable results. The multiple imputations will be generated using Novo Nordisk trial number 95364707 as seed number. In addition to the seed number, it is specified that the dataset is sorted by participant ID.

4.2.3 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 multiple imputation approach is done as above with the first step replaced by:

1. Imputation: Defines an imputation model using semaglutide 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 BMI (kg/m^2) (in categories <35, 35-<40, ≥40) as factors and baseline body weight (kg) as covariate. No interactions will be included. If the imputation model cannot be fit due to inadequate numbers of retrieved participants in one or more groups, then the imputation model will be reduced until the model can be fit. Reduction will be done in a fixed order by first removing gender, then collapsing the two highest baseline BMI-groups into one (≥35) and finally removing baseline BMI-group. 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 5% responder analysis an analysis using participants with missing week 44 assessment as non-responders in the logistic regressions will be done.

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 as factor and baseline body weight (kg) as covariate.

4.2.4 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 trial intervention until end of treatment or until first discontinuing of randomised trial intervention. For participants who experience other intercurrent events (weight management drugs or bariatric surgery) before completion 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 trial intervention as factor 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.

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 trial intervention as factor and baseline body weight (kg) as covariate.

Table 4-1 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	RD-MI/ WO-MI	J2R-MI, TP-MI, ANCOVA for unequal variances
			Hypothetical	MMRM	-	-
≥5% body weight reduction from week 0 to week 44	Binary	FAS	Treatment policy	LR	RD-MI/ WO-MI	J2R-MI, TP-MI, Non-responder
			Hypothetical	LR	MMRM	-

4.3 Secondary Estimands Analyses

4.3.1 Confirmatory Secondary Estimands

The confirmatory secondary estimands are defined in Section 1.1.

4.3.1.1 Definition of Endpoints

The confirmatory secondary endpoints are:

- ≥10% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44)
- ≥15% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 44)
- Change in waist circumference from baseline (week 0) to end of treatment (week 44)

4.3.1.2 Main Analytical Approach

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 trial intervention as factor and baseline waist circumference as covariate.

The analysis model for the responder endpoints will be a logistic regression using randomised trial intervention as factor and baseline body weight (kg) as covariate.

4.3.1.3 Sensitivity Analyses

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

4.3.1.4 Supplementary Analyses

The confirmatory secondary endpoints will be analysed using the same analysis model as used to address the additional estimand for the primary endpoints.

The analysis model for change in waist circumference will be a mixed model for repeated measurements (MMRM). The MMRM will be fitted using randomised trial intervention as factor and baseline waist circumference 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 analysis model for the responder endpoints will be 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 a responder or not. This classification will then be analysed using a logistic regression model with randomised trial intervention as factor and baseline body weight (kg) as covariate.

Table 4-2 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
≥10% body weight reduction from week 0 to week 44	Count of participant	Binary	Treatment policy	FAS	LR	RD-MI/ WO-MI	non-responder
			Hypothetical	FAS	LR	MMRM	
≥15% body weight reduction from week 0 to week 44	Count of participant	Binary	Treatment policy	FAS	LR	RD-MI/ WO-MI	non-responder
			Hypothetical	FAS	LR	MMRM	
Change in waist circumference from week 0 to week 44	cm	Continuous	Treatment policy	FAS	ANCOVA	RD-MI/ WO-MI	J2R-MI
			Hypothetical	FAS	MMRM		

4.3.2 Supportive Secondary Endpoints Analyses

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 as a factor 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 as a factor 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.

Table 4-3 Analyses and imputation methods to address the secondary and additional estimands for 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	RD-MI/WO-MI
			Hypothetical	FAS	MMRM	
Change in body mass index from week 0 to week 44	kg/m^2	Continuous	Treatment policy	FAS	ANCOVA	RD-MI/WO-MI
			Hypothetical	FAS	MMRM	
≥20% body weight reduction from week 0 to week 44	Count of participant	Binary	Treatment policy	FAS	LR	RD-MI/WO-MI
			Hypothetical	FAS	LR	MMRM
Change in systolic blood pressure from week 0 to week 44	mmHg	Continuous	Treatment policy	FAS	ANCOVA	RD-MI/WO-MI
			Hypothetical	FAS	MMRM	
Change in diastolic blood pressure from week 0 to week 44	mmHg	Continuous	Treatment policy	FAS	ANCOVA	RD-MI/WO-MI
			Hypothetical	FAS	MMRM	
Change in lipids • Triglycerides • Total cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol from week 0 to week 44	mg/dL mmol/L	Continuous	Treatment policy	FAS	ANCOVA	RD-MI/WO-MI
			Hypothetical	FAS	MMRM	
Change in hsCRP from week 0 to week 44	mg/dL	Continuous	Treatment policy	FAS	ANCOVA	RD-MI/WO-MI
			Hypothetical	FAS	MMRM	
Change in HbA_{1c} from week 0 to week 44	%-point mmol/mol	Continuous	Treatment policy	FAS	ANCOVA	RD-MI/WO-MI
			Hypothetical	FAS	MMRM	

Analyses addressing the primary, secondary and additional estimands for responder endpoints

For all analyses of responder endpoints including both primary and secondary responder endpoints (≥5%, ≥10%, ≥15%, ≥20% body weight reduction 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.

Analyses corrected to address the situation if no responder for ≥5%, ≥10%, ≥15%, ≥20% body weight reduction from week 0 to week 44 in one treatment group

If no responder for ≥5%, ≥10%, ≥15%, ≥20% body weight reduction at week 44 for one treatment group, the logistic regression will not fit. Thus, Firth's approximation will be implemented in order to provide valid inference in this situation.

4.4 Exploratory Endpoints Analyses

Exploratory endpoints are listed in Section 1.1. Exploratory endpoints will be summarised by descriptive statistics.

4.5 Other Safety Analysis

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 based on the number of TEAEs and SAEs. All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

4.6 Other Analysis

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

4.7 Subgroup Analysis

Not applicable for this trial.

4.8 Interim Analysis

Not applicable for this trial.

4.9 Changes to Protocol-planned Analysis

- The WO-MI model has been specified for the main imputation model if the full RD-MI model cannot be fit.
- Firth's approximation has been specified for the situation of no responders in either treatment group for ⩾5%, ⩾10%, ⩾15%, ⩾20% body weight reduction
- In the text describing that "In general, the on-treatment period will therefore be from the date of first trial product administration to date of last trial product administration" the following has been added "(+14 days)" to emphasize that the lag-time after last trial product administration is included in the on-treatment period.

- It is clarified that TP-MI imputation is performed with penalties applied to both treatment groups.
- 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.