# Cover Page for Statistical Analysis Plan

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### 9.1.9 Documentation of statistical methods

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# Statistical Analysis Plan

Protocol title: Efficacy and safety of subcutaneous semaglutide 2.4 mg once-weekly in subjects with obesity and prediabetes

## Substance: semaglutide

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

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# Version History

This Statistical Analysis Plan (SAP) for study NN9536-4734 is based on the protocol version 4.0 dated 24 Feb 2023.

| SAP Version | Date | Change | Rationale |
|---|---|---|---|
| 1.0 | | Not Applicable | Original version |

# List of abbreviations

| | |
|---|---|
| AE | adverse event |
| ANCOVA | analysis of covariance |
| BMI | body mass index |
| bpm | beats per minute |
| CI | confidence interval |
| cm | centimetre |
| CVD | cardiovascular disease |
| FAS | full analysis set |
| FPG | fasting plasma glucose |
| HbA1c | glycated haemoglobin |
| HDL | high density lipoprotein |
| ICH | International Council on Harmonization |
| 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 |
| NICE | National Institute for Health and Care Excellence |
| NR | non-responders |
| OR | odds ratio |
| RD-MI | multiple imputation using retrieved subjects |
| SAP | statistical analysis plan |
| s.c. | subcutaneous |
| T2D | type 2 diabetes |
| TFL | tables, figures and listings |
| TP | tipping point |
| VLDL | very low density lipoprotein |
| WLQ | work limitations questionnaire |

# 1 Introduction

This SAP is based on protocol version 4.0 dated 24Feb2023. Changes from the protocol are provided in section 4.8.

## 1.1 Objectives, Endpoints, and Estimands

### Primary objective (week 0 to week 52)

To confirm the superiority of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo, both as adjuncts to a reduced-calorie diet and increased physical activity in subjects with obesity and prediabetes, on body weight and reversal to normoglycemia.

### Secondary objectives (week 0 to week 52)

To compare the efficacy of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo on:

- glucose metabolism
- cardiovascular risk factors
- other factors related to body weight

### Secondary safety objective (week 0 to week 57)

To compare the safety and tolerability of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo.

### Exploratory objectives

### Main phase (week 0 to week 52)

To compare the efficacy of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo on physical functioning, vitality, work productivity, and progression to T2D.

### Main and extension phase (week 0 to week 80)

To explore the change in body weight, reversal to normoglycemia, glucose metabolism, cardiovascular risk factors, other factors related to body weight, and progression to T2D in subjects after treatment with semaglutide s.c. 2.4 mg once-weekly or semaglutide placebo followed by an off-treatment period.

### Co-primary estimands

The primary clinical question of interest is: what is the average treatment effect of semaglutide s.c. 2.4 once-weekly as an adjunct to a reduced-calorie diet and increased physical activity, in subjects with obesity and prediabetes, measured by relative change from baseline to week 52 in body weight and reversal to normoglycaemia, regardless of discontinuation or dose reduction of randomised treatment and regardless of initiating other glucose-lowering medication or anti-obesity therapies (weight management drugs or bariatric surgery) (“treatment policy” strategy).

The estimand is described by the following attributes (according to International Council for Harmonisation (ICH) E9(R1) 1):

- Treatment condition: The randomised treatment regardless of discontinuation or dose reduction of randomised treatment or initiation of other glucose-lowering medication or anti-obesity therapies (as defined above)
- Other intercurrent events: none
- Population: Subjects with obesity and prediabetes
- Endpoints: The two primary endpoints relative change in body weight and reversal to normoglycaemia, both from baseline to week 52
- Population-level summary: For change in body weight, the treatment effect will be quantified by the difference in mean changes between treatment conditions. For reversal to normoglycaemia, the treatment effect will be quantified by the odds ratio between treatment conditions.

A similar estimand applies to all supportive secondary endpoints, which is called the secondary estimand.

Rationale for estimand: The primary (and secondary) estimand aims at reflecting how patients with obesity are treated in clinical practice.

**Additional estimands**

An additional clinical question of interest is: what is the average treatment effect of semaglutide s.c. 2.4 mg once-weekly as an adjunct to a reduced-calorie diet and increased physical activity, in subjects with obesity and prediabetes, measured by relative change from baseline to week 52 in body weight and reversal to normoglycaemia, had they remained on their randomised treatment for the entire planned duration of the trial and not initiated other glucose-lowering medication or anti-obesity therapies (weight management drugs or bariatric surgery) ("hypothetical" strategy).

The estimand is described by the following attributes (according to ICH E9(R1) 1):

- Treatment condition: The randomised treatment if subjects had adhered for the entire duration of the trial and not initiated other glucose-lowering medication or anti-obesity therapies (as defined above)
- Other intercurrent events: none
- Population: Subjects with obesity and prediabetes
- Endpoints: The primary endpoints relative change in body weight and reversal to normoglycaemia, both from baseline to week 52
- Population-level summary: For relative change in body weight, the treatment effect will be quantified by the difference in mean changes between treatment conditions. For reversal to normoglycaemia, the treatment effect will be quantified by the odds ratio between treatment conditions.

Rationale for estimand: The additional estimand aims at reflecting the treatment effect in the absence of intercurrent events.

Similar additional estimands also apply to supportive secondary objectives in the population.

### 1.1.1 Primary, secondary and exploratory endpoints

#### 1.1.1.1 Primary endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in body weight | From randomisation (week 0) to end of treatment (week 52) | % |
| Change to normoglycemia* | From randomisation (week 0) to end of treatment (week 52) | Count of subjects |

* Normoglycemia is defined as having both $HbA_{1c}$ < 6.0% (< 42 mmol/mol) and FPG < 5.5 mmol/L (< 99 mg/dL)
Change to normoglycaemia at end of treatment regardless of the glycaemic status at randomisation

### 1.1.2 Secondary endpoints

#### 1.1.2.1 Confirmatory secondary endpoints

Not applicable for this trial

#### 1.1.2.2 Supportive secondary endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in $HbA_{1c}$ | From randomisation (week 0) to end of treatment (week 52) | %-points |
| Change in FPG | From randomisation (week 0) to end of treatment (week 52) | mmol/L |
| Change in waist circumference | From randomisation (week 0) to end of treatment (week 52) | cm |
| Change in systolic blood pressure | From randomisation (week 0) to end of treatment (week 52) | mmHg |
| Change in lipids<br>• Triglycerides<br>• Total cholesterol<br>• High density lipoprotein (HDL) cholesterol<br>• Low density lipoprotein (LDL) cholesterol<br>• Very low density lipoprotein (VLDL) cholesterol | From randomisation (week 0) to end of treatment (week 52) | % |

In addition to the protocol specified endpoints, the following supportive secondary endpoints are defined:

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in body weight | From randomisation (week 0) to end of treatment (week 52) | kg |
| Achieving body weight reduction ≥ 5% | From randomisation (week 0) to end of treatment (week 52) | Count of subjects |
| Achieving body weight reduction ≥ 10% | From randomisation (week 0) to end of treatment (week 52) | Count of subjects |
| Achieving body weight reduction ≥ 15% | From randomisation (week 0) to end of treatment (week 52) | Count of subjects |
| Achieving body weight reduction ≥ 20% | From randomisation (week 0) to end of treatment (week 52) | Count of subjects |
| Change in pulse | From randomisation (week 0) to end of treatment (week 52) | bpm |

### 1.1.3 Exploratory endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in EuroQol five dimensions three level (EQ-5D-3L) index score | From randomisation (week 0) to end of treatment (week 52) | Score points |
| Change in EQ-5D-3L visual analogue scale (VAS) score | From randomisation (week 0) to end of treatment (week 52) | Score points |
| Change in Work Limitations Questionnaire 25-item version (WLQ-25) Six-item Physical Demands scale | From randomisation (week 0) to end of treatment (week 52) | Score points |
| Change in WLQ-25 total score | From randomisation (week 0) to end of treatment (week 52) | Score points |
| Change to normoglycemia* | From randomisation (week 0) to end of extension phase (week 80) | Count of subjects |
| Change in body weight | From randomisation (week 0) to end of extension phase (week 80) | % |
| Change in $HbA_{1c}$ | From randomisation (week 0) to end of extension phase (week 80) | %-points |
| Change in FPG | From randomisation (week 0) to end of extension phase (week 80) | mmol/L |
| Change in waist circumference | From randomisation (week 0) to end of extension phase (week 80) | cm |
| Change in systolic blood pressure | From randomisation (week 0) to end of extension phase (week 80) | mmHg |
| Change in lipids<br>• Triglycerides<br>• Total cholesterol<br>• High-density lipoprotein (HDL) cholesterol<br>• Low-density lipoprotein (LDL) cholesterol<br>• Very low-density lipoprotein (VLDL) cholesterol | From randomisation (week 0) to end of extension phase (week 80) | % |
| Progression to T2D** | From randomisation (week 0) to end of treatment (week 52) | Count of subjects |
| Progression to T2D** | From randomisation (week 0) to end of extension phase (week 80) | Count of subjects |

* Normoglycemia is defined as having both HbA1c < 6.0% (< 42 mmol/mol) and FPG < 5.5 mmol/L (< 99 mg/dL)
**Diagnosis of T2D is defined as HbA1c ≥6.5% (≥ 48 mmol/mol) and/or FPG ≥ 7.0 mmol/L (≥ 126 mg/dL) verified with a repeated blood sample within 4 weeks.

In addition to the protocol specified endpoints, the following exploratory endpoint is defined:

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in pulse | From randomisation (week 0) to end of treatment (week 80) | bpm |

## 1.2 Study Design

The trial design is provided in the protocol section 4.1.

A database lock is planned after completion of the 'end of trial visit' (week 80) of the extension phase. One clinical trial report (CTR) will be prepared including the main and the extension phase of the trial.

# 2 Statistical Hypotheses

Statistical hypotheses for the primary estimands with primary endpoints, 1) relative change in body weight (%) from randomisation (week 0) to end of treatment (week 52) and 2) reversal to normoglycaemia (yes/no) at end of treatment (week 52) 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:

$\mu$ = ([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.

## 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 favor of semaglutide s.c. 2.4 mg.

The steps in the hierarchical testing procedure are as follows:

- Step 1: Superiority of semaglutide s.c. 2.4 mg versus placebo with respect to primary estimand with endpoint relative change in body weight (%) from randomisation (week 0) to end of treatment (week 52).

- Step 2: Superiority of semaglutide s.c. 2.4 mg versus placebo with respect to primary estimand with endpoint reversal to normoglycaemia at end of treatment (week 52).

# 3 Analysis Sets

The following populations and observation periods are defined:

| Population | Description |
|---|---|
| Full analysis set | Full analysis set (FAS): All subjects randomised. Exclusion of data from analyses should be used restrictively, and normally no data should be excluded from the FAS. Subjects will be analysed according to the randomised treatment |
| Safety analysis set | All subjects randomly assigned to trial treatment and who take at least 1 dose of trial product. Subjects are analysed according to the treatment they actually received. |

| Observation period | Description |
|---|---|
| In-trial | The time period where the subject is assessed in the trial. The in-trial observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive):<br>• 'End of trial' visit<br>• withdrawal of consent<br>• last contact with subject (for subjects lost to follow-up)<br>• death |
| In-trial (main phase) | The time period where the subject is assessed in the main phase of the trial. The in-trial (main phase) observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive):<br>• safety visit<br>• withdrawal of consent<br>• last contact with subject (for subjects lost to follow-up)<br>• death |
| On-treatment | The time period where subjects 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 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 excluding potential off-treatment time intervals triggered by at least two consecutive missed doses.<br><br>For the evaluation of AEs and potential pregnancies, the lag time for each on-treatment time interval is 5 weeks (35 days). |

Any observation excluded from the analysis database will be documented before database lock with the reason for exclusion provided. Efficacy endpoints will be analysed using the FAS; safety endpoints will be analysed using the safety analysis set (SAS).

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods. The in-trial (main phase) period defines the patient years of observation (PYO) during the main phase of the trial as the total time duration in the period.

# 4 Statistical Analyses

## 4.1 General Considerations

### Handling of missing baseline data

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 subjects is used as the baseline value.

## 4.2 Primary Endpoints Analyses

The primary endpoints are change in body weight (%) and reversal to normoglycaemia, both from baseline (week 0) to end of treatment (week 52) as listed in Section 1.1.1.1.

All tests are tests of superiority of semaglutide s.c. 2.4 mg once-weekly to semaglutide placebo.

### 4.2.1 Definition of Endpoints

Normoglycemia is defined as having both $HbA_{1c}$ < 6.0% (< 42 mmol/mol) and FPG < 5.5 mmol/L (< 99 mg/dL)

### 4.2.2 Main Analytical Approach

### Analyses addressing the primary estimand

The following statistical analyses and imputation method are designed to address the primary estimand.

The analysis model for change in body weight (%) will be a linear regression (ANCOVA), assuming unequal variances with randomised treatment as factor and baseline body weight (kg) as covariate. The estimated treatment difference between semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

The statistical model for the reversal to normoglycaemia endpoint is a logistic regression using randomised treatment as factor and baseline $HbA_{1c}$ and FPG as covariates. The estimated odds ratio (OR) between semaglutide s.c. 2.4 mg once-weekly and semaglutide placebo will be reported together with the associated two-sided 95% confidence interval and corresponding p-value.

All available data at week 52 are used and missing values at week 52 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.2 For subjects in the semaglutide s.c. 2.4 mg once-weekly and the semaglutide placebo groups, missing measurements at week 52 for non-retrieved subjects are imputed using assessments from retrieved subjects in each treatment 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 52 for subjects on randomised treatment (at week 52) are imputed by sampling from available measurements at week 52 from subjects on randomised treatment in the relevant randomised treatment arms. The multiple imputation approach is done in three steps:

1.**Imputation:** Defines an imputation model using retrieved subjects from FAS and done within groups defined by randomised treatment. The model will be a linear regression of the endpoint - body weight/ HbA1c/ FPG at week 52 with gender (male/female), baseline BMI (kg/m2) (in categories <35, 35-<40, ≥40) as factors and baseline body weight (kg)/ baseline HbA1C/ baseline FPG, timing of the LAO-OT of the endpoint and LAO-OT of the endpoint as covariates. No interactions will be included. If the imputation model still cannot be fit due to small group size 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 collapsing the two highest baseline BMI groups into one (≥35) and finally removing baseline BMI group. If the model still cannot be fit, the imputation will be done regardless of the randomised treatment arm. If no LAO-OT exists post-baseline then LAO-OT will be the baseline value of the endpoint and the timing will be 0. If any subjects are on-treatment with missing values at week 52, an imputation model for missing body weight/ HbA1C/ FPG at week 52 will be defined using subjects on-treatment and with available observations at week 52 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 52 body weight/ HbA1c/ FPG values for each randomised treatment arm. This will be done 1,000 times and results in 1,000 complete data sets.

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.

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 95364734 as seed number. In addition to the seed number, it is specified that the dataset is sorted by subject ID.

**Analyses addressing the additional estimand**

The additional estimand for change in body weight (%) will be assessed using a mixed model for repeated measurements (MMRM) approach. Week 52 assessments for retrieved subjects are not used in this analysis. The MMRM will use assessments only from subjects who are taking the randomised treatment until end of treatment or until first discontinuation of randomised treatment or initiation of glucose-lowering medication or other anti-obesity therapies (weight management drugs or bariatric surgery). The MMRM will be fitted using change and the same factors and covariate as for the primary analysis all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

The additional estimand for the reversal to normoglycaemia endpoint will be analysed according to the following procedure:

1) $HbA_{1c}$ (%) will be analysed in an MMRM using assessments only from subjects who are taking the randomised treatment until end of treatment or until first discontinuation of randomised treatment or initiation of glucose-lowering medication or other anti-obesity therapies (weight management drugs or bariatric surgery). The MMRM will be fitted using randomised treatment as factor and baseline $HbA_{1c}$ (%) as covariate nested within visit. An

unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

2) FPG (mmol/L) will be analysed in the same MMRM as for $HbA_{1c}$ (%), but with FPG (mmol/L) as outcome and baseline FPG (mmol/L) as covariate.

For subjects with missing $HbA_{1c}$ (%) and/or FPG (mmol/L) at week 52, individual values will be predicted from the MMRM analyses and used to classify each subject as normoglycaemic or not. This classification will then be analysed using a logistic regression model with randomised treatment as factor and baseline $HbA_{1c}$ (%) and FPG (mmol/L) as covariates.

### 4.2.3 Sensitivity Analyses

Jump to reference multiple imputation approach (J2R-MI): Missing values of body weight at week 52 for both the semaglutide 2.4 mg and placebo group are imputed by sampling among all available assessments at week 52 in the placebo group. This approach makes the assumption that subjects 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 subjects from FAS with a week 52 measurement. The model will be a linear regression of body weight at week 52 with gender (male/female), baseline BMI (kg/m2) (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 subjects 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 52 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. The approach is to explore a range of penalties for both treatment groups at week 52, 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.

Non-retrieved subjects as non-responders: For the analysis of reversal to normoglycemia an analysis using non-retrieved subjects as non-responders in the logistic regressions will be done. This analysis also targets the MAR assumption.

Tipping-point non-responder analysis (TP-NR): A proportion of missing data will be set as non-responders corresponding to a penalty in the range from 0% to 100% for both treatment groups at week 52. The results will be presented together with reference lines indicating the mean proportion of non-responders after multiple imputation to show when the penalty changes favouritism compared with RD-MI. This analysis targets the MAR assumption.

Subset of subjects with pre-diabetes at baseline: A sensitivity analysis of the primary estimand for the endpoint of reversal to normoglycaemia will be performed only for the subset of subjects who are pre-diabetic at randomisation based on the re-derived glycaemic status. The analysis performed will be similar to the primary analysis of this endpoint.

Subjects who are normoglycaemic or diagnosed with T2D at baseline will be excluded from this analysis. Diagnosis of T2D is defined as HbA1c ≥6.5% (≥ 48 mmol/mol) and/or FPG ≥ 7.0 mmol/L (≥ 126 mg/dL) verified with a repeated blood sample within 4 weeks. Subjects who have missed the repeated blood sample within 4 weeks will continue to be considered as pre-diabetic and will be included in the sensitivity analysis.

### 4.2.4 Supplementary Analysis

Not applicable for this trial.

**Table 1 Analysis and imputation methods to address the effectiveness and efficacy estimands for primary endpoints**

| Endpoint | Endpoint type | Analysis Set | Estimand | Statistical model | Imputation model | Sensitivity Analysis |
|---|---|---|---|---|---|---|
| Primary Endpoint | | | | | | |
| Change in body weight (%) | Continuous | FAS | Treatment | ANCOVA | RD-MI | J2R-MI, TP-MI |
| | | | Hypothetical | MMRM | | |
| Change to normoglycaemia | Binary | FAS | Treatment | LR | RD-MI | Non responders, TP, Subset of subjects with pre-diabetes at baseline |
| | | | Hypothetical | LR | MMRM | |

## 4.3 Secondary Endpoints Analyses

### 4.3.1 Confirmatory Secondary Endpoints Analyses

Not applicable for this trial.

### 4.3.2 Supportive Secondary Endpoints Analyses

The supportive secondary endpoints as listed in section 1.1.2.2 will be analysed as explained below.

**Analyses addressing the 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 imputation model is the same as for the primary endpoints with body weight replaced by the endpoint to be analysed. The statistical model for continuous endpoints will be ANCOVA assuming unequal variances with factors and covariate as for the primary endpoint weight with baseline body weight replaced by the baseline

assessment of the endpoint to be analysed. The statistical model for body weight responder endpoints will be logistic regression with factors and covariates as the primary endpoint reversal to normoglycaemia with the baseline HbA1c and FPG replaced by baseline body weight as covariate.

**Analyses addressing the additional estimand**

The supportive secondary continuous endpoints will be analysed to address the additional estimand using the same MMRM as described for the primary endpoint body weight with randomised treatment as factor and baseline assessment of the endpoint as covariate.

The body weight 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 as responder variable in the model. For subjects with missing body weight at week 52, individual values will be predicted from the MMRM analyses and used to classify each subject as responder or not. This classification will then be analysed using a logistic regression model with randomised treatment as factor and baseline body weight as covariate.

**Analyses addressing the primary, secondary and additional estimands**

For all analyses of responder endpoints including both primary and secondary endpoints (change to normoglycaemia, ≥5%, ≥10%, ≥15%, ≥20% body weight reduction), 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 2 Analysis 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 | kg | Continuous | Treatment policy | FAS | ANCOVA | RD-MI |
| | | | Hypothetical | FAS | MMRM | |
| Change in $HbA_{1c}$ from week 0 to week 52 | %-points<br>mmol/mol | Continuous | Treatment policy | FAS | ANCOVA | RD-MI |
| | | | Hypothetical | FAS | MMRM | |
| Change in FPG from week 0 to week 52 | mmol/L<br>mg/dL | Continuous | Treatment policy | FAS | ANCOVA | RD-MI |
| | | | Hypothetical | FAS | MMRM | |
| Change in waist circumference from week 0 to week 52 | cm | Continuous | Treatment policy | FAS | ANCOVA | RD-MI |
| | | | Hypothetical | FAS | MMRM | |
| Change in systolic blood pressure from week 0 to week 52 | mmHg | Continuous | Treatment policy | FAS | ANCOVA | RD-MI |
| | | | Hypothetical | FAS | MMRM | |
| Change in lipids<br>Triglycerides<br>Total cholesterol<br>High density lipoprotein (HDL) cholesterol<br>Low density lipoprotein (LDL) cholesterol<br>Very low density lipoprotein (VLDL) cholesterol<br>from week 0 to week 52 | mg/dL<br>mmol/L | Continuous | Treatment policy | FAS | ANCOVA | RD-MI |
| | | | Hypothetical | FAS | MMRM | |
| Body weight reduction ≥ 5% from week 0 to week 52 | Count of subjects | Binary | Treatment policy | FAS | LR | RD-MI |
| | | | Hypothetical | FAS | LR | MMRM |
| Body weight reduction ≥ 10% | | Binary | Treatment policy | FAS | LR | RD-MI |

| | | | | | | |
|---|---|---|---|---|---|---|
| from week 0 to week 52 | Count of subjects | | Hypothetical | FAS | LR | MMRM |
| Body weight reduction ≥ 15% from week 0 to week 52 | Count of subjects | Binary | Treatment policy | FAS | LR | RD-MI |
| | | | Hypothetical | FAS | LR | MMRM |
| Body weight reduction ≥ 20% from week 0 to week 52 | Count of subjects | Binary | Treatment policy | FAS | LR | RD-MI |
| | | | Hypothetical | FAS | LR | MMRM |
| Change in pulse from week 0 to week 52 | bpm | Continuous | Hypothetical | FAS | MMRM | |

## 4.4 Exploratory Endpoints Analyses

The exploratory endpoints are listed in section 1.1.3 and will be analysed as explained below.

**Analyses addressing the secondary estimand**

The endpoints related to EQ-5D-3L index score, EQ-5D-3L VAS score, WLQ-25 physical demands score and WLQ-25 total score addressing the primary estimand will be analysed using the J2R imputation approach as used for the sensitivity analysis of the primary endpoint change in body weight. The statistical model will be the same linear regression ANCOVA assuming unequal variances as for the primary endpoint with treatment as a factor and the baseline value of the endpoint as a covariate. The analysis of WLQ-25 will only be performed for the subjects employed at baseline and only those assessments taken while the subject was employed will be included. In addition, subjects for whom a baseline score cannot be calculated according to the scaling and scoring manual due to too many items being rated as “does not apply to my job” are excluded from the analysis.

Additionally, WLQ-25 time management score, WLQ-25 mental – interpersonal score, WLQ-25 output score and WLQ-25 at-work productivity loss score will be analysed as mentioned above.

**Analyses addressing the additional estimand**

The endpoints related to EQ-5D-3L index score, EQ-5D-3L VAS score, WLQ-25 domain scores – time management score, mental-interpersonal score, output score, physical demands score and WLQ-25 total score 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. The analysis of WLQ-25 will only be performed for the subjects employed at baseline and only those assessments taken while the subject was employed will be included. In addition, subjects for whom a baseline score cannot be

calculated according to the scaling and scoring manual due to too many items being rated as "does not apply to my job" are excluded from the analysis.

### Other analyses

The exploratory endpoints related to change in body weight, HbA1c, FPG, waist circumference, systolic blood pressure, lipids, pulse, change to normoglycaemia and progression to T2D at week 80 will be summarised using descriptive statistics.

**Table 3 Analysis and imputation methods to address the effectiveness and efficacy estimands for exploratory endpoints**

| Endpoint | Unit | Endpoint type | Strategy | Analysis set | Statistical model | Imputation approach |
|---|---|---|---|---|---|---|
| Change in EuroQol five dimensions three level (EQ-5D-3L) index score from week 0 to week 52 | Score points | Continuous | Treatment policy | FAS | ANCOVA | J2R-MI |
| | | | Hypothetical | FAS | MMRM | |
| Change in EQ-5D-3L visual analogue scale (VAS) score from week 0 to week 52 | Score points | Continuous | Treatment policy | FAS | ANCOVA | J2R-MI |
| | | | Hypothetical | FAS | MMRM | |
| Change in Work Limitations Questionnaire 25-item version (WLQ-25) Six-item Physical Demands scale from week 0 to week 52 | Score points | Continuous | Treatment policy | FAS | ANCOVA | J2R-MI |
| | | | Hypothetical | FAS | MMRM | |
| Change in WLQ-25 Time Management scale from week 0 to week 52 | Score points | Continuous | Treatment policy | FAS | ANCOVA | J2R-MI |
| | | | Hypothetical | FAS | MMRM | |
| Change in WLQ-25 Output scale from week 0 to week 52 | Score points | Continuous | Treatment policy | FAS | ANCOVA | J2R-MI |
| | | | Hypothetical | FAS | MMRM | |
| Change in WLQ-25 Mental Output Tasks Demands scale from week 0 to week 52 | Score points | Continuous | Treatment policy | FAS | ANCOVA | J2R-MI |
| | | | Hypothetical | FAS | MMRM | |
| Change in WLQ-25 total score from week 0 to week 52 | Score points | Continuous | Treatment policy | FAS | ANCOVA | J2R-MI |
| | | | Hypothetical | FAS | MMRM | |
| Change in WLQ-25 At-Work Productivity Loss Score from week 0 to week 52 | % | Continuous | Treatment policy | FAS | ANCOVA | J2R-MI |
| | | | Hypothetical | FAS | MMRM | |
| Change to normoglycemia* at week 80 | Count of subject | Binary (only descriptive statistics) | | FAS | | |

| Endpoint | Unit | Endpoint type | Strategy | Analysis set | Statistical model | Imputation approach |
|---|---|---|---|---|---|---|
| Change in body weight from week 0 to week 80 | % | Continuous (only descriptive statistics) | | FAS | | |
| Change in $HbA_{1c}$ from week 0 to week 80 | %-points | Continuous (only descriptive statistics) | | FAS | | |
| Change in FPG from week 0 to week 80 | mmol/L | Continuous (only descriptive statistics) | | FAS | | |
| Change in waist circumference from week 0 to week 80 | cm | Continuous (only descriptive statistics) | | FAS | | |
| Change in systolic blood pressure from week 0 to week 80 | mmHg | Continuous (only descriptive statistics) | | FAS | | |
| Change in lipids<br>• Triglycerides<br>• Total cholesterol<br>• High-density lipoprotein (HDL) cholesterol<br>• Low-density lipoprotein (LDL) cholesterol<br>• Very low-density lipoprotein (VLDL) cholesterol<br>from week 0 to week 80 | % | Continuous (only descriptive statistics) | | FAS | | |
| Progression to T2D** at week 52 | Count of subject | Binary (only descriptive statistics) | | FAS | | |
| Progression to T2D** at week 80 | Count of subject | Binary (only descriptive statistics) | | FAS | | |
| Change in pulse from week 0 to week 80 | bpm | Continuous (only descriptive statistics) | | FAS | | |

* Normoglycemia is defined as having both HbA1c < 6.0% (< 42 mmol/mol) and FPG < 5.5 mmol/L (< 99 mg/dL)
**Diagnosis of T2D is defined as HbA1c ≥6.5% (≥ 48 mmol/mol) and/or FPG ≥ 7.0 mmol/L (≥ 126 mg/dL) verified with a repeated blood sample within 4 weeks.

### 4.5 Other Safety Analysis

Observed data for safety assessments will be summarised by descriptive statistics.

### 4.6 Other Analysis

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

#### 4.6.1 Subgroup Analysis

The subgroup analyses for this study will be reported outside the CSR. All the details of the subgroup analyses will be documented in a separate non-CSR SAP.

### 4.7 Interim Analysis

Not applicable for this trial.

### 4.8 Changes to Protocol-planned Analysis

No changes were made to the analysis planned in the protocol. However, additional endpoints are included, and the details are provided in this SAP. Further clarifications of the analyses are also provided.

The additional endpoints and their analyses are summarised below:

Supportive secondary endpoints:

- Change in body weight (kg) from week 0 to week 52
- Body weight reduction ≥ 5% from week 0 to week 52
- Body weight reduction ≥ 10% from week 0 to week 52
- Body weight reduction ≥ 15% from week 0 to week 52
- Body weight reduction ≥ 20% from week 0 to week 52
- Change in pulse (bpm) from week 0 to week 52

  All these endpoints will be analysed as described in Table 2.

Exploratory endpoint

- Change in pulse from week 0 to week 80

This endpoint will be descriptively summarised.

Also, it is specified that change in body weight, HbA1c, FPG and lipids will be analysed in SI-units.

# 5 Sample size determination

See protocol section 9.2.

# 6 References

1. International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Guideline on statistical principals for clinical trials: Addendum on estimands and sensitivity analysis in clinical trials. ICH E9(R1). Final version (20 November 2019). 2019.

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

3. Work Limiting Questionnaire© Version 1.0: May 2018. Mapi Research Trust

4. Subject questionnaire scoring of WLQ-25: VV-TMF-5555841

5. Valuing health-related quality of life: An EQ-5D-5L value set for England

6. EQ-5D-3L User Guide Version 6.0. December 2018