Cover Page for Statistical Analysis Plan

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16.1.9 Documentation of statistical methods

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

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Statistical Analysis Plan

Trial ID: NN9924-4234

PIONEER 5 –Renal impairment

Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes and moderate renal impairment

Trial phase: Phase 3a

Authors:

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Department: [redacted]

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List of Abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	Adverse Event
ANOVA	Analysis of Variance
BG	Blood Glucose
BMI	Body Mass Index
CDF	Cumulative Distribution Function
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CoEQ	Control of Eating Questionnaire
CRF	Case Report Form
CRP	C-reactive Protein
CTR	Clinical Trial Report
DTR-QoL	Diabetes Therapy-Related Quality of Life
DTSQs	Diabetes Treatment Satisfaction Questionnaire status
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EAC	Event Adjudication Committee
ECG	Electrocardiogram
EoT	End-of-Text
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
GLP-1	Glucagon-like Peptide-1
HRQoL	Health-Related Quality of Life
IWQOL-Lite-CT	Impact of Weight on Quality of Life – Lite Clinical Trials version
IWRS	Interactive Web Response System
LLoQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
MAR	Missing at Random
MCS	Mental Component Score
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimally Important Difference
MMRM	Mixed Model for Repeated Measurements
MNAR	Missing Not at Random
PCS	Physical Component Score
PD	Pharmacodynamics
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Status
PK	Pharmacokinetics
PP	Per Protocol

PRO	Patient Reported Outcomes
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	safety analysis set
SD	Standard Deviation
SE	Standard Error
SF-36v2 (acute version)	Short Form 36 version 2.0 Health Survey (acute version)
TEAE	treatment-emergent adverse events

1 Introduction

1.1 Trial information

This is a 26-week, randomised, double-blind, placebo-controlled, parallel-group, multicentre, multinational trial with 2 arms comparing the efficacy and safety of oral semaglutide with placebo in subjects with type 2 diabetes mellitus and moderate renal impairment.

1.1.1 Primary Objective

To compare the effect of once-daily dosing of 14 mg oral semaglutide versus placebo, both in combination with metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin on glycaemic control in subjects with type 2 diabetes mellitus and moderate renal impairment (metformin alone, SU alone or in combination with metformin, basal insulin alone or in combination with metformin).

1.1.2 Secondary Objectives

To compare the effect of once-daily dosing of 14 mg oral semaglutide versus placebo, both in combination with metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin on body weight in subjects with type 2 diabetes mellitus and moderate renal impairment.

To compare the safety and tolerability of once-daily dosing of 14 mg oral semaglutide versus placebo, both in combination with metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin in subjects with type 2 diabetes mellitus and moderate renal impairment.

1.1.3 Trial Design

Subjects will be randomised in a 1:1 manner to receive either a dose of 14 mg oral semaglutide or placebo once daily. The total trial duration for the individual subject will be approximately 33 weeks. The trial includes a 2-week screening period, followed by a 26-week randomised treatment period and a follow-up period of 5 weeks. For further details, see the trial protocol.

1.2 Scope of the Statistical Analysis Plan

This statistical analysis plan (SAP) is based on the protocol for trial NN9924-4234 “Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes and moderate renal impairment”, version 2.0 (14 November 2016), and includes more detailed procedures for executing

the statistical analyses of the primary and secondary endpoints. Statistical analyses and a number of clarifications additional to those specified in the trial protocol are pre-specified with this SAP. All changes to the statistical analyses planned in the trial protocol are documented in Section 3.

Novo Nordisk will be responsible for the statistical analyses and reporting.

2 Statistical considerations

2.1 General considerations

The blinding of the randomised treatments will be maintained until the database has been released for statistical analysis.

Data from all sites will be analysed and reported together.

In statistical analyses where stratification is included, the three levels of antidiabetic background medication at screening (metformin, SU +/-metformin, basal insulin +/- metformin) and the two levels of renal function (eGFR 30 - 44 mL/min/1.73 m2 and eGFR 45 - 59 mL/min/1.73 m2 as per CKD-EPI) will be included based on the actual information collected through the eCRF. In case of missing eCRF information the information collected from the IWRS system will be used.

The details of the region variables included in statistical analyses were not specified in protocol. The regions are: Europe (Denmark, Finland, Israel, Poland, Russian Fed., Sweden, United Kingdom) and North America (United States).

The latest available measurement, at or prior to the randomisation visit, will be used as the baseline measurement. If no measurement(s) have been obtained, at or prior to randomisation, the baseline value will be left missing.

Laboratory values below the lower limit of quantification (LLoQ) will be set to ½LLoQ. Number of values below LLoQ by treatment and visit will be summarised if deemed relevant.

Results from a statistical analysis will as a minimum be presented by the estimated treatment contrasts for oral semaglutide 14 mg vs. placebo with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference.

If no statistical analysis is specified, data will be presented using relevant summary statistics.

2.2 Primary and secondary estimands

Two estimands addressing different aspects of the trial objective will be defined; a primary de-facto (effectiveness) estimand and a secondary de-jure (efficacy) estimand:

- Primary estimand – ‘Treatment policy’

– de-facto treatment difference (oral semaglutide versus placebo) at week 26 for all randomised subjects regardless of adherence to randomised treatment and initiation of rescue medication.

The treatment policy estimand assesses the expected glycaemic benefit in a future population that results from subjects initiating treatment with oral semaglutide including potential rescue medication(s). Generalisation of this estimand depends among other things on the extent to which the use of rescue medication in this trial reflects clinical practice and the adherence to trial product administration in this trial reflects the behaviour of the target population. Accordingly, data collected regardless of discontinuation of trial product or initiation of rescue medication(s) will be used to draw inference.

- Secondary estimand – 'Hypothetical'
  – de-jure treatment difference (oral semaglutide versus placebo) at week 26 for all randomised subjects if all subjects adhered to treatment and did not initiate rescue medication.

The hypothetical estimand assesses the glycaemic benefit a future subject is expected to achieve if initiating and continuing treatment with oral semaglutide. It is considered a clinically relevant estimand as it provides information to treating clinicians about the expected glycaemic efficacy of oral semaglutide for purposes of treating individual subjects. Generalisation of this estimand depends among other things on the extent to which the adherence to trial product administration in this trial reflects the behaviour of the target population. Accordingly, only data collected prior to discontinuation of trial product or initiation of rescue medication will be used to draw inference. This will avoid confounding from rescue medication.

Analogously, two estimands will be pre-defined for the remaining secondary endpoints addressing the secondary objective.

2.3 Missing data considerations at week 26

When estimating the primary estimand, the proportion of missing data, i.e., data that do not exist even though subjects are intended to stay in the trial regardless of treatment status and initiation of rescue medication(s), is expected to be maximum 10% based on the oral semaglutide phase 2 trial (NN9924-3790). Thus, missing data will mainly be due to withdrawal from trial or lost to follow-up.

When estimating the secondary estimand, the proportion of missing data is expected to be higher

(20%) since data collected after discontinuation of trial product or initiation of rescue medication(s) will be set to missing. The 20% of missing data is based on the oral semaglutide phase 2 trial (NN9924-3790) that indicates that a low starting dose with gradual dose escalation diminishes gastrointestinal AEs compared with more aggressive dosing regimens. Across treatment arms the main reasons for missing data are expected to be early treatment discontinuation due to gastrointestinal AEs and eventually initiation of rescue medication. Initiation of rescue medication is expected to be more frequent in the placebo arm. Whereas a higher proportion of subjects are expected to discontinue treatment due to AEs in the oral semaglutide arm. So overall the frequency of missing data is expected to be similar across treatment arms.

Descriptive summaries and graphical representation of extent, reason(s) for and pattern of missing data will be presented by treatment arm.

2.4 Sample size calculation

Both the primary endpoint, change from baseline to week 26 in HbA_{1c} and the confirmatory secondary endpoint, change from baseline to week 26 in body weight are planned to be tested for superiority of oral semaglutide vs. placebo.

The sample size calculation is made to ensure a power of at least 90% for testing HbA_{1c} superiority of oral semaglutide vs. placebo out of the two pre-specified confirmatory hypotheses shown in Figure 2-1. The hierarchical testing procedure is used to control the overall type I error at a nominal two-sided 5% level. The statistical testing strategy[1] is built on the principle that glycaemic effect will have to be established in terms of HbA_{1c} superiority before testing for added benefits in terms of body weight superiority.

The sample size is calculated using the calcPower function in the R package, gMCP[2], using 10000 simulations. The two pre-specified confirmatory tests are assumed to be independent. Since some of the tests are positively correlated, the assumption of independence is viewed as conservative.

The sample size assumptions for treatment effects (TE), adjusted treatment effects and the standard deviation (SD) are given in Table 2-1. These are based on the oral semaglutide phase 2 results (NN9924-3790) and supported by results from the s.c. semaglutide phase 2 trial (NN9535-1821).

Subjects are allowed to be on metformin alone, SU alone or in combination with metformin, basal insulin alone or in combination with metformin as background medication; if they need rescue medication it is expected to have an effect on glycaemic control and the treatment effect compared to oral semaglutide will therefore be equalised. Furthermore a conservative approach for handling of missing data will be performed. An adjustment in treatment effect will be implemented for the

10% of subjects who are expected to discontinue trial product or initiate rescue medication and for the
10% of subjects who are expected to have actual missing data. The treatment effects used in the sample size calculation will be adjusted according to no effect in these subjects. The adjusted treatment effect for testing superiority is defined as: 0.8×TE + 0.2×TE×0

Table 2-1 Assumptions used in the sample size calculation

Oral semaglutide vs. placebo	Treatment effect (TE)	Adjusted TE, superiority	Standard deviation
HbA_{1c}(%-point)	-0.5	-0.4	1.1
Body weight (kg)	-2	-1.6	4

With the above assumptions, allocating 162 subjects to each of the oral semaglutide and placebo arms provides at least 90% power to confirm HbA_{1c} superiority of oral semaglutide vs. placebo. In total 2×162 = 324 subjects are planned to be randomised. Calculated powers for individual hypotheses are presented in Table 2-2.

Table 2-2 Calculated powers for individual hypotheses

Statistical test	HbA_{1c} superiority	Body weight superiority
Power (%)	91%	86%

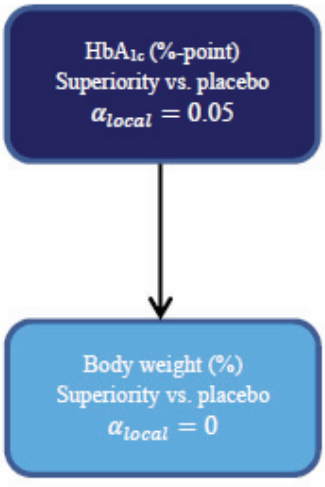


Figure 2-1 Graphical illustration of the testing procedure

The overall significance level of $\alpha = 0.05$ (two-sided) is initially allocated to the HbA_{1c} superiority test of oral semaglutide vs. placebo. The local significance level (α-local) will be reallocated to the next body weight superiority hypothesis, if the HbA_{1c} superiority hypothesis is confirmed. The sample size is based on the hypotheses in the dark box.

2.5 Definition of analysis sets

The following analysis sets will be defined:

Full analysis set (FAS): Includes all randomised subjects. Subjects in the FAS will contribute to the evaluation "as randomised".

Safety analysis set (SAS): Includes all subjects exposed to at least one dose of trial product. This will be referred to as contributing to the evaluation "as treated".

2.6 Data selections and observation periods

Unless subjects withdraw their informed consent, data collection will continue for the full duration of the trial. The full duration of the trial is defined as up to and including:

- the follow-up visit (V14) for subjects on trial product
- the latest occurring visit of the end-of-treatment visit (V13) or the follow-up premature discontinuation visit (V14A), for subjects who have discontinued trial product prematurely.

Subjects and data to be used in an analysis will be selected in a two-step manner:

- Firstly, subjects will be selected based on the specified analysis set
- Secondly, data points on the selected subjects from the first step will be selected based on the specified observation period

Definition of the observation periods:

In-trial: This observation period represents the time period where subjects are considered to be in the trial, regardless of discontinuation of trial product or initiation of rescue medication. The in-trial observation period starts at randomisation (as registered in the IWRS) and ends at the date of:

- the last direct subject-site contact, which is scheduled to take place 5 weeks after planned last dose of trial product at the follow-up visit
- withdrawal for subjects who withdraw their informed consent

- the last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up
- death for subjects who die before any of the above

On-treatment: This observation period represents the time period where subjects are considered treated with the trial product. The observation period is a subset of the in-trial observation period. It starts at the date of first dose of trial product. Two slightly different end dates will be needed to cover all assessments appropriately.
For adjudicated events, ECGs, eye examination category, anti-semaglutide antibodies, and AEs including hypoglycaemic episodes, the observation period ends at the first date of any of the following:

- the follow-up visit (V14)
- the follow-up premature discontinuation visit (V14A)
- the last date on trial product +38 days
- the end-date for the in-trial observation period

The follow-up visit is scheduled to take place 5 weeks after the last date on trial product corresponding to approximately five half-lives of oral semaglutide. The visit window for the follow-up visit is +3 days.

For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) the observation period ends at the last date on trial product +3 days. This will be used in order to ensure specificity to reversible effects of treatment.

On-treatment without rescue medication: This observation period is a subset of the on-treatment observation period, where subjects are considered treated with trial product, but have not initiated any rescue medications. Specifically it starts at date of first dose of trial product and the observation period ends at the first date of any of the following:

- the last dose of trial product +3 days
- initiation of rescue medication

The in-trial observation period will be the primary observation period when estimating the primary estimand. The on-treatment without rescue medication observation period will be the primary observation period when estimating the secondary estimand. The on-treatment observation period will be considered supportive for evaluating efficacy. Safety will be evaluated based on the in-trial and the on-treatment observation periods.

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period. For adjudicated events, the onset date will be the EAC adjudicated onset date.

Before data are locked for statistical analysis and the randomisation code is broken, a review of all data will take place. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group. Exclusion of data from analyses will be used restrictively, and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

2.7 Confirmatory hypotheses

For the primary HbA_{1c} endpoint and the secondary confirmatory body weight endpoint, the following one-sided hypotheses are planned to be tested for oral semaglutide versus placebo. Let the mean treatment difference be defined as μ = (oral semaglutide minus placebo):

- HbA_{1c} superiority
  - H0: $\mu \geq 0.0$%-point against Ha: $\mu < 0.0$%-point
- Body weight superiority
  - H0: $\mu \geq 0.0$ kg against Ha: $\mu < 0.0$ kg

Operationally the hypotheses will be evaluated by two-sided tests at the 5% significance level.

2.8 Multiplicity and criteria for confirming hypotheses

The type I error for testing the two confirmatory hypotheses related to the HbA_{1c} and body weight endpoints will be preserved in the strong sense at 5% (two-sided) using the hierarchical testing strategy as outlined in Figure 2-1.

Superiority will be considered confirmed if the mean treatment difference is supporting the corresponding alternative hypothesis and the two-sided p-value from the primary analysis of the primary estimand is strictly below the 5% two-sided significance level. This is equivalent to using a one-sided p-value (nominal $\alpha = 0.025$) and a one-sided 2.5% overall significance level.

2.9 Primary endpoint

The primary endpoint is change from baseline to week 26 in HbA_{1c}.

2.9.1 Primary analysis for the primary estimand

The primary estimand will be estimated based on the FAS using week 26 measurements from the in-trial observation period. The primary statistical analysis will be a pattern mixture model using multiple imputation to handle missing data assuming that the missing data mechanism is missing at random (MAR) within the groups used for imputation. Imputation of missing data at week 26 will be done within 4 groups of subjects defined by randomised treatment arm, and whether subjects at week 26; (i) have discontinued treatment or initiated rescue medication or (ii) are still on treatment and have not initiated rescue medication. It is hereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who at week 26 are similar in terms of randomised treatment arm and treatment adherence/rescue medication status.

Missing values for each group will be imputed as follows:

- An analysis of covariance (ANCOVA) with stratification factors as categorical fixed effects and baseline HbA_{1c} measurement as a covariate will be fitted to observed values of the change from baseline in HbA_{1c} at week 26.
- The estimated parameters for location and dispersion will be used to impute 1000 values for each subject with missing week 26 data based on the two stratification factors and baseline HbA_{1c}. Thus, 1000 complete data sets will be generated including observed and imputed values.

Analysis used for confirming superiority versus placebo at week 26:
For each of the 1000 (now complete) imputed data sets, the change in HbA_{1c} from baseline to week 26 will be analysed using an ANCOVA with treatment, region, stratification factors and the interaction between the two stratification factors as categorical fixed effects and baseline HbA_{1c} as covariate. The results obtained from analysing the datasets will be combined using Rubin's rule[3] to draw inference.

From this analysis the estimated treatment difference between oral semaglutide and placebo together with associated two-sided 95% confidence interval and unadjusted two-sided p-value for testing no difference from zero will be presented.

2.9.2 Primary analysis for the secondary estimand

The secondary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 26 from the on-treatment without rescue medication observation period. The primary analysis for the secondary estimand will be a Mixed Model for Repeated Measurements (MMRM). A restricted maximum likelihood (REML) will be used. The model will include all post baseline HbA_{1c} measurements collected at scheduled visits up to and including week 26 as dependent variables. The independent effects included in the model will be treatment, stratification factors, the interaction between the two stratification factors and region as categorical fixed effects

and baseline HbA_{1c} as a covariate, all nested within visit. An unstructured covariance matrix for HbA_{1c} measurements within the same subject will be employed, assuming measurements from different subjects are independent.

The MMRM is a well-established method that accounts for the uncertainty pertaining to missing data. This analysis assumes that the missing data mechanism is MAR. Under this assumption the statistical behaviour of the missing data (given the observed responses and model fixed effects and covariates) is assumed to be same as the observed data.

For subjects who do not have post-baseline assessments for planned visits available in the on-treatment without rescue medication period, the baseline value will be carried forward to the first planned visit, if this falls within 8 weeks, to ensure that all randomised subjects will contribute to the statistical analysis.

2.9.3 Sensitivity analyses

To investigate the sensitivity of the primary analysis results, complementary and separate analyses will be performed for the primary and secondary estimand. In line with European Medicines Agency recommendations[5] and with a report from the US National Research Council[6], these analyses will primarily evaluate the sensitivity of the results due to the impact of missing data.

The evaluation of the robustness of the primary analysis results will primarily be based on a pattern mixture model approach using multiple imputations. An overview of the sensitivity analyses for each of the estimands are specified below followed by a more detailed description of the three different pattern mixture models used.

2.9.3.1 Sensitivity analyses for the primary estimand

The estimation of the primary estimand will be repeated using the following sensitivity analyses:

- A comparator multiple imputation analysis based on FAS using the in-trial observation period
- A comparator multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely based on FAS using the in-trial observation period
- A tipping-point multiple imputation analysis based on FAS using the in-trial observation period

2.9.3.2 Sensitivity analyses for the secondary estimand

The estimation of the secondary estimand will be repeated using the following sensitivity analysis:

- A tipping-point multiple imputation analysis based on FAS using the on-treatment without rescue medication observation period

2.9.3.3 Pattern mixture models

Common for the three pattern mixture model sensitivity analyses is that they all aim to stress-test the primary HbA_{1c} results by changing the assumptions for part or all missing data in the oral semaglutide treatment arms, while maintaining the missing at random data assumption for the placebo arm:

- *Comparator multiple imputation analysis:* In this sensitivity analysis missing data at week 26 for all subjects will be imputed to resemble the distribution of the week 26 values observed in the placebo treatment arm. In effect, this imputation approach removes the treatment difference between oral semaglutide and placebo for all subjects randomised to oral semaglutide, given that oral semaglutide is better than placebo.

- *Comparator multiple imputation analysis differentiating between reasons for discontinuing treatment prematurely:* In this sensitivity analysis only missing data at week 26 for subjects who discontinue oral semaglutide treatment due to treatment related AE(s) will be imputed to resemble the distribution of the week 26 values observed in the placebo treatment arm. Treatment related AEs are defined as AEs classified as possible or probable related to trial product as reported by the investigator. In effect this imputation approach removes the treatment difference between oral semaglutide and placebo for this selected group of subjects randomised to oral semaglutide. This sensitivity analysis is less conservative as compared to the first sensitivity analysis.

- *Tipping-point multiple imputation analysis:* In this sensitivity analysis, missing data will first be imputed according to the primary analysis. Secondly, for the oral semaglutide treatment arm a penalty will be added to the imputed values at week 26. The approach is to gradually increase this penalty until a confirmed HbA_{1c} conclusion from the primary analysis is changed. The specific value of the penalty that changes the conclusion will be used to evaluate the robustness of the primary analysis result.

Assessment of sensitivity analyses

The results from the sensitivity analyses will be collectively used to interpret the robustness of the trial results for HbA_{1c}. Due to the sensitivity analyses inherent conservative nature, it will not be a requirement that all confirmatory hypotheses are consistently confirmed across the sensitivity analyses. Thus, no absolute success criteria will be pre-defined for each sensitivity analysis. The sensitivity results in totality will be used to substantiate the credibility of the trial results.

2.10 Secondary endpoints

2.10.1 Confirmatory secondary endpoints

Change from baseline to week 26 in body weight (kg) will be a confirmatory secondary endpoint.

The primary and secondary estimands will be estimated using the same approaches as described for the primary HbA_{1c} endpoint. Body weight will only be tested for superiority. Baseline body weight will be used as a covariate instead of baseline HbA_{1c} in both the multiple imputation and MMRM analysis models.

Superiority will be considered confirmed if the mean treatment difference is supporting the corresponding hypothesis and the two-sided p-value from the analysis of the primary estimand is strictly below its updated local two-sided significance level resulting from the closed testing procedure in Figure 2-1. Sensitivity analyses similar to the ones pre-specified for testing superiority for the primary HbA_{1c} endpoint will be made to evaluate the robustness of the body weight results.

2.10.2 Supportive secondary endpoints

2.10.2.1 Efficacy endpoints

The below supportive secondary efficacy endpoints will be evaluated for:

- The primary estimand based on FAS using the in-trial observation period
- The secondary estimand based on FAS using the on-treatment without rescue medication observation period

No sensitivity analyses are planned for the supportive secondary endpoints.

Continuous efficacy endpoints

Change from baseline to week 26 in:

- Fasting plasma glucose (FPG)
- Body weight (%)
- Body mass index (BMI)
- Waist circumference
- Fasting lipid profile (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides)
- C-reactive protein (CRP)

BMI will be calculated based on body weight and height based on the formulae:

$$\text{BMI } kg/m^2 = \text{body weight (kg)}/(\text{height (m)} \times \text{height (m)}) \text{ or } (kg/m^2 = [lb/in^2 \times 703])$$

The above continuous endpoints will be analysed separately using similar model approaches as for the primary endpoint with the associated baseline response as a covariate. Fasting lipid profile

endpoints and C-reactive protein endpoint will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

For evaluation of the primary estimand, the analyses will be performed at week 26. This will result in imputation of missing data within 4 groups as described for the week 26 evaluation in Section 2.9.1.

For evaluation of the secondary estimand, the MMRM based primary analysis will include all scheduled post-baseline measurement up to and including week 26. From this model the estimated treatment differences (ratios) will be presented at week 26 with 95% confidence intervals and two-sided p-values for test of no difference. The baseline value will be carried forward to the first planned visit, if this falls within 8 weeks.

Binary efficacy endpoints

If a subject after week 26 achieves (yes/no):

- $HbA_{1c} < 7.0\%$ (53 mmol/mol) (ADA) target
- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) (AACE) target
- Weight loss $\geq 5\%$
- Weight loss $\geq 10\%$
- $HbA_{1c} < 7.0\%$ (53 mmol/mol) without hypoglycaemia (treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemia) and no weight gain
- HbA_{1c} reduction $\geq$ 1%-point (10.9 mmol/mol) and weight loss $\geq 3\%$

When addressing the treatment policy estimand the 'without hypoglycaemia' component of the composite endpoint will also include non-treatment-emergent events of severe or BG-confirmed symptomatic hypoglycaemia as data collected regardless of discontinuation of trial product or initiation of rescue medication(s) is used. The above six endpoints will be evaluated after week 26.

The above six binary endpoints will be analysed using a logistic regression model with treatment, stratification factors, the interaction between the two stratification factors and region as fixed effects and baseline response as covariate (i.e. baseline HbA_{1c} for binary HbA_{1c} endpoints, baseline weight for weight endpoints and both baseline HbA_{1c} and baseline weight for the binary endpoints that combines both parameters).

Missing data for the above six binary endpoints will be accounted for using multiple imputation techniques. For the treatment policy estimand the binary endpoints will be calculated as dichotomisations of the 1000 multiple imputations underlying the primary MI analysis. For the hypothetical estimand the model will be implemented using a sequential imputation approach assuming MAR. The imputation will be done as described below:

- Intermittent missing values in the on-treatment without rescue observation period are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each treatment group separately and 1000 copies of the dataset will be generated.
- A sequential regression approach for imputing monotone missing values at planned visits will be implemented starting with the first visit after baseline and sequentially continuing to the planned end of treatment visit. For each treatment group an analysis of covariance model will be used to impute missing values at each planned visit. The model will include stratification factors as categorical effects and baseline and post-baseline values prior to the visit in question as covariate.

The binary endpoints will be derived as dichotomisations of the 1000 multiple imputations from the sequential imputation.
For both estimands, each of the 1000 datasets will be analysed using a logistic regression model with treatment, region, stratification factors and the interaction between stratification factors as fixed effects and baseline value as covariate (i.e. baseline HbA_{1c} for binary HbA_{1c} endpoints, baseline body weight for body weight endpoints and both baseline HbA_{1c} and baseline body weight for the composite binary endpoints that comprise both parameters). The results will be combined using Rubin's rule to draw inference.

Only observed data within the corresponding observation period will be included for the 'without hypoglycaemia' component of the composite endpoint. Because the number of hypoglycaemic episodes is expected to be very low in this trial, the observed data is considered sufficient when addressing both estimands.

Time to event endpoints

- Time to additional anti-diabetic medication (to support the treatment policy estimand)
- Time to rescue medication (to support the hypothetical estimand)

Definition of additional anti-diabetic medication: New anti-diabetic medication and/or intensification of anti-diabetic medication initiated at or after randomisation and before (planned) end-of-treatment.

Definition of rescue medication: New anti-diabetic medication and/or intensification of anti-diabetic medication initiated at or after randomisation and before last date on trial product. This is a subset of the additional anti-diabetic medication.

The following rules will be applied based on the concomitant medication data reported by the investigator, to determine whether or not the recorded anti-diabetic medication is new anti-diabetic medication or intensification of anti-diabetic medication.

1. ***New anti-diabetic medication***: Anti-diabetic medication (4th-level ATC code) that is initiated at or after randomisation and is new compared to the anti-diabetic background medication at randomisation (see above) and with a dosing duration of more than 21 days

2. ***Intensification of anti-diabetic medication***: A more than 20% increase in the dose of anti-diabetic medication at or after randomisation as compared to the anti-diabetic medication dose at randomisation (5th-level ATC code not changed) and with a dosing duration of more than 21 days.

More than 21 days are chosen as a minimum duration for the medication to be considered as 'anti-diabetic medication'. This threshold is set to ensure that short-term durations (i.e., ≤ 21 days) of anti-diabetic medication (e.g., in connection with concurrent illnesses) are not included because such intensifications are not likely to affect the effect endpoints.

As an initial 20% reduction of the total insulin dose is recommended at the randomisation visit for all subjects using insulin as background medication, the background dose is defined as the total insulin dose taken before the 20% reduction.

Treatment policy estimand: Time to additional anti-diabetic medication

The analysis supporting the treatment policy estimand is addressed for the FAS using the in-trial observation period and additional anti-diabetic medication will be considered an event regardless of whether or not subjects prematurely discontinued treatment. Time from randomisation to additional anti-diabetic medication will be analysed using a Cox proportional hazards model with treatment, region, stratification factors and the interaction between stratification factors as categorical fixed effects and the baseline HbA_{1c} value as a covariate. From this analysis the estimated hazard ratio between oral semaglutide and placebo together with associated two-sided 95% CIs and unadjusted two-sided p-values will be presented. The endpoint aims to address the need of additional anti-diabetic medication regardless of whether this is due to lack of effect or related to tolerability of the trial product. Switching to another anti-diabetic treatment is therefore also considered an event and withdrawn subjects or subject lost to follow-up will be considered as having an event (started on additional anti-diabetic medication) on the day of withdrawal. Subjects will be censored on the day before the planned end-of-treatment visit.

Hypothetical estimand: Time to rescue medication

The analysis supporting the hypothetical estimand is addressed for the FAS using the on-treatment without rescue medication observation period. Time from first dose of trial product to initiation of rescue medication will be analysed using the same model as described above. The endpoint aims to address a lack of effect of treatment with trial product. Only initiation of rescue medication as add-on to randomised treatment is considered an event; switching to another anti-diabetic treatment is not considered an event (initiation of rescue medication) and as a consequence subjects will be

censored on the day before date of last trial product. Potential events occurring between randomisation and first date on trial product will be included in the analysis as events on first date of trial product, in order to account for all events of rescue medication initiation.

2.10.2.2 Safety endpoints and safety assessments

The safety endpoints and safety assessments will be evaluated based on SAS using the on-treatment observation period and based on SAS using the in-trial observation period unless otherwise stated. The following endpoints and assessments are used to support the safety objectives.

Adverse events

- Number of treatment-emergent adverse events (TEAEs) during exposure to trial product, assessed up to approximately 31 weeks

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding.

A TEAE is defined as an AE with onset in the on-treatment observation period (see definition of observation periods in Section 2.6).

TEAEs will be summarised in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 patient years of observation time (R) for the on-treatment observation period. Supportive summaries of AEs will be made for the in-trial observation period. The development over time in gastrointestinal AEs will be presented graphically.

Other safety endpoints

Change from baseline to week 26 in:

- Amylase
- Lipase
- Pulse
- Systolic blood pressure
- Diastolic blood pressure

The above safety endpoints will be evaluated using the primary analysis for the primary estimand based on SAS using the in-trial observation period and using the primary analysis for the secondary estimand based on SAS using the on-treatment observation period. Results will be presented at week 26. Amylase and lipase endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

Change from baseline to week 26 in:

- Urinalysis
- Urinary albumin to creatinine ratio
- Electrocardiogram (ECG) evaluation
- Physical examination
- Eye examination category

Note that the urinary albumin to creatinine ratio is measured twice, so the mean will be used as endpoint.

Any occurrence of anti-semaglutide antibodies (yes/no) up to approximately 31 weeks:

- Anti-semaglutide binding antibodies
- Anti-semaglutide neutralising antibodies
- Anti-semaglutide binding antibodies cross reacting with native GLP-1
- Anti-semaglutide neutralising antibodies cross reacting with native GLP-1

Anti-semaglutide binding antibodies up to approximately 31 weeks:

- Anti-semaglutide binding antibody levels

Other safety assessments

- Haematology
- Biochemistry (except for amylase and lipase)
- Calcitonin

The above safety endpoints and assessments will be summarised descriptively by treatment arm and visit. Categorical safety endpoints and assessments will be summarised as counts and relative frequencies. Calcitonin will also be presented by gender.

Hypoglycaemia endpoints

- Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 31 weeks
- Treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 31 weeks (yes/no)

Classification of hypoglycaemia

Hypoglycaemic episodes will be summarised for the SAS and the on-treatment observation period only.

Treatment emergent: hypoglycaemic episodes will be defined as treatment-emergent if the onset of the episode occurs within the on-treatment observation period (see definition of observation periods in Section 17.2 in the Protocol).

Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05.59 both inclusive.

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia and the ADA classification of hypoglycaemia (see Figure 2-2).

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)[7]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose (PG) levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

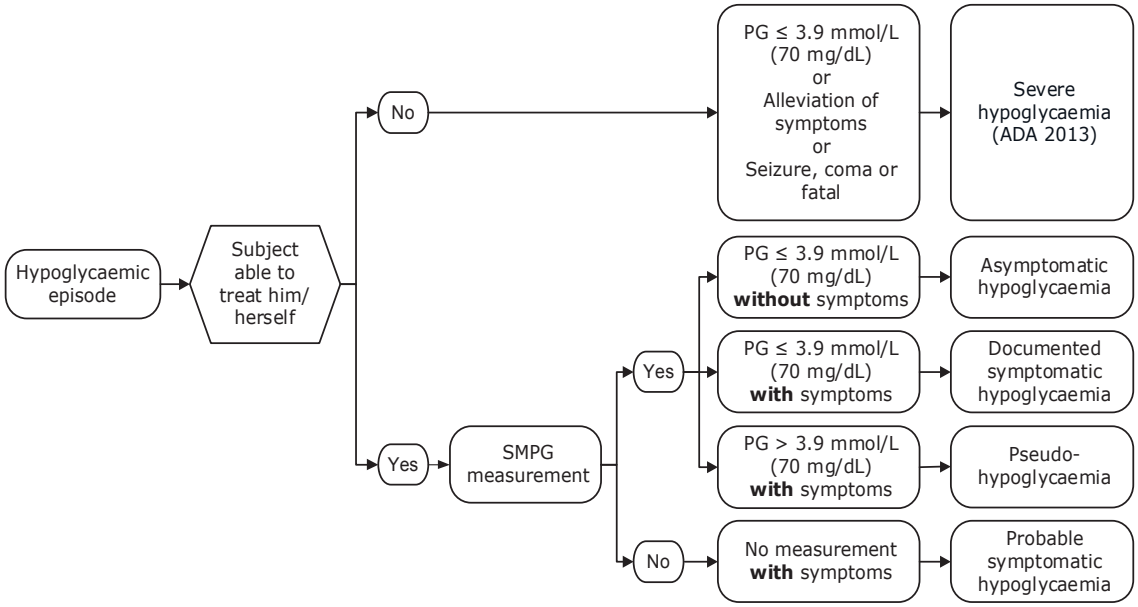
Novo Nordisk uses the following classification in addition to the ADA classification:

- Severe or BG-confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[8] or BG-confirmed by a plasma glucose value < 3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia.

ADA classification[8] of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured PG concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.

- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a PG determination but that was presumably caused by a PG concentration ≤ 3.9 mmol/L (70 mg/dL).



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 2-2 ADA classification of hypoglycaemia

Data on treatment-emergent hypoglycaemic episodes will be presented in terms of the number of subjects with at least one episode, the percentage of subjects with at least one episode (%), the total number of episodes and the episode rate per 100 patient years of observation time.

Analysis of severe or BG-confirmed symptomatic hypoglycaemic endpoints

The number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes will be evaluated for the on-treatment period using a negative binomial regression model with a log-link function and the logarithm of the duration of the subject's on-treatment observation period as offset. The model will include treatment, stratification factors and the interaction between the two stratification factors and region as fixed factors and baseline HbA_{1c} as covariate. The linear predictor of the model will be reduced if deemed necessary.

The binary endpoint showing whether a subject has at least one treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episode will be analysed using a logistic regression

model with treatment, stratification factors, the interaction between the two stratification factors and region as fixed factors and baseline HbA_{1c} as covariate. The linear predictor of the model will be reduced if deemed necessary.

2.10.2.3 Pharmacokinetic endpoints

- Semaglutide plasma concentrations for population PK analysis
- SNAC plasma concentrations

The semaglutide plasma concentrations and SNAC plasma concentrations collected in this trial will be evaluated using relevant summary statistics. In addition, the semaglutide plasma concentration will be part of a meta-analysis across the oral semaglutide phase 3a trials, see more details in section 2.12.

2.11 Interim Analysis

No interim analyses or other analyses of unblinded data will be performed before the database is locked.

2.12 Pharmacokinetic and/or pharmacodynamic modelling

Data from this trial will be evaluated using population pharmacokinetic analysis and exposure-response for semaglutide. The purpose of the population pharmacokinetic analysis will be:

- To describe the covariate factors (such as weight, age, gender, race and ethnicity) that influence semaglutide exposure
- To estimate a steady-state exposure level for each subject with pharmacokinetic data, in order to facilitate subsequent exposure-response analyses

The purpose of the exposure-response analyses will be to support the recommended dose, by investigating response and potentially side effects across the exposure range.

The population pharmacokinetic (PK) and exposure-response analyses will be conducted as a meta-analysis, including all relevant oral semaglutide phase 3a trials with PK assessments. A separate modelling analysis plan will be prepared before first database lock in the oral semaglutide phase 3a programme, outlining details of the analyses. The modelling will be performed by Quantitative Clinical Pharmacology at Novo Nordisk A/S and will be reported separately from the clinical trial report.

2.13 Patient reported outcomes

Change from baseline to week 26 in:

- SF-36v2™ ® (acute version) health survey: Scores from the 8 domains and summaries of the physical component score and the mental component score
- Diabetes Treatment Satisfaction Questionnaire – status version (DTSQs): Individual items and treatment satisfaction score (6 of the 8 items summed)

A more detailed description of the handling of the patient reported outcomes (PRO) questionnaires used in the trial is provided in the following sections.

No multiplicity adjustments will be done for the PRO questionnaires.

2.13.1 SF-36v2® (acute version) health survey

The SF-36v2® Health Survey (SF-36v2) (acute version) instrument is a commonly used generic instrument measuring health-related quality of life (HRQoL)/general health status across disease areas including diabetes. The SF-36v2 is a PRO questionnaire for adults with a 1-week recall period contains 36 items.

A total of 35 items measure eight domains of functional health and well-being as well as two component summary scores: physical functioning (10 items), role limitation due to physical health problems (4 items), bodily pain (2 items), general health perceptions (5 items), vitality (4 items), social functioning (2 items), role limitations due to emotional problems (3 items) and general mental health (5 items), mental component summary (MCS) score, physical component summary (PCS) score. There is an additional single item giving information on health change over the past week.

Domain scores
Norm-based scores (NBS) will be derived using the QualityMetric Health Outcomes™ Scoring Software1 including the 2009 US general population norm. The most recent version of the QualityMetric Health Outcomes™ Scoring Software available at time of licensing was used for the specific trial (version 4.5 for PIONEER 5). Table 2-3 provides an overview of the domains. NBS standardises domain and component scores into T-scores using the means and standard deviations from the US general population. Higher scores on all domains and component summary measures (PCS and MCS) indicate better HRQoL/general health status. Item 2 (i.e. Question 2 in CRF) is not included in any score.

Table 2-3 Overview of domains for SF-36v2® (acute version)

Domain	Items numbers of items included in domain	Comment
Physical Functioning (PF)	Items 3a-j	
Role Limitations Due to Physical Health (Role-Physical; RP)	Items 4a-d	

Domain	Items numbers of items included in domain	Comment
Bodily Pain (BP)	Items 7, 8	Both item scores reversed
General Health Perceptions (General Health; GH)	Items 1, 11a-d	Item scores 1, 11b and 11d reversed
Vitality (VT)	Items 9a, 9e, 9g, 9i	Item scores 9a and 9e reversed
Social Functioning (SF)	Items 6, 10	Item score 6 reversed
Role Limitations Due To Emotional Problems (Role-Emotional; RE)	Items 5a-c	
Mental Health (MH)	Items 9b, 9c, 9d, 9f, 9h	Item scores 9d and 9h reversed
Physical component summary (PCS)	NA	The PCS score is a weighted average of the 8 domain scores.
Mental component summary (MCS)	NA	The MCS score is also a weighted average of the 8 domain scores. Weights differ from PCS to MCS.

Missing data at instrument level will be handled using the Maximum Data Recovery method: The method applies a value to a domain item rendered missing if at least one of the items in that domain has valid data. A domain score is considered missing if all item values in the domain are missing. PCS and MCS are calculated when at least seven of the eight domains have valid data, either actual or estimated. However, to calculate PCS, the PF domain must be one of the seven domains having valid data. Also, to calculate MCS, the MH domain must be one of the seven domains having valid data.

The domains will be evaluated using the primary analysis for the treatment policy estimand for the CTR. The domains will be evaluated using the primary analysis for the hypothetical estimand in a report separate from the CTR.

Responder threshold values

The responder threshold values, in terms of T-score points for change from baseline are defined in Table 2-4[4].

Table 2-4 Responder thresholds for SF-36v2 (acute version)

Domain	Responder threshold
Physical Functioning (PF)	4.3
Role Limitations Due to Physical Health (Role-Physical; RP)	4.0
Bodily Pain (BP)	5.5
General Health Perceptions (General Health; GH)	7.0
Vitality (VT)	6.7
Social Functioning (SF)	6.2
Role Limitations Due To Emotional Problems (Role-Emotional; RE)	4.6
Mental Health (MH)	6.7
Physical component summary (PCS)	3.8
Mental component summary (MCS)	4.6

Responder analyses will be based on the responder threshold values and are described in Section 2.13.3.

2.13.2 Diabetes Treatment Satisfaction Questionnaire – status version (DTSQs)

The DTSQs questionnaire will be used to assess subject's treatment satisfaction. This questionnaire contains 8 items that measures the treatment satisfaction for subjects' diabetes treatment in terms of convenience, flexibility and general feelings regarding treatment (see Table 2-5).

Table 2-5 Overview of items in DTSQs questionnaire

Item No.	Item text	Response scale
1	How satisfied are you with your current treatment?	6 = very satisfied, 5, 4, 3, 2, 1, 0 = very dissatisfied
2	How often have you felt that your blood sugars have been unacceptably high recently?	6 = most of the time, 5, 4, 3, 2, 1, 0 = none of the time
3	How often have you felt that your blood sugars have been unacceptably low recently?	6 = most of the time, 5, 4, 3, 2, 1, 0 = none of the time
4	How convenient have you been finding your treatment to be recently?	6 = very convenient, 5, 4, 3, 2, 1, 0 = very inconvenient
5	How flexible have you been finding your treatment to be recently?	6 = very flexible, 5, 4, 3, 2, 1, 0 = very inflexible
6	How satisfied are you with your understanding of your diabetes?	6 = very satisfied, 5, 4, 3, 2, 1, 0 = very dissatisfied
7	Would you recommend this form of treatment to someone else with your kind of diabetes?	6 = Yes, I would definitely recommend the treatment, 5, 4, 3, 2, 1, 0 = No, I would definitely not recommend the treatment
8	How satisfied would you be to continue with your present form of treatment?	6 = very satisfied, 5, 4, 3, 2, 1, 0 = very dissatisfied

Item scores

The DTSQs items are scored on a 7-point graded response scale ranging from 6 to 0. Higher scores indicate higher levels of treatment satisfaction for DTSQs items 1, 4 -8. For items 2 and 3 a higher score indicates a higher patient perceived experience of hyperglycaemia and hypoglycaemia, respectively. Thus, lower scores indicate a perception of blood glucose levels being "none of the time" unacceptably high (item 2) or low (item 3). If data are missing for an item, the item score is treated as missing. No reversal of item scores will be done.

Treatment satisfaction score

The domain score of total treatment satisfaction (total treatment satisfaction score) is computed by adding the six items scores 1, 4-8. The score has a minimum of zero and a maximum of 36. A higher treatment satisfaction score indicates a higher level of treatment satisfaction. No reversals of items are necessary prior to computing the treatment satisfaction score.

Missing data at instrument level will be handled in the following way. For computing the total treatment satisfaction score consisting of six items, missing data from one item is allowed.

Scoring algorithm:

- Step 1: Sum the existing item scores (i.e. either 5 or 6 item scores)

- Step 2: Divide this sum by the number of existing item scores
- Step 3: Multiply by 6 (the number of items in the total treatment satisfaction scale)

Responder threshold values
Half of a standard deviation (SD) of the baseline DTSQs item and domain scores were used as distribution-based approach defining the responder thresholds. The thresholds are derived from baseline DTSQs data across trial arms. Responder analyses will be based on the responder threshold values and are described in section 2.13.3.

2.13.3 Responder analyses

Responder analyses will be reported in a report separate from the CTR for SF-36v2® and DTSQs. These additional analyses were not in scope during the development process of the protocols for the NN9924 phase 3a programme. Responder analyses will be conducted for both estimands, for the same time points that are defined for the analyses of PRO endpoints and separately for each domain.

For descriptive statistics the following subject responder categorisation is applied for all relevant time points and domains:

- Responder (improvement): Individual change from baseline in score ≥ positive responder threshold
- Non-responder (no change): Individual change from baseline in score > negative responder threshold value and < positive responder threshold value
- Non-responder (worsening): Individual change from baseline in score ≤ negative responder threshold value

The following binary subject responder definition is applied for all relevant time points and scores:

- Responder: Individual change from baseline in score ≥ positive responder threshold
- Non-responder: Individual change from baseline in score < positive responder threshold

The binary responder endpoints will be analysed as the other supportive secondary binary effect endpoints (Section 2.10.2.1). Estimated proportions and differences in proportions will be reported in addition to odds and odds ratios.

3 Changes to the statistical analyses planned in the protocol

The main analyses were described in the protocol for the trial NN9924-4234. However, clarifications, more detailed descriptions of endpoints and analyses are provided in this SAP. The changes from the protocol of NN9924-4234 are summarised below:

- Section 2.1: It has been specified which countries belong to which regions.
- Section 2.2: The primary and secondary estimand has changed name from de-facto and de-jure to treatment policy and hypothetical, respectively.
- Section 2.9.1: The set of fixed effects used in the pattern mixture multiple imputation model has been reduced to stratification factors only. The actual distribution over the full design of region, stratification factors and the interaction between the two stratification factors is too sparse to fit the imputation model.
- Section 2.9.2: For the MMRM analyses, it is specified that for subjects who do not have post-baseline assessments for planned visits available in the on-treatment without rescue medication period, the baseline value will be carried forward to the first planned visit, if the first planned visit do not fall later than 8 weeks after randomisation, to ensure that all randomised subjects will contribute to the statistical analyses.
- Section 2.9.3: The amount of sensitivity analyses has reduced for the trial. The tipping point analysis has been kept for both the primary and the secondary estimand as an approach for performing a sensitivity analysis under the missing not at random (MNAR) assumption. In other words, the tipping point approach is like a progressive stress-testing to assess how severe departures from missing at random (MAR) must be in order to overturn conclusions from the primary analysis. This sensitivity analysis is considered sufficient to stress-test the secondary estimand, thus the three MI sensitivity analyses of the secondary estimand have been omitted in section 2.9.3.2. In addition to the tipping point analysis, two sensitivity analyses for primary estimand has been kept, to get a better understanding of the primary results.
- The LOCF sensitivity analysis specified in the trial protocol (section 17.3.3.2) has been omitted. It is judged not to add additional value to the evaluation of the effect. This is because it seems unrealistic that data from a subject with missing data would have been stable from the point of dropout to trial completion.
- Section 2.10.2.1: The following binary endpoints will not be included in the analysis:
  - HbA_{1c} reduction $\geq$ 1%-point (10.9 mmol/mol)
  - Weight loss $\geq$ 3%

  autonomously but as components of the composite endpoint

– HbA_{1c} reduction ≥ 1%-point (10.9 mmol/mol) and weight loss ≥ 3% .

- Section 2.10.2.1: For the binary efficacy endpoints, it has been specified with more details how missing data in the analyses for the hypothetical estimand will be imputed using a sequential imputation approach assuming MAR.

- Section 2.10.2.1: It is specified that the CRP endpoints will be log-transformed prior to analysis.

- Section 2.10.2.1: A clarification of the 'without hypoglycaemia' component in composite binary endpoints has been added. The specification on how to analyse the binary component 'without hypoglycaemia' in the composite endpoint 'HbA_{1c} <7% (53 mmol/mol) without hypoglycaemia (severe or BG-confirmed symptomatic hypoglycaemia) and no weight gain' has not been described in the statistical section in the protocol. The specification is therefore included.

- Section 2.10.2.1: The definitions of rescue medication and additional antidiabetic medication used for the time-to-event endpoints were added along with discussion on additional antidiabetic medication. Furthermore, the accompanying statistical analyses have been further clarified.

- Section 2.10.2.2: It has been specified that all safety laboratory results (except amylase and lipase) are safety assessments and not safety endpoints as written in the trial protocol.

- Section 2.13: Additional details regarding the patient reported outcomes (SF-36v2 acute version and DTSQs) are provided.

- Section 2.13: The primary analysis for the primary estimand of SF-36v2(acute version) and for both estimands of DTSQs will be reported in the CTR. The primary analysis for the secondary estimand of SF-36v2 (acute version) will be presented in a report separate from and after finalisation of the CTR.

- Section 2.13.3: The responder analyses of both PROs (SF-36v2 (acute version) and DTSQs) will be presented in a report separate from and after finalisation of the CTR.

4 References

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16.1.9.1 Pre-defined MedDRA search – list of preferred terms

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