Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04707469
Sponsor trial ID:	NN9924-4635
Official title of study:	Efficacy and safety of once-daily oral semaglutide 25 mg and 50 mg compared with 14 mg in subjects with type 2 diabetes
Document date*	23 December 2022

*Document date refers to the date on which the document was most recently updated.

Statistical Analysis Plan

NN9924-4635

PIONEER PLUS

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

[redacted]

Biostatistics

Table of contents

Page

Table of figures

Page

Table of tables

Page

Version history

This Statistical Analysis Plan (SAP) for trial NN9924-4635 is based on the protocol version 7.0 dated 16SEP2022.

SAP Version	Date	Change	Rationale
1.0	03Oct2022	Not Applicable	Original version
2.0	04Oct2022	Minor corrections	
3.0	23Dec2022	Specification the how to handle region Australia and strata variable in the imputation models	To avoid potential estimation problems
		Clarification that in the week 68 analyses the treatment discontinuation/rescue medication during the 68 weeks period will used when defining imputation groups	Clarification
		Analysis that mimics a 2-stage randomisation design	Investigate potential effect if 25 mg or 50 mg is used as intensification.
		Added time to event analyses of rescue medication	To investigate the use of rescue medication
		Correction of typos in the section describing the hypoglycaemia analyses	Correction of typos

• Introduction

Objectives and endpoints

Primary and secondary objectives, and estimands

Primary objective	To confirm superiority of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on HbA_{1c} reduction in subjects with T2D on stable dose of 1-3 OADs.
Secondary objectives	To confirm superiority of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on body weight reduction in subjects with T2D on a stable dose of 1-3 OADs.
	To compare the efficacy of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on parameters related to glycaemic control in subjects with T2D on a stable dose of 1-3 OADs.
	To compare the efficacy of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on parameters related to weight-related outcomes in subjects with T2D on a stable dose of 1-3 OADs.
	To compare the safety and tolerability of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily in subjects with T2D on stable dose of 1-3 OADs.

Estimands

For the primary and the confirmatory secondary objective, estimands of primary interest and additional estimands are defined. The estimands are used to address the trial objectives in terms of two different aspects of the treatment effect of oral semaglutide 14, 25 and 50 mg. Three intercurrent events are considered: Premature trial treatment discontinuation (due to any reason), change in dose and initiation of additional anti-diabetic medication. Intercurrent events are events occurring after treatment initiation that affect the interpretation or the existence of the measurements associated with the questions of interest.

The estimands for the primary objective are introduced below and the attributes of the estimands are summarised in Table 1. Additional details are available in Section 0.

Similar estimands are applied to the objective related to superiority in change in body weight.

The primary estimand addresses the main question of interest: What is the efficacy of oral semaglutide 25 and 50 mg versus oral semaglutide 14 mg on change from baseline to week 52 in HbA1c in subjects with T2D on stable dose of 1-3 OADs regardless of premature trial treatment discontinuation, changes in dose and initiation of additional anti-diabetic medication.

For this estimand, the treatment policy strategy is applied for all intercurrent events (**Table 3**). Data collection will continue after an intercurrent event and the collected data will be included in analyses regardless of the occurrence of the event.

Results based on the primary estimand are expected to mirror the clinical practice scenario because the estimand considers both the efficacy and tolerability of oral semaglutide. In addition, a similar estimand is represented in the label for Rybelsus®.

The additional estimand addresses an additional question of interest: What is the efficacy of oral semaglutide 25 and 50 mg versus oral semaglutide 14 mg on change from baseline to week 52 in HbA1c in subjects with T2D on stable dose of 1-3 OADs regardless of change in dose of trial treatment and if all subjects had remained on trial treatment without use of rescue medication.

For this estimand, a hypothetical strategy is applied for two of the intercurrent events (premature trial treatment discontinuation and initiation of rescue medication). The treatment policy strategy is used to handle any changes in trial treatment dose level because this intercurrent event is part of the pre-specified treatment regimen.

The additional estimand is considered relevant because it quantifies the achievable treatment effect without potentially confounding effects of any rescue medication. Further, results obtained with the additional estimand allows for comparison with results from the oral semaglutide phase 3a programme (PIONEER), which applied a similar additional estimand.

Similar estimands are defined for the other efficacy objectives.

Table 1 Overview of estimands and their attributes

Objective	Estimand category	Attributes				
		Treatment condition	**Variable / endpoint**	**Population of interest**	**Intercurrent events and strategy**	**Population-level summary measure**
Primary objective: To confirm superiority of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on HbA_{1c} reduction in subjects with T2D on stable dose of 1-3 OADs	Primary	The effect of high doses of oral semaglutide with or without additional anti-diabetic medication versus the effect of oral semaglutide 14 mg with or without additional anti-diabetic medication, both as add-on to stable dose of 1-3 OADs	Change in HbA_{1c} from baseline to week 52	T2D subjects as defined by the protocol inclusion and exclusion criteria	**Treatment policy** strategy for: • Premature trial treatment discontinuation • Dose change • Initiation of additional anti-diabetic medication	Difference in means
	Additional*	The effect of high doses of oral semaglutide without rescue medication versus the effect of oral semaglutide 14 mg without rescue medication, both as add-on to stable dose of 1-3 OADs			**Hypothetical** strategy for: • Premature trial treatment discontinuation • Initiation of rescue medication **Treatment policy** strategy for: • Dose change	
Secondary objective: To confirm superiority of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on body weight reduction in subjects with T2D on stable dose of 1-3 OADs	Secondary	The effect of high doses of oral semaglutide with or without additional anti-diabetic medication versus the effect of oral semaglutide 14 mg with or without additional anti-diabetic medication, both as add-on to stable dose of 1-3 OADs	Change in body weight from baseline to week 52	T2D subjects as defined by the protocol inclusion and exclusion criteria	**Treatment policy** strategy for: • Premature trial treatment discontinuation • Dose change • Initiation of additional anti-diabetic medication	Difference in means
	Additional*	The effect of high doses of oral semaglutide without rescue medication versus the effect of oral semaglutide 14 mg without rescue medication, both as add-on to stable dose of 1-3 OADs			**Hypothetical** strategy for: • Premature trial treatment discontinuation • Initiation of rescue medication **Treatment policy** strategy for: • Dose change	

* Not related to the confirmatory hypotheses

Primary and secondary endpoints

Primary endpoint

Endpoint title	Timeframe	Unit
Change in glycated haemoglobin (HbA_{1c})	From baseline (week 0) to week 52	%-point

Secondary endpoints

Confirmatory secondary endpoints

Endpoint title	Timeframe	Unit
Change in body weight	From baseline (week 0) to week 52	kg

Supportive secondary endpoints

Endpoint title	Timeframe	Unit
Change in fasting plasma glucose (FPG)	From baseline (week 0) to week52	mmol/l
Achievement of HbA_{1c} <7% (Yes/No)	At week 52	Count of subjects
Achievement of HbA_{1c} ≤6.5% (Yes/No)	At week 52	Count of subjects
Relative change in body weight	From baseline (week 0) to week 52	Percentage (%)
Change in waist circumference	From baseline (week 0) to week 52	cm
Achievement of weight loss ≥5% (Yes/No)	At week 52	Count of subjects
Achievement of weight loss ≥10% (Yes/No)	At week 52	Count of subjects
Adverse events	From baseline (week 0) to follow-up visit (week 73)	Count of events

The endpoints specified at week 52 will also be analysed at week 68.

Trial design

This is a 68-week, randomised, active-controlled, double-blinded, three-armed, multi-centre, multinational clinical trial.

Eligible subjects will be randomised in a 1:1:1 manner to receive either:

- oral semaglutide 50 mg once daily
- oral semaglutide 25 mg once daily
- oral semaglutide 14 mg once daily

Randomisation will be stratified by baseline anti-diabetic medication: ± SU, ±SGLT2 inhibitor, ±terminated DPP-4 inhibitor. Consequently, randomisation will comprise 8 strata for combinations of SU, SGLT2 inhibitor, and terminated DPP-4 inhibitor. Metformin is not included in the stratification. A 30% cap on DPP-4 inhibitor users will be implemented to equalise the representation of baseline background anti-diabetic medication across the population.

The trial comprises a 2-week screening period to assess the subject's eligibility followed by a randomisation visit (V2) and a 68-week treatment period. The treatment period is divided into a dose escalation period of 8-16 weeks and a maintenance period of 52-60 weeks. After the end-of-treatment visit (V16), all subjects will enter a follow-up period of 5 weeks, ended by a follow-up visit (V17), which corresponds to the end of the trial. The planned total trial duration for the individual subject is approximately 75 weeks (including screening).

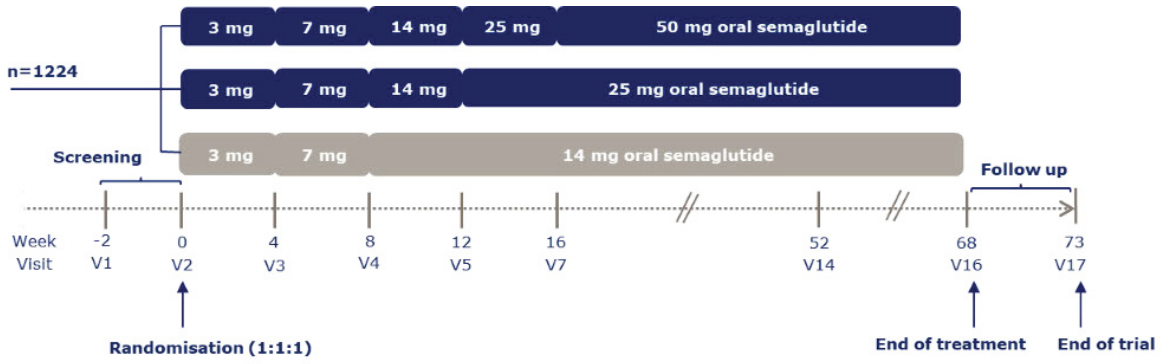

Figure 1 Trial design

• Statistical hypotheses

Four confirmatory hypotheses will be evaluated based on the primary and secondary estimand. For the primary endpoint, change in HbA1c from baseline to week 52, the following confirmatory one-sided hypothesis of superiority will be tested for both oral semaglutide 50 mg and 25 mg versus oral semaglutide 14 mg. Let the mean treatment difference (higher dose of oral semaglutide - oral semaglutide 14 mg) be defined as μ. The null (H_0) and alternative (H_A) hypotheses to be tested are:

H_0: $\mu \geq 0$ %-point against H_A: $\mu < 0$ %-point

For the confirmatory secondary endpoint, change in body weight from baseline to week 52, the following confirmatory one-sided hypothesis of superiority will be tested for both oral semaglutide 50 mg and 25 mg versus oral semaglutide 14 mg:

H_0: $\mu \geq 0$ kg against H_A: $\mu < 0$ kg

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

Multiplicity Adjustment

Adjustment for multiplicity associated with the testing of the four confirmatory hypotheses will be done using the weighted Bonferroni-based closed testing procedure described in Bretz et al.[1] and outlined in Figure 2. The type I error will be preserved in the strong sense at a nominal two-sided 5% level. The first hypothesis to be tested is superiority of oral semaglutide 50 mg vs 14 mg on change from baseline in HbA1c. It will be tested at the overall significance level (5%) while allocating 0% local significance level to the remaining of the hypotheses. For this hypothesis, and in general, if a hypothesis is confirmed, then the significance level will be reallocated according to the weight and the direction of the arrows going from the confirmed hypothesis to the next hypotheses as specified in Figure 2. Each of the four hypotheses will be tested at their updated local significance level (α-local). This process will be repeated until no further hypotheses can be confirmed.

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 is strictly below its local two-sided significance level as defined by the closed testing procedure. This is equivalent to using a one-sided p-value (nominal $\alpha = 0.025$) and a one-sided 2.5% overall significance level in the closed testing procedure.

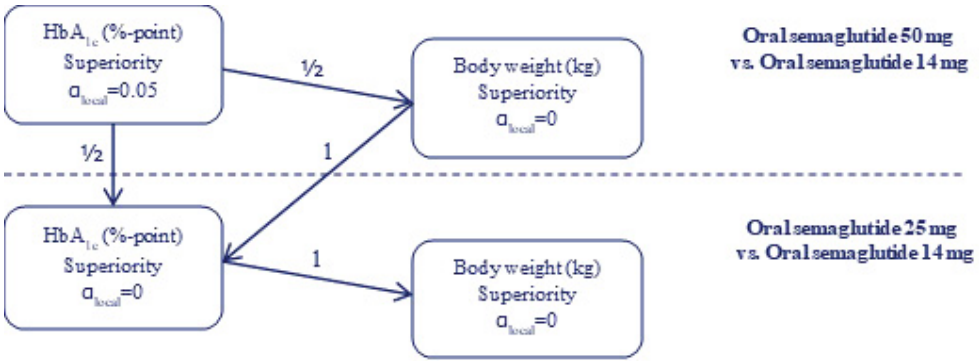

Figure 2 Graphical illustration of the closed testing procedure

The overall significance level of α = 0.05 (two-sided) is initially allocated to the hypothesis of superiority of oral semaglutide 50 mg vs 14 mg on change from baseline in HbA1c (top left box). If a hypothesis is confirmed, the local significance level (α-local) will be reallocated according to the weight given by the directed edges between boxes (hypotheses).

- # Sample size determination

Please refer to section 9.2 in the protocol.

• Analysis sets

The following populations are defined:

Table 2 Overview of defined populations

Population	Description
Full analysis set (FAS)	All subjects randomised. Subjects contribute to a treatment group based on the trial treatment they were randomised to receive.
Safety analysis set (SAS)	All subjects who receive at least 1 dose of trial treatment. Subjects contribute to a treatment group based on the trial treatment they actually received.

The FAS will be used in the evaluation of the efficacy endpoints, the SAS will be used for the evaluation of the safety endpoints, exclusively.

• Statistical analyses

General considerations

Data from all sites will be analysed and reported together.

In statistical analyses where stratification is accounted for, the background medication at screening 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 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.
Results from a statistical analysis will as a minimum be presented by the estimated treatment contrasts for each high dose vs. 14 mg oral semaglutide with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference.

Missing data

The amount of missing data when estimating the primary and secondary estimands (i.e. data that are not available even though all efforts were made to ensure that subjects stayed in the trial regardless of premature discontinuation of trial treatment or initiation of additional anti-diabetic treatment) is expected to be low. At week 52, the proportion of subjects with missing data was 5-7% across trials in the PIONEER programme. Missing data will be missing mainly be due to subjects withdrawing consent or being lost to follow-up. In the statistical analyses, missing data will be handled in line with the strategies applied for the pre-defined intercurrent events.

Data selections and observation periods

Unless subjects withdraw their informed consent, data collection will continue for the planned full duration of the trial for the individual subject. The full duration of the trial is defined as up to and including the follow-up visit (V17) for subjects completing trial treatment and subjects who have discontinued trial treatment prematurely.
As described in Section 0 the trial objectives relating to efficacy will be addressed using two different types of estimands. The primary and secondary estimands applying a treatment policy strategy to all intercurrent events and the additional supportive estimands applying a hypothetical strategy to the intercurrent events of premature trial treatment discontinuation and initiation of additional anti-diabetic medication. The handling of the intercurrent events with respect to data collection and analysis is specified in Table 3.

Table 3 Handling of intercurrent events for the estimands

Intercurrent event	**Primary and secondary estimands**	**Additional supportive estimands**
Premature trial treatment discontinuation	Data collected after the intercurrent event is used in analysis in line with a reatment-policy strategy, i.e. disregarding the occurrence of the intercurrent event	Data collected after the intercurrent event will be excluded and treated as missing in analysis, i.e. using a hypothetical strategy
Initiation of additional anti-diabetic medication		
Change of dose		Data collected after the intercurrent event and used in analysis in line with a treatment-policy strategy, i.e. disregarding the occurrence of the intercurrent event

Additional anti-diabetic medication is defined as new anti-diabetic medication and/or intensification of anti-diabetic medication initiated at or after randomisation and before planned end of treatment. Rescue medication is used to designate additional anti-diabetic medication initiated while on trial treatment, i.e. before last dose of trial product.

Observation periods will be used to select data for analyses in line with the strategies applied for the intercurrent events. Subjects and data to be used in an analysis will be selected in a two-step manner:

- First, subjects will be selected based on the specified analysis set.
- Second, data points on the selected subjects from the first step will be selected based on the specified observation period.

For the efficacy and safety evaluations, three different observation periods will be defined:

- The **in-trial** observation period – the time period from when a subject is randomised until the final scheduled visit, including any period after initiation of additional anti-diabetic medication or discontinuation of trial treatment.
- The **on-treatment** observation period – the time period when a subject is on trial treatment, including any period after initiation of rescue medication.
- The **on-treatment without rescue medication** observation period – the time period when a subject is on trial treatment, excluding any period after initiation of rescue medication.

The **in-trial** observation period begins at the date of randomisation and ends at the final scheduled visit, which can be one of the below:

- the follow-up visit (V17) for subjects who complete treatment and for subjects who discontinue trial treatment prematurely

- the last contact for subjects who withdraw from trial, are lost to follow-up or die

The **on-treatment** observation period begins at the date of first dose of trial treatment; the end date depends on the assessment being evaluated:

For all efficacy assessments and certain safety assessments (laboratory assessments, physical examination and vital signs), a plus-3-day window (i.e. the 3-day visit window) is used and the period ends at the first of the following time points:

- last dose of trial treatment plus a 3-day window
- end of the in-trial observation period

For the remaining safety assessments (eye examination categories, AEs, and hypoglycaemic episodes), a plus-38-day window (i.e. the 5-week follow-up period plus the 3-day visit window) is used and the period ends at the first of the following time points:

- the follow-up visit (V17)
- the last dose of trial treatment +38 days
- end of the in-trial observation period

The **on-treatment without rescue medication** observation period begins at the date of the first dose of trial treatment and ends at the first of the following time points:

- end of the on-treatment observation period
- initiation of rescue medication (if any)

For the efficacy endpoints, the primary and secondary estimands will be evaluated based on data from the in-trial observation period and the additional supportive estimands will be evaluated based on data from the on-treatment without rescue medication observation period thereby selecting data in line with the strategies applied for the intercurrent events as shown in Table 3. The safety evaluation will primarily be based on the on-treatment observation period, except for deaths and AE types with potentially long latency between onset and diagnosis, for which the in-trial observation period will be used. The observation period determines what data subjects contributes with to a specific analysis. Baseline values are by definition included in all observation periods; other data points collected outside the observation period used for an analysis will be considered missing.

Before data are locked for statistical analysis, a review of all data will take place. Exclusion of data from analyses should 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 before unblinding. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

Subject disposition

Subject disposition will be summarised by treatment arm using descriptive statistics.

Primary endpoint analysis

Definition of endpoint

The primary endpoint is the change in HbA1c (%-point) from baseline (week 0) to week 52.

Main analytical approach

Primary analysis for the primary estimand

The primary estimand defined in Table 3 will be estimated based on the FAS using week 52 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 week-52 data will be done within 6 groups of subjects defined by randomised treatment arm, and whether subjects at week 52 (i) are still on treatment and have not initiated rescue medication or (ii) have discontinued treatment or 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 52 are similar in terms of randomised treatment arm and trial treatment discontinuation/rescue medication status. For each imputation group, an analysis of covariance model (ANCOVA) with stratification factor and region as factors and baseline HbA_{1c} as covariate will be used to impute 1000 values for each subject with missing week 52 data. For the imputation groups where the subjects have discontinued treatment or initiated rescue medication the time (days) from randomisation until discontinuation or initiation of rescue medication will also be included as a covariate.

The 1000 complete data sets will be analysed using an ANCOVA with treatment, stratification factor and region as factors and baseline HbA_{1c} as covariate. The results obtained from analysing the datasets will be combined using Rubin's rule2 to draw inference.

The regions to be used in the statistical analyses are defined as Europe, North America, Australia and Asia. When addressing the treatment policy estimand, the imputation is to be done within groups defined by randomised treatment and treatment adherence at time of evaluation. Due to the low number of subjects in region Australia the region variable included in the imputation model will be reduced in levels avoiding estimation problems due to sparse data. The regions to be used in these imputations are defined as Europe, North America and Asia with Australia included in region Asia.

Similarly, if estimation issues are encountered due to low number of subjects in some of the strata levels, then the smallest group will be merged with the next smallest. This process will be continued until the estimation issue is no longer present.

Sensitivity analysis

In line with ICH E9 (R1), sensitivity analyses will be performed investigating the robustness of the conclusions made on the basis of the primary analyses towards the impact of missing data.

Tipping-point multiple imputation analysis: The assumption of MAR within groups used for imputation will be evaluated by a tipping point sensitivity analysis. Missing data will first be imputed as for the primary analysis. Secondly, for each of the 25 mg and 50 mg oral semaglutide treatment arms, a penalty will be added to the imputed week-52 values. The approach is to gradually increase this penalty until the confirmed HbA_{1c} conclusion from the primary analysis is changed. For each hypothesis tested, the specific value of the penalty that changes the conclusion will be used to evaluate the robustness of the primary analysis results.

Return to baseline multiple imputation analysis: subjects with missing data at week 52 will have their change from baseline value imputed as 0 plus a random error. The error is randomly drawn from a normal distribution with a mean of 0 and a variance equal to the residual variance estimated from the MMRM for observed values of change from baseline in HbA_{1c}, adjusted for the same covariates and factors as in the primary analysis. For missing values from patients who are still on treatment, it will be assumed that those data are missing at random and they will be imputed based on the observed data from the subjects who completed the trial on treatment in the same treatment arm.

Supplementary analyses

Analysis for the additional estimand

The additional estimand will be estimated based on the FAS using post-baseline measurements up to and including week 52 from the on-treatment without rescue medication observation period. The analysis for the additional estimand will be a Mixed Model for Repeated Measurements (MMRM).

A restricted maximum likelihood will be used. The model will include all post baseline HbA_{1c} measurements collected at scheduled visits up to and including week 52 as dependent variables. The independent effects included in the model will be treatment, stratification factor 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.

Secondary endpoints analysis

Confirmatory secondary endpoints

Definition of endpoints

The confirmatory secondary endpoint is the change in body weight (kg) from baseline (week 0) to week 52.

Main analytical approach

The secondary estimand will be estimated in the same way as for the primary endpoint with baseline HbA_{1c} replaced by baseline body weight as the covariate.

Sensitivity analysis

A tipping-point multiple imputation analysis similar to the one performed for the primary endpoint will be performed.

Supplementary analyses

Analysis for the additional estimand

The additional estimand will be estimated in the same way as for the primary endpoint with baseline HbA_{1c} replaced by baseline body weight as the covariate.

Supportive secondary endpoints

.1.1.1 Efficacy endpoints

The below supportive secondary efficacy endpoints will be evaluated for

- similar to the primary estimand based on FAS using the in-trial observation period
- similar to the additional estimand based on FAS using the on-treatment without rescue medication observation period

No sensitivity analyses are planned for these.

Continuous efficacy endpoints

Change from baseline to week 68 in:

- HbA_{1c}
- Body weight (kg)

Change from baseline to week 52 and 68 in:

- Body weight (%)
- FPG
- BMI
- Waist circumference
- Fasting lipid profiles (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)

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 (for both primary estimand and additional estimand).

Fasting lipid profile endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

For the analyses for estimand similar to the primary estimand at week 68 the imputation groups will be defined by randomised treatment and whether the subject had discontinued randomised treatment or initiated rescue at week 68.

Additionally an analysis of Body weight (%) after 68 weeks will analysed separately using similar model approaches as for the primary endpoint with the associated baseline response as a covariate only including subjects with a baseline BMI>=27.

To investigate the potential effect of intensification with 25 mg or 50 mg for subjects in need of intensification an analysis that mimics 2-stage randomisation design will be performed for HbA1c and body weight.

The analysis of HbA1c will only include subjects who at week 12 are still on treatment and have not reached the glycaemic target of HbA1c < 7. The change from week 12 to week 52 will be analysed using similar model approaches as for the primary analysis. Week 12 HbA1c will be included in the model as a covariate instead of baseline HbA1c.

The analysis of body weight will be similar but only include subject who are still on treatment and have not reached a body weight loss of at least 5% at week 12 and include week 12 body weight as a covariate instead of HbA1c.

Binary efficacy endpoints

Subjects who after 52 weeks of treatment achieve (yes/no):

- HbA_{1c} < 7.0 % (53 mmol/mol) (ADA) target*
- HbA_{1c} ≤ 6.5 % (48 mmol/mol) (AACE) target
- Weight loss ≥ 5 %
- Weight loss ≥ 10 %

The above four endpoints will be evaluated after week 68 as well.

Missing data

Missing data for the above binary endpoints will be accounted for using multiple imputation techniques. For the estimand similar to the primary estimand the binary endpoints will be calculated as dichotomisations of the 1000 multiple imputations underlying the MI analysis of the corresponding continuous endpoint. For the additional 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 will be 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 a 1000 copies of the data set 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 strata and

region as categorical effect and baseline and post-baseline values prior to the visit in question as covariates.

The binary endpoints will be derived as dichotomisations of the 1000 multiple imputations from the sequential imputation.

For both estimands, each of the 1000 data sets will be analysed using a logistic regression model with treatment, strata and region 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 HbA_{1c} and baseline body weight for the composite endpoints that comprises both parameters). The results will be combined using Rubin's rule to draw inference.

Time to event endpoint

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 1. *New anti-diabetic medication* or 2. *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 is chosen as a minimum duration for the medication to be considered as 'anti-diabetic medication'. This threshold is set to ensure that the 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.

Time to rescue medication

The analysis aims to address lack of effect and only initiation of rescue medication as add-on to randomised treatment is considered an event. Switch to other anti-diabetic treatment is not considered an event 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 at day 0, in order to count all events of rescue medication. The analysis using FAS and the on-treatment observation period. Time from first dose of trial product to initiation of rescue medication will be analysed using a Cox proportional hazards model with treatment, stratification factor and region as categorical fixed effects and baseline HbA_{1c} as a covariate.

Exploratory endpoints analysis

Not applicable for this trial.

Safety analyses

Adverse events

Number of adverse events (AEs) during exposure to trial product, assessed up to approximately 73 weeks.

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

AEs 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.

The development over time in gastrointestinal AEs will be presented graphically.

Hypoglycaemia

Classification of hypoglycaemia		
Level	**Glycaemic criteria**	**Description**

Classification of hypoglycaemia		
Hypoglycaemia alert value (level 1)	≤ 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (level 2)	< 3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (level 3)	No specific glucose threshold	[1]Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery

Severe hypoglycaemia

[1]Severe hypoglycaemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Nocturnal hypoglycaemia

Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.

Analysis of Severe (level 3) or clinical significant hypoglycaemia (level 2) hypoglycaemic endpoints

The number of Severe (level 3) or clinical significant hypoglycaemia (level 2) hypoglycaemic episodes in the on-treatment observation period will be analysed 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 factors for treatment, stratification factor and region as fixed factors and baseline HbA_{1c} as covariate.

The binary endpoint showing whether a subject has at least one Severe (level 3) or clinical significant hypoglycaemia (level 2) hypoglycaemic episode in the on-treatment observation period

will be analysed using a logistic regression model with treatment, stratification factor and region as fixed factors and baseline HbA_{1c} as covariate.

Other safety endpoints

Change from baseline to week 52 and 68 in:

- 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 additional estimand based on SAS using the on-treatment observation period. Endpoints will be analysed separately as described above for continuous efficacy endpoints. Results will be presented at week 52 and 68.

Safety endpoints not mentioned above and assessments will be summarised descriptively by treatment arm and visit. Categorical safety endpoints will be summarised as counts and relative frequencies.

Interim analyses

A partial database lock will be performed at the end of the treatment period for all subjects, i.e., after the date of the last subject last treatment visit. A partial database lock is implemented to support potential earlier access of oral semaglutide 25 and 50 mg to the patient population expected to benefit from higher doses.

All efficacy analyses will be performed based on the data from the partial database lock. No efficacy assessments are collected after last subject last treatment, and so unblinding of Novo Nordisk staff will be after all subjects have completed treatment. Therefore, efficacy results cannot be biased by the early unblinding. Impact on PK and safety evaluation after partial database lock is considered minor as most subjects will have completed the follow-up visit, and subjects and investigators remain blinded. Full analysis of PK and safety will be performed after the full database lock.

A detailed plan for data handling, blinding, data analysis, and operational aspects of the partial database lock and the database update will be finalised before the partial database lock.

The result of the evaluation at partial database lock will not be shared with investigators or subjects before the full database lock, and only a minimum number of Novo Nordisk staff will know the randomisation code at subject level. There will be no change in study design regardless of the outcome of the evaluation at partial database lock.

The database will be updated after the partial database lock to include the remaining data. The full database lock will be performed, as per the usual procedures, after the date of the last subject last visit.

The early DBL will not impact the analyses as the analyses described in this SAP will not be modified after the early DBL and the results reported in the CSR will be based on all collected data.

• Supporting documentation

Appendix 1 List of abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
BMI	Body mass index
CSR	Clinical Study Report
DBL	Database Lock
FAS	Full Analysis Set
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed Model for Repeated Measurements
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set

• References

1. Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. Biometrical Journal. 2011;53(6):894-913.
2. Little RJA, Rubin DB. Statistical analysis with missing data. New York: Wiley. 1987. xiv, 278 p. p.