

Cover Page for Statistical analysis plan

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16.1.9 Documentation of statistical methods

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Statistical analysis plan [Link](#)

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Statistical Analysis Plan

Trial ID: NN9924-4221

PIONEER 6 – Cardiovascular outcomes

**A trial investigating the cardiovascular safety of oral
semaglutide in subjects with type 2 diabetes**

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List of abbreviations

AE	adverse event
BMI	body mass index
CI	confidence interval
CKD-Epi	Chronic Kidney Disease Epidemiology Collaboration
CTR	clinical trial report
eCRF	electronic case report form
DMC	data monitoring committee
EAC	event adjudication committee
eGFR	glomerular filtration rate, estimated
FAS	full analysis set
HbA _{1c}	glycosylated haemoglobin
HR	hazard ratio
ITT	intention-to-treat
IV/WRS	interactive voice/web response system
LLoQ	lower limit of quantification
LSLV	last subject last visit
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
PYO	patient years of observation time
SAP	statistical analysis plan
s.c.	subcutaneous(ly)

1 Introduction

1.1 Trial information

This trial is a randomised, double-blind, placebo-controlled trial to assess the cardiovascular safety of oral semaglutide versus placebo when added to standard of care in subjects with type 2 diabetes at high risk of cardiovascular events.

Primary objective

The primary objective is to confirm that treatment with oral semaglutide does not result in an unacceptable increase in cardiovascular risk compared to placebo (rule out 80% excess risk) in subjects with type 2 diabetes at high risk of cardiovascular events.

Secondary objectives

The secondary objectives are to compare the efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes at high risk of cardiovascular events.

Trial design

Subjects will be randomised 1:1 to receive either oral semaglutide or placebo. The randomisation will be stratified according to evidence of cardiovascular disease at screening (presence of cardiovascular disease or presence of cardiovascular risk factors only). The stratum ‘presence of cardiovascular disease’ consists of subjects at least 50 years of age and recognised as fulfilling **at least one** item of inclusion criterion no. **3a-h** at screening, whereas the stratum ‘presence of cardiovascular risk factors only’ consists of subjects at least 60 years of age and recognised as fulfilling **at least one** item of inclusion criterion no. **3i-l** and **not** fulfilling **any** of the items of inclusion criterion no. **3a-h** at screening (see protocol, section 6.2).

The trial will be event-driven and will be continued until at least 122 first major adverse cardiovascular events (MACE) confirmed by the external event adjudication committee (EAC) have accrued. Throughout the remainder of this statistical analysis plan (SAP), MACEs will be defined as MACEs confirmed by adjudication. Adverse events with fatal outcome where the EAC have adjudicated the cause of death as undetermined cause of death will also be counted as a cardiovascular death.

The recruitment period is expected to last 7 months. The treatment period for each subject is expected to be between 12 and 19 months, depending on the time-point of recruitment and the accrual of first MACEs. The follow-up period is 5 weeks to allow for wash-out of trial product.

1.2 Scope of the statistical analysis plan

This SAP is based on the protocol for trial NN9924-4221, version 5.0 (03 November 2016), and includes more detailed procedures for executing the statistical analyses of the primary and

secondary endpoints. Statistical analyses (additional to those specified in the trial protocol) and a number of changes and clarifications are pre-specified within this SAP. All changes to the statistical analyses planned in the trial protocol are documented in section [3](#).

2 Statistical considerations

General considerations

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

The blinding of the randomised treatments will be maintained until the database has been released for statistical analysis. No interim analyses or other analyses of unblinded or between group data will be performed before the database is locked, with the exception of those highly confidential analyses performed by an external independent statistician to support the deliberations of the data monitoring committee (DMC) or in direct response to a recommendation by the DMC.

Data from all sites will be analysed and reported together.

In statistical analyses where stratification is included, the evidence of cardiovascular disease at screening (presence of cardiovascular disease or presence of cardiovascular risk factors only) will be included based on the actual information collected through the electronic case report form (eCRF). In case of missing eCRF information the information collected in the interactive voice/web response system (IV/WRS) 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.

Laboratory values below the lower limit of quantification (LLoQ) will be set to $\frac{1}{2}$ LLoQ. The number of values below the LLoQ will be summarised by treatment group and visit if deemed relevant.

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

Estimand

The trial aims to confirm that treatment with oral semaglutide does not result in an unacceptable increase (80% excess risk) in cardiovascular risk compared to placebo in subjects with type 2 diabetes at high risk of cardiovascular events. Time from randomisation to first MACE will be the primary endpoint and treatment arms will be compared using the hazard ratio. This is an event-driven trial and information is planned to be collected on all randomised subjects until at least 122 first MACEs have accumulated during the planned trial duration of 19 months.

Estimand – ‘Treatment policy’:

- Treatment policy estimand comparing oral semaglutide and placebo for all randomised subjects. Subjects who discontinue treatment with trial product should be followed according to the

planned visit schedule. Evaluation of the primary estimand will include all first MACEs collected during the trial as defined by the in-trial observation period (see section [2.2](#)) regardless of adherence to randomised treatment.

2.1 Sample size calculation

Firstly, the primary endpoint, time from randomisation to first occurrence of a MACE composite endpoint consisting of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke will be tested for non-inferiority using a 1.8 non-inferiority margin.

Secondly, if non-inferiority is confirmed, the endpoint will be tested for superiority. The type-I-error will be preserved in the strong sense at 5% (two-sided) when using the hierarchical testing strategy.

The sample size is made to ensure a power of 90% for testing the confirmatory hypothesis for the primary endpoint with respect to non-inferiority. Based on a logrank test, a total of 122 first MACEs will provide 90% power to rule out a hazard ratio exceeding 1.8, assuming a true hazard ratio of 1.0.

In order to have a total of 122 first MACEs with trial duration of 19 months and 1,588 subjects randomised to each treatment group (1:1 randomisation), in total 3,176 subjects, the following is assumed based on the trials EX2211-3748 (LEADER[®]) and NN9535-3744 (SUSTAIN 6):

- First MACEs occur at a rate of 3 per 100 patient years of observation time (PYO) in both treatment groups throughout the trial
- Recruitment into the trial occurs uniformly during 7 months
- The lost to follow-up rate is 1% per year throughout the trial
- Last subject last visit (LSLV) occurs 19 months after first subject was randomised

[Table 2–1](#) shows expected trial duration for different event rates under the same assumptions as described above for the other parameters.

[Table 2–2](#) shows the power of the superiority test for different true hazard ratios of oral semaglutide vs. placebo, and for different expected number of accrued first MACEs. Furthermore, the power calculations are based on the actual recruitment time of 225 days, anticipated total trial duration of 619 days and a lost-to-follow-up rate of 1% per year throughout the trial. The first MACE rate is set to 3.3 per 100 PYO.

Table 2–1 Expected trial duration according to event rates

Event rate per 100 PYO in both treatment arms	2.5	2.75	3.0	3.25	3.5
Expected trial duration from randomisation of subject to LSLV (months)	22.2	20.4	19	17.8	16.7

Table 2–2 Calculated powers for the superiority test

True hazard ratio of oral semaglutide vs. placebo	0.75	0.8	0.85	0.90
Power (%), 122 events	36	24	15	9
Power (%), 130 events	38	25	15	9
Power (%), 140 events	40	27	16	9

2.2 Definition of analysis sets

The following analysis set is defined:

- Full analysis set (FAS): includes all randomised subjects. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation “as randomised”.

In this trial, two observation periods will be defined:

- **In-trial observation period:** This observation period will include information assessed from randomisation to the date of the follow-up visit regardless of adherence to randomised treatment. For subjects withdrawn or lost to follow-up the end date will be the date of last contact with the subject (site visit or by telephone). If a subject dies during trial, the end date will be the date of death. If a subject dies after the follow-up visit and the death is linked by adjudication to a MACE occurring during the trial, the end date will be the date of death.
- **On-treatment observation period:** This observation period is a subset of the in-trial observation period and will include information assessed on or after the first date of trial product up to and including the first date of (i) last date on trial product +38 days or (ii) 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. In addition, the ascertainment window includes the follow-up visit window of +3 days after last date on trial product.

Subjects not having a MACE within the observation period will be censored at the end of the observation period in the analysis of the primary endpoint assuming independent censoring for subjects withdrawn or lost to follow-up. Hence, a subject censored at a given time should be representative of those still at risk at that time point. For events confirmed by the EAC, the onset date used will be the onset date given by the EAC. EAC confirmed events with EAC given onset date either before randomisation or after the in-trial observation period will be presented in listings in the clinical trial report (CTR). For events not subjected to adjudication or not confirmed by the EAC, the onset date for the adverse event (AE) reported by the investigator will be used.

2.3 Trial completers, treatment completers, and lost to follow-up

Trial completers are defined as subjects who either attend the follow-up visit (visit P18) or who die while considered an active trial participant.

Treatment completers are defined as exposed subjects who are still on trial product at the end of treatment visit and hence, have not discontinued treatment permanently earlier in the trial. Subjects who die while on trial product are also considered treatment completers.

A subject is considered lost to follow-up for visit P18 if the subject does not complete the trial and does not withdraw consent.

Subjects who do not complete the trial and for whom a vital status cannot be determined before database lock are considered lost to follow-up for vital status.

2.4 Primary endpoint

The primary endpoint of the trial is:

- Time from randomisation to first occurrence of a MACE composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

The analysis of the primary endpoint will be carried out for the treatment policy estimand using data from subjects in the FAS and in-trial observation period. The statistical analysis of the primary endpoint will be a stratified Cox proportional hazards model with treatment group (oral semaglutide, placebo) as fixed factor. The model will be stratified by evidence of cardiovascular disease at screening (presence of cardiovascular disease or presence of cardiovascular risk factors only). From this model the estimated hazard ratio (HR) (oral semaglutide/placebo) together with the 2-sided 95% confidence interval (CI) will be presented. Non-inferiority of oral semaglutide versus placebo will be considered confirmed if the upper limit of the two-sided 95% confidence interval for the HR is strictly below 1.8 or equivalently if the p-value for the one-sided Wald test of

$$H_0: HR \geq 1.8 \text{ against } H_A: HR < 1.8$$

is strictly less than 2.5% (or equivalent to 5% for a two-sided Wald test).

A cumulative incidence function plot that accounts for the competing risk of non-cardiovascular death will be presented with number of subjects at risk at specific time points. The validity of the assumption of proportional hazards will be assessed graphically by the use of Schoenfeld residuals.

If the analysis of the primary endpoint confirms non-inferiority of oral semaglutide vs. placebo, it will be tested if oral semaglutide is also superior to placebo. Operationally the above analysis of the primary endpoint will be repeated and superiority of oral semaglutide vs. placebo is confirmed if the upper limit of the two-sided 95% confidence interval for the HR is strictly below 1.0.

2.4.1 Sensitivity analyses

To explore the robustness of the analysis of the primary endpoint the following sensitivity analyses will be performed. One sensitivity analysis will include additional covariates, whereas two other sensitivity analyses will be based on a different estimand evaluating the effect while subjects are on trial product, that is, prior to any permanent discontinuation of trial product. The two latter, will focus on events occurring during the on-treatment observation period and the on-treatment observation period using a more narrow period (+ 7 days) after the last of trial product, respectively. All three sensitivity analyses will be based on FAS and analysed using the same model as the analysis of the primary endpoint including the censoring rules and the assumption of independent censoring for subjects with shorter observation period than the trial duration.

Sensitivity analysis 1: Including additional covariates

This sensitivity analysis will explore the analysis of the primary endpoint by fitting a stratified Cox regression analysis and estimating the treatment hazard ratio (oral semaglutide/placebo) with a two-sided 95% CI while including the additional covariates sex, region, baseline age, diabetes duration, smoking history, and eGFR at baseline. The model will be stratified by evidence of cardiovascular disease at screening (presence of cardiovascular disease or presence of cardiovascular risk factors only). The analysis will be based on the FAS and the in-trial observation period.

Age, duration of diabetes, and renal function (eGFR as per CKD-Epi) at baseline will be included as continuous variables. The other covariates will contain the following levels:

- Sex: Female; male
- Region: Africa (Algeria and South Africa); Asia (India, Malaysia, Taiwan, and Thailand); Europe (Denmark, Germany, Israel, Italy, The Netherlands, Poland, Romania, Spain, Turkey, and the United Kingdom); North America (Canada and the United States); and South America (Argentina, Brazil, and Mexico)
- Smoking history: Current smoker; Never smoked; Previous smoker

Sensitivity analysis 2: Ascertainment window of 38 days after last date on trial product

This sensitivity analysis will include all first MACEs that are collected in the on-treatment observation period.

Sensitivity analysis 3: Ascertainment window of 7 days after last date on trial product

This sensitivity analysis will include all first MACEs that are collected on or after the first date on trial product up to and including the last date on trial product +7 days.

Sensitivity analysis 4: Tipping point analysis

If superiority is established for the primary endpoint, the following sensitivity analysis is performed. The primary analysis assumes independent censoring for patients who are lost to follow-up or who withdrew consent. To investigate the impact of this assumption on the superiority results of the primary analysis, a tipping point analysis will be made. In this analysis, subjects in the oral semaglutide treatment group will have their event times imputed with an increasing penalty in the sense that their risk of MACE is increased (the penalty) following censoring compared to while under observation. The placebo subjects will be imputed with no penalty, i.e. assuming same event before and after censoring. One thousand (1000) imputed data sets will be analysed for each penalty using the above Cox model and results will be combined using Rubin's rule. The tipping point is then defined as the penalty needed to turn around the superiority conclusion.

Sensitivity analysis 5: Including out-of-trial events

If superiority is established for the primary endpoint, two sensitivity analyses including out-of-trial observations will be performed. The analyses will include MACEs collected in the in-trial observation period and

- 1) reported EAC-confirmed deaths with EAC date of death after the in-trial period and before date of planned follow-up visit for subjects who withdrew consent or were lost to follow-up
- 2) reported MACEs with onset after the in-trial period and before global last patient last visit.

2.4.2 Exploratory subgroup analyses of the primary endpoint

The consistency in the treatment effect for the primary endpoint will be explored separately by the below defined subgroups based on baseline information:

- Sex: Female; male
- Age: < 65 years; ≥ 65 years
- Region: North America (Unites States and Canada); rest of the world
- Race: White; Black or African American; Asian; Other
- Body mass index (BMI): ≤ 30 kg/m²; > 30 kg/m²

- HbA_{1c}: $\leq 8.5\%$; $> 8.5\%$
- Myocardial infarction or stroke prior to randomisation: Yes; no
- Renal function (eGFR) as per CKD-Epi: $< 60 \text{ mL/min/1.73 m}^2$; $\geq 60 \text{ mL/min/1.73 m}^2$
- Evidence of cardiovascular disease at screening: Presence of cardiovascular disease; presence of cardiovascular risk factors only

The subgroup analyses will be based on the FAS using the in-trial observation period. For each subgroup analysis, the primary endpoint will be analysed using a stratified Cox proportional hazards model with an interaction between treatment group (oral semaglutide, placebo) and the relevant subgroup as fixed factor. The model will be stratified by evidence of cardiovascular disease at screening (presence of cardiovascular disease or presence of cardiovascular risk factors only). From this model, the estimated hazard ratio for (oral semaglutide/placebo) together with corresponding 2-sided 95% CI for each subgroup level will be presented. A forest plot showing the estimated hazard ratio and 95% CI by each subgroup level will be presented to explore the consistency of the primary analysis results across subgroup levels together with a p-value for an interaction effect. Merging of subgroup levels may be necessary if the amount of data is otherwise too small to perform the subgroup analysis. In this case, the subgroup levels will be merged by combining the two levels with the smallest number of subjects until each level has a sufficient number of events.

2.5 Secondary endpoints

2.5.1 Safety endpoints

Time to event endpoints

- Time from randomisation to first occurrence of an expanded composite cardiovascular endpoint consisting of: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina requiring hospitalisation or hospitalisation for heart failure
- Time from randomisation to first occurrence of each of the individual components in the expanded composite cardiovascular endpoint
- Time from randomisation to first occurrence of a composite endpoint consisting of: all-cause death, non-fatal myocardial infarction or non-fatal stroke
- Time from randomisation to all-cause death
- Time to first AE leading to permanent trial product discontinuation

The analyses of the above time-to-event endpoints will be the same as the primary analysis. The analyses will be based on the FAS and performed for both the in-trial and on-treatment observation periods, except for time to first AE leading to permanent trial product discontinuation which will only be based on the period from date of first dose on trial product to end of treatment visit. For subjects who are withdrawn or lost to follow up, the period will end at date of withdrawal. The cumulative incidence over time will be presented graphically based on the cumulative incidence

function accounting for competing risks. When competing risks are not present the cumulative incidence function reduces to a Kaplan-Meier based estimate.

Analysis of time from randomisation to first occurrence of fatal or non-fatal myocardial infarction, and to first occurrence of fatal or non-fatal stroke will also be performed in a similar manner as defined above.

Adverse events

- Number of serious AEs

All AEs will be coded using version 20.1 of the Medical Dictionary for Regulatory Activities (MedDRA).

Serious 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). The summaries will be based on FAS and performed for both the in-trial and the on-treatment observation periods. Furthermore, events confirmed by adjudication and AEs leading to discontinuation of trial product will be summarised as above.

Continuous safety endpoints

Change from baseline to last assessment of:

- Pulse
- Systolic and diastolic blood pressure

Change from baseline will be summarised using descriptive statistics by treatment group for all scheduled visits and for last available assessment based on FAS and performed for both the in-trial and the on-treatment observation periods.

Other safety endpoints

- Eye examination category

This endpoint will be summarised using counts and relative frequencies.

Other continuous safety assessments

- Biochemistry
- Haematology
- Calcitonin

The above assessments will be summarised using descriptive statistics by treatment group for all scheduled visits and for last available assessment based on FAS and performed for both the in-trial and the on-treatment observation periods. Calcitonin will also be presented by sex.

2.5.2 Efficacy endpoints

Change from baseline to last assessment of:

- HbA_{1c}
- Body weight
- Lipids

Change from baseline will be summarised using descriptive statistics by treatment group for all scheduled visits and for last available assessment based on FAS and performed for both the in-trial and the on-treatment observation periods.

2.6 Adverse events and adjudication

The PIONEER 6 trial employs selective safety data reporting (see protocol, section 12.2). Adverse events reported that can not be considered systematically collected as per protocol will not be included in the CTR. However, all events sent for adjudication, whether systematically collected or not, will be presented in listings in the CTR.

Fatal myocardial infarction and stroke are defined as EAC confirmed events of myocardial infarction or stroke where the EAC has related a death to the event. Other EAC confirmed events of myocardial infarction and stroke are defined as non-fatal.

The adjudication process will continue until database lock. Events occurring after the in-trial observation period will be presented in listings in the CTR.

3 Changes to the statistical analyses planned in the protocol

The main analyses were described in the protocol for trial NN9924-4221. However, clarifications as well as more detailed descriptions of endpoints and analyses are provided in this SAP. The changes from protocol NN9924-4221 are summarised below:

- Based on the findings in SUSTAIN 6, where subcutaneous (s.c.) administration of semaglutide showed a significant hazard ratio of s.c. semaglutide vs. placebo in the analysis of the same primary endpoint as in this trial, it has been decided to add a superiority test in the testing hierarchy in PIONEER 6. Hence, if non-inferiority of oral semaglutide vs. placebo is confirmed, a test for superiority will also be conducted. Consequently, the secondary confirmatory endpoint time from randomisation to first occurrence of an expanded composite cardiovascular endpoint is now a secondary endpoint, and no sensitivity analyses will be carried out for this endpoint.
- The consistency in the treatment effect for the primary endpoint will also be explored separately in a number of subgroups.
- Definitions of trial completers and treatment completers have been added. In addition, two types of lost to follow-up are specified: Lost to follow-up (subjects who do not complete the trial and do not withdraw consent), and lost to follow-up for vital status (subjects who do not complete the trial and where vital status is not determined at database lock).
- The levels of the covariates in sensitivity analysis 1 have been specified.
- The primary estimand has changed name from de-facto to treatment policy.
- Where relevant, Kaplan-Meier plots have been replaced with cumulative incidence plots, because Kaplan-Meier estimates do not take into account the possible confounding of competing risks.
- Sensitivity analyses have been added in the case that the outcome of the primary analysis shows superiority of oral semaglutide vs. placebo.
- The analysis of time to permanent discontinuation of trial product due to AE(s) has been replaced by an analysis of time to first AE leading to permanent trial product discontinuation.
- Analysis of time from randomisation to first occurrence of fatal or non-fatal myocardial infarction, and to first occurrence of fatal or non-fatal stroke has been added.
- It has been specified that efficacy endpoints will be presented using summary statistics instead of performing statistical analyses. Since the trial is event driven the actual treatment period will vary from approximately 11 to 19 months between subjects completing the trial, so there will

not be a common landmark visit at the end of trial. For this reason the analyses of change from baseline to last assessment for the efficacy endpoints have been removed.

- It has been specified that continuous safety endpoints will be presented using summary statistics instead of performing statistical analyses. The reason for this is that the endpoints were included to ensure that the investigators can monitor the individual subjects and to allow for detection of potential safety signals on a trial-level that is not reflected in adverse event reporting. In addition, biochemistry, haematology and calcitonin endpoints have been downgraded to assessments.
- It has been clarified how to handle special situations with respect to event adjudication of adverse events.