Cover Page for Statistical Analysis Plan

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Official title of study:	SELECT - Semaglutide effects on cardiovascular outcomes in people with overweight or obesity
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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.

Statistical Analysis Plan

Trial ID: EX9536-4388

SELECT - Semaglutide effects on cardiovascular outcomes in people with overweight or obesity

Author:

[redacted] Statistician

Biostatistics GLP-1 & CV 1

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List of abbreviations

ANCOVA	analysis of covariance
BMI	body mass index
BP	blood pressure
CI	confidence interval
CV	cardiovascular
DBL	data base lock
DMC	data monitoring committee
EAC	event adjudication committee
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQol five dimensions five level
EQ-5D-VAS	EuroQol five dimensions visual analogue scale
HbA_{1c}	glycosylated haemoglobin
HDL	high density lipoprotein
HF	heart failure
HHF	hospitalisation for heart failure
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
LDL	low density lipoprotein
MACE	major adverse cardiovascular event
MI	myocardial infarction
MMRM	mixed model for repeated measurements
PAD	peripheral arterial disease
SAP	statistical analysis plan
s.c.	subcutaneous
T2D	type 2 diabetes
TTE	time-to-event
UACR	urinary albumin to creatinine ratio
WRSSM	weight-related sign and symptom measure

1 Introduction

1.1 Trial information

1.1.1 Rationale

People with overweight or obesity are at high risk for cardiovascular (CV) disease. Semaglutide has shown CV risk reduction and impact on CV risk factors including overweight, dysglycaemia and increased blood pressure in subjects with type 2 diabetes (T2D). Whether semaglutide will reduce CV risk and mortality in subjects with established CV disease and overweight or obesity is not known.

1.1.2 Objectives, endpoints and estimand

Primary objective

To demonstrate that semaglutide subcutaneously (s.c.) 2.4 mg once weekly lowers the incidence of major adverse cardiovascular events (MACE) versus semaglutide placebo, both added to standard of care in subjects with established CV disease and overweight or obesity.

Key secondary objective

To compare the effect of semaglutide s.c. 2.4 mg once weekly versus semaglutide placebo, both added to standard of care in subjects with established CV disease and overweight or obesity with regards to mortality.

Primary endpoint

The primary endpoint is time from randomisation to first occurrence of a major adverse cardiovascular event, a composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

Confirmatory secondary endpoints

Time from randomisation to:

- CV death
- First occurrence of a composite heart failure endpoint consisting of: heart failure hospitalisation, urgent heart failure visit or CV death
- All-cause death

Primary estimand

The primary estimand for all objectives is an intention-to-treat estimand evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment and changes to background medication.

1.1.3 Design

This is a randomised, double-blind, parallel group, placebo-controlled trial comparing semaglutide 2.4 mg with semaglutide placebo both administered (subcutaneous) s.c. once weekly in subjects with established CV disease and overweight or obesity. Subjects are randomised in a 1:1 ratio to receive either semaglutide 2.4 mg or semaglutide placebo as an adjunct to standard of care.

The trial is event driven; therefore, end of trial is scheduled according to accrual of events. The trial will employ a group sequential design with one interim testing for superiority. Under the design assumptions, the trial duration is approximately 59 months following randomisation of the first subject. 17,500 subjects are planned to be randomly assigned to trial products. A schematic overview of the trial design is shown in Figure 1–1.

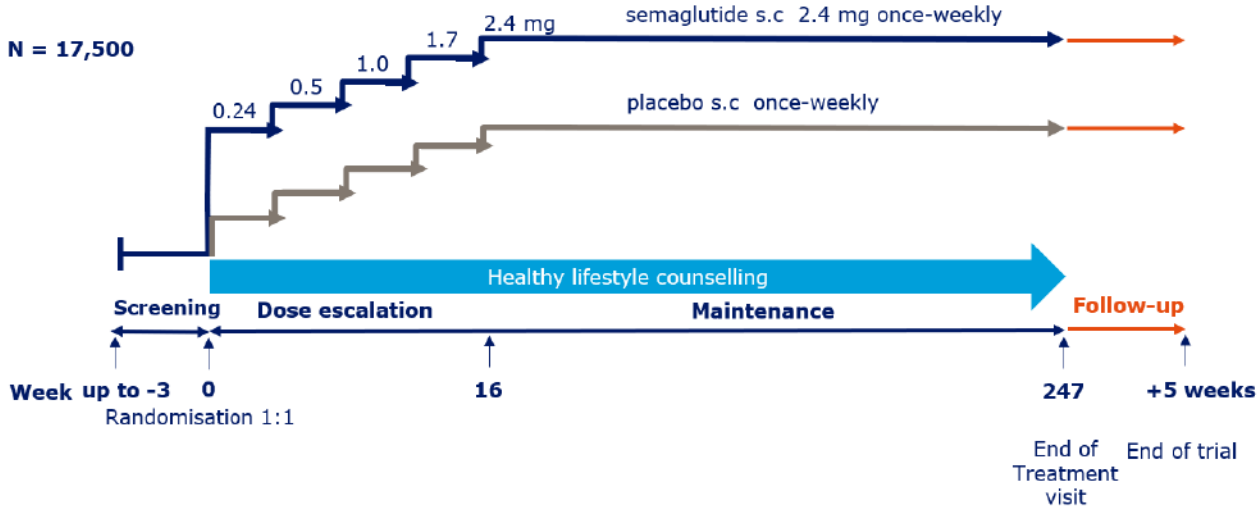

Figure 1–1 Trial design

1.2 Scope of the statistical analysis plan

The SAP includes elaborations on statistical analyses outlined in the protocol for the SELECT trial (EX9536-4388) as well as details on the interim testing for superiority. Any changes to the SAP final version 1.0 will be documented in a change log.

An external independent statistical service provider will conduct the interim analysis, see also section 3. Novo Nordisk is responsible for all other statistical analyses and reporting of data but will remain blinded to treatment allocations until data base lock (DBL).

2 Statistical considerations

2.1 Sample size determination

The trial is designed with 90% power to confirm superiority for the primary endpoint, i.e., reject the null-hypothesis of a hazard ratio (HR) ≥ 1.0 against the one-sided alternative of HR < 1.0, where HR is the hazard ratio of semaglutide 2.4 mg versus semaglutide placebo.

The trial is designed with one interim testing for superiority of the primary endpoint when two thirds of the total planned number of primary endpoint events has been accrued. Testing for futility is not included. The Lan-DeMets alpha spending function, approximating the O'Brien-Fleming's stopping boundaries, is used to test superiority at a study-wise one-sided type I error rate of 2.5%. The one-sided alpha spending function is given by

$$f(t) = \min\{2 - 2 \cdot \Phi(z_{\frac{\alpha}{2}} / \sqrt{t}), \alpha\}$$

where t is the proportion of information included in the interim analysis (accrued primary endpoint events relative to the total planned primary endpoint events), Φ denotes the standard normal cumulative distribution function, α is the overall one-sided alpha of 2.5% and $z_{\alpha/2}$ is the 98.75% quantile of the standard normal distribution. Based on a randomisation ratio of 1:1 and a design HR of 0.83 a total of 1,225 primary endpoint events are required.

For calculating the number of randomised subjects, the following is assumed:

- uniform recruitment in 28 months (2,500 subjects every 4 months)
- annual primary endpoint rate in the semaglutide placebo group of 2.2%
- annual lost to follow-up rate in both treatment groups of 1%

The assumption of 2,500 subjects being randomised every four months is based on what has been achieved in trial EX1250-4080 (DEVOTE). The annualised rate of subjects with a first MACE (primary endpoint) is based on the event rates seen in SUSTAIN 6 and EX2211-3748 (LEADER). These event rates were compared to the event rates in other non-T2D CVOTs (FOURIER, SCOUT and IRIS[1,2,3]) and adjusted to the inclusion and exclusion criteria of the current trial. In the SCOUT trial, which was conducted in subjects with overweight or obesity, the subgroup that only had established CV disease had ~30% fewer MACE events compared with the subgroup that had established CV disease and T2D. Based on this literature, an event rate around half of that seen in LEADER and SUSTAIN 6, is assumed when including subjects with prior MI, prior stroke or symptomatic PAD but without T2D. Accordingly, the overall annualised event rate across the two treatment arms is assumed to be 2.0%, (i.e. 1.8% in the semaglutide 2.4 mg arm and 2.2% in the semaglutide placebo arm). With these assumptions the number of events accrued over a period of 7 years with various sample sizes is seen on the below figure.

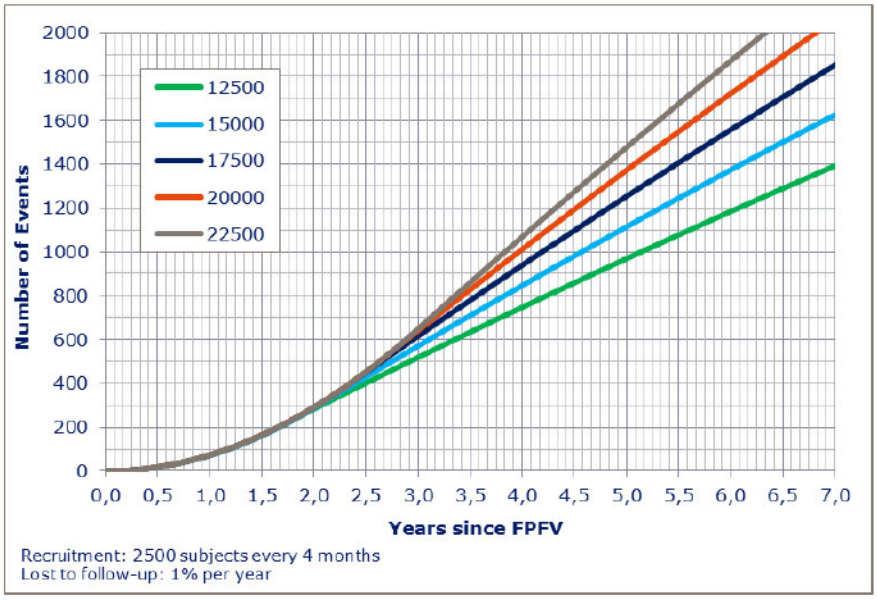

Figure 2–1 Number of events over time with various sample sizes

With a sample size of 17,500 subjects, and under the alternative hypothesis, the 1,225 events are accrued between months 58 and 59.

A Cox model as described in section 2.3 is used for the interim testing using the fixed sample one-sided lower p-value from the score test. Only a fixed sample p-value below the boundary specified by the error spending function will allow the DMC to recommend early trial termination for superiority. Table 2-1 provides the boundaries based on analyses performed after 817 and 1,225 events, along with the approximate hazard ratio estimates that correspond to those boundaries if the analyse are timed exactly to that schedule. The actual stopping boundaries will be based on the exact number of events available for the interim analysis.

Table 2-1 Stopping boundary scales at interim and scheduled termination

Stopping boundary scale	Interim 817 events	Scheduled termination 1,225 events
Hazard ratio	0.8389	0.8924
Nominal significance level	0.00605	0.02314

Figure 2–2 below shows the probability of stopping the trial at the interim (blue curve) and the overall power for confirming superiority for the primary endpoint (red dashed curve) as a function of alternative values for the true HR. The design HR of 0.83 is marked with a dashed vertical reference line. The stopping probability at the interim and overall power for the design HR of 0.83 can be seen to be 56% and 90%, respectively.

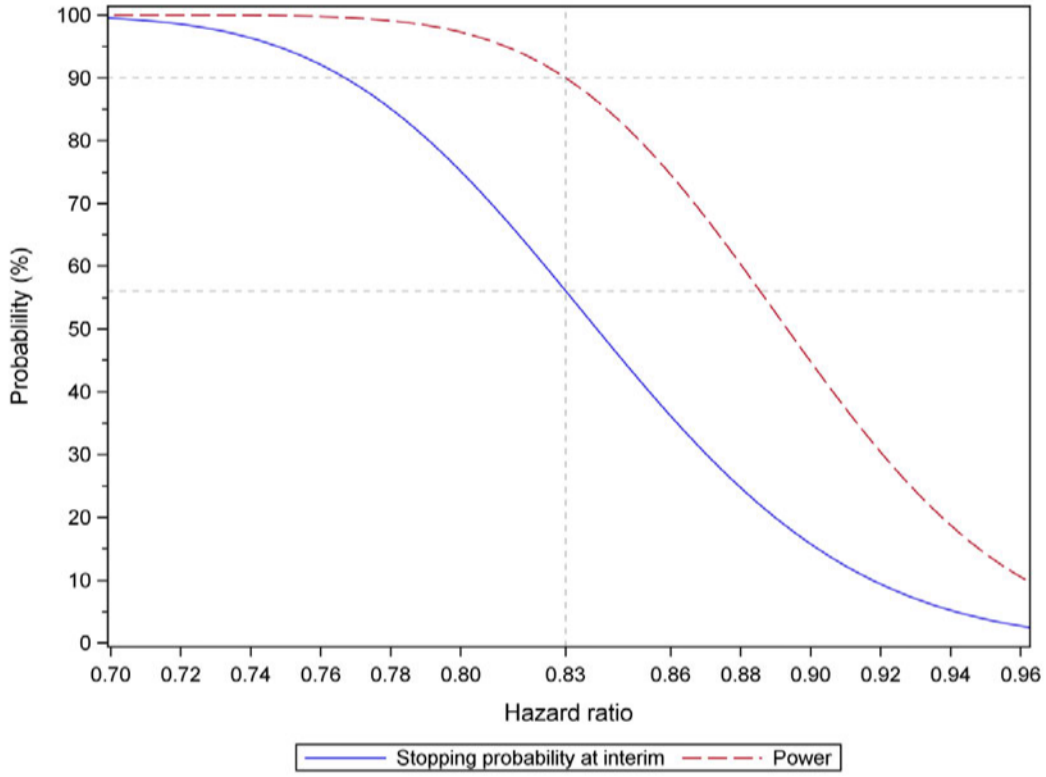

Figure 2–2 Stopping probability at interim and overall power as a function of the hazard ratio

In summary, under the assumed design assumptions, the sample size calculation provides the following information about the trial and expected trial conduct:

Table 2-2 Key numbers and timelines

Randomisation ratio	Number of randomised subjects	Number of events interim/total	Duration of recruitment period	Duration of trial	Timing of interim	Mean observation time interim/total
1:1	17,500	817/1,225	28 months	59 months	44 months	30/44 months

2.2 General considerations

For confirmatory endpoints controlled for multiplicity (see section 2.4.1), estimated treatment effects are presented together with two-sided 95% confidence intervals (CIs) and one-sided p-values for tests of the hypotheses of superiority. For reporting of results, the HR and the 95% CI are accompanied by the two-sided p-value.

For non-confirmatory endpoints, estimated treatment effects are reported together with two-sided 95% CI and two-sided p-values.

Baseline value is defined as the eligible measurement associated with the randomisation visit, if this measurement is taken before or at the date of first dose. If a randomisation assessment is missing or if it is taken after the date of first dose, then the assessment from screening is used as the baseline assessment, if available. For measurements only taken at screening (e.g. HbA_{1c}) the eligible screening measurement will be the baseline value.If more than one measurement is associated with the same visit, the earliest measurement is considered eligible.

Missing data are defined as data that are planned to be collected and can be observed but are not present in the database. This implies that data that are structurally missing due to death or administrative censoring are not considered missing. Unless explicitly stated unobserved data pertaining to subjects who are lost to follow-up or withdrawn and would not have been administratively censored at the time point in question, are considered missing irrespectively of vital status as collected at end of trial.

2.2.1 Definition of analysis set

The full analysis set (FAS) is defined as all unique randomised subjects and grouped according to the treatment assigned at randomisation.

If a subject is randomised more than once, only the subject ID and treatment corresponding to the first randomisation will be included in FAS. The additional randomised subject IDs will be excluded from FAS. The list of subject ID's to exclude will be part of the DBL minutes.

2.2.2 Definition of observation periods

A trial completer is defined as a subject that either attends the end-of-trial follow-up visit or who dies while active in the trial.

A subject is considered lost to follow-up (LTFU) if the subject does not complete the trial and does not withdraw consent. The date and status for LTFU are determined by investigator at trial completion, either following interim testing or after accrual of the total planned number of primary endpoint events.

In-trial observation period

The in-trial observation period for a subject is defined as the period from date of randomisation to the first of (both inclusive):

- date of follow-up visit
- date when subject withdrew consent
- date of last contact with subject for subjects who are LTFU

- date of death

On-treatment observation period

A time-point in the in-trial observation period is considered as on-treatment if any dose of trial product has been administered within the previous 5 weeks (35 days). The on-treatment observation period is defined as all times which are considered on-treatment, so it may consist of several time intervals with gaps between.

First on-treatment observation period

The first on-treatment observation period is defined as the on-treatment observation period until first time being off treatment for 5 consecutive weeks (35 days). Thus it is the first time interval in the on-treatment period.

2.2.3 Estimands

Primary estimand (intention-to-treat)

The estimand for all objectives is an intention-to-treat estimand, evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment and changes to background medication. The estimand is addressed using FAS and the in-trial observation period.

Intercurrent events

Intercurrent events are events including, but not limited to, or associated with the following:

- randomised treatment adherence
- change in background medication modifying CV risk
- bariatric surgery
- initiation of chronic renal replacement therapy
- withdrawal
- lost-to follow up
- death (if not part of endpoint)

These are reported using descriptive statistics.

Handling of intercurrent events for the statistical analyses of the primary endpoint is described in Table 6-1.

Secondary estimand for selected time-to-event endpoints

This estimand covers confirmatory endpoints and is evaluating the effect of the randomised treatment intervention in all randomised subjects had they remained on their randomised treatment

for the entire trial. The estimand is addressed using FAS and the first on-treatment observation period.

Secondary estimand for body weight

This estimand is evaluating the effect of the randomised treatment intervention after 52 weeks on change in body weight, in all randomised subjects had they remained on their randomised treatment for 52 weeks. The estimand is addressed using FAS and the first on-treatment observation period restricted to the first 52 weeks of the trial .

2.2.4 Time-to-event endpoints, censoring and competing risks

Time-to-event endpoints are in general time-to-first-event endpoints but will for simplicity be denoted time-to-event (TTE) endpoints.

If adjudicated, the TTE endpoints are defined based on outcomes of the EAC evaluations. While vital status is ascertained systematically throughout the trial until DBL, other event types cannot be systematically collected after withdrawal, lost-to-follow-up, or after end-of-trial visit as illustrated in Figure 2–3. For this reason, any event occurring after the in-trial observation period is not included in analyses, unless otherwise stated.

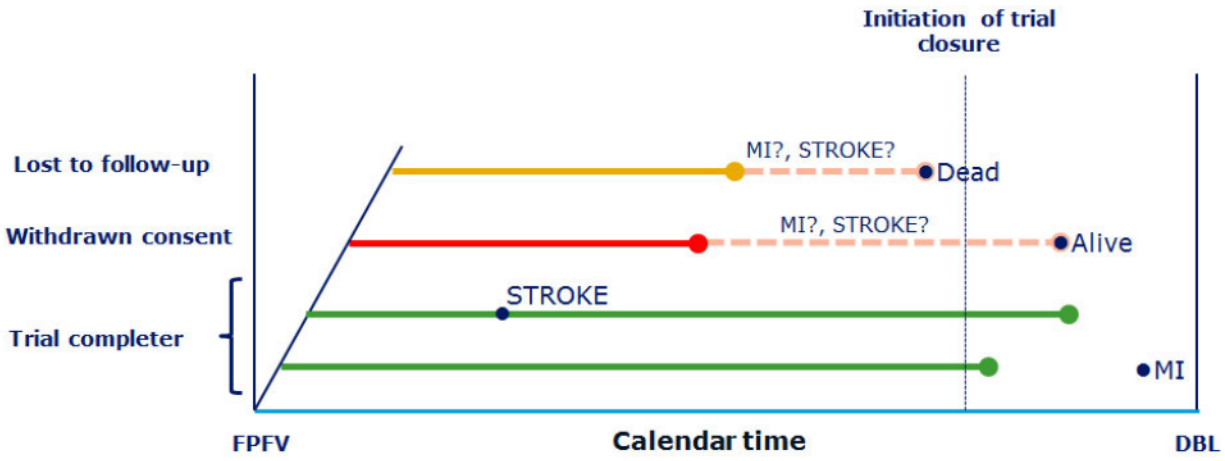

Figure 2–3 In-trial observation periods used in analysis of time-to-event endpoints reflected by bold lines for four different subject examples

If a subject experience the event of interest during the in-trial observation period, the observation of the TTE is the time from randomisation to the date of event.

The observation of the TTE is censored if the event of interest does not happen during the in-trial observation period and if the subject is still alive at the end of the observation period. The general

assumption for censored observations is that the risk of experiencing an event is not changed by censoring, i.e. an assumption of independent censoring. This is a reasonable assumption for administrative censoring at end-of-trial visit but may not be for subjects withdrawing or subjects lost to follow-up. Sensitivity analysis addressing the assumption of independent censoring is planned for the primary endpoint, see section 2.3.2.

The observation of the TTE is terminated if the event of interest does not happen before the death of the subject unless death is part of the endpoint. Terminating events (competing risks) is potentially present for all TTE endpoints except for all-cause death; for the primary endpoint, non-CV death is a competing risk terminating the observation for the event of interest (MACE). Figure 2–4 illustrates competing risk as a multi-state model for the primary endpoint. The hazard of interest is denoted by $\lambda(t)$, t being time since randomisation.

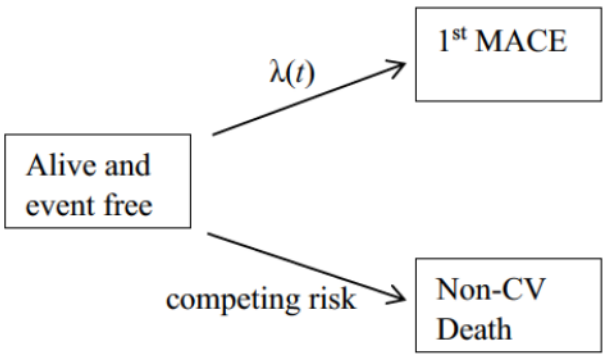

Figure 2–4 Multi-state model illustrating competing risk for primary endpoint

Unless otherwise specified, the statistical analyses of TTE endpoints are done by using a Cox proportional hazards model with treatment group (semaglutide 2.4 mg, semaglutide placebo) as fixed factor under the assumption of independent censoring. Terminated observations (due to competing risks) are technically treated as censored observations, but not part of the independent censoring assumption. The population-level summary measure for TTE endpoints is the HR for semaglutide 2.4 mg versus semaglutide placebo. The assumption of proportional hazards is investigated by residuals. Tied event times are handled using the exact method and confidence intervals are based on the profile likelihood.

Cumulative incidence functions for TTE endpoints are estimated by the Aalen-Johansen estimator which accounts for the competing risks.

Table 6-2 gives an overview of the TTE endpoints including any competing risk and whether the TTE endpoint is EAC-confirmed.

2.2.5 Continuous and binary endpoints

If 10% or more of subjects from FAS have missed the week 104 visit due to trial termination earlier than planned (stopping after interim testing or event rates higher than expected) the timing of the endpoint will change to week 52.

The population-level summary measure for continuous endpoints is the mean difference for semaglutide 2.4 mg versus semaglutide placebo. Lipid endpoints and hsCRP are logarithmic transformed and the mean difference on the logarithmic scale is back-transformed to original scale and reported as geometric mean ratios. The population-level summary measure for binary endpoints is the odds ratio for semaglutide 2.4 mg versus semaglutide placebo.

Table 6-3 gives an overview of the continuous and binary endpoints.

2.3 Primary endpoint

Time from randomisation to first occurrence of a composite MACE endpoint consisting of

- CV death
- Non-fatal myocardial infarction (MI)
- Non-fatal stroke.

Fatal MI is defined as an EAC-confirmed MI occurring within (≤) 30 days of an EAC-confirmed CV death classified with cause of death being MI. All other MIs are defined as non-fatal. A similar definition is applied for fatal/non-fatal stroke.

Deaths attributed to the category "undetermined cause of death" are presumed cardiovascular death.

2.3.1 Primary analysis

The primary analysis will address the primary estimand (intention-to-treat). The HR for comparing semaglutide 2.4 mg versus semaglutide placebo is estimated from a Cox proportional hazards model with treatment group (semaglutide 2.4 mg, semaglutide placebo) as fixed factor together with the two-sided 95% CI and one-sided fixed design p-value for hypothesis testing. The score test from the Cox model is used for testing. The following superiority hypothesis is tested:

$$H_0: HR \geq 1.0 \text{ against } H_a: HR < 1.0$$

Superiority of semaglutide 2.4 mg versus semaglutide placebo is considered confirmed if the associated H_0 is rejected. The nominal significance level is calculated using the alpha spending function and the actual observed number of events available for the analysis. Final inference on termination is adjusted for the group sequential design by using the likelihood ratio ordering.

Competing risk from non-CV death is handled as censorings in the Cox analysis as described in section 2.2.4. Please, refer to Table 6-1 for handling of other intercurrent events.

Each component of the primary endpoint is included as a secondary endpoint, see sections 2.4.1 and 2.4.2.

2.3.2 Sensitivity analyses

If superiority is established for the primary endpoint, the following sensitivity analyses are performed. The primary analysis assumes independent censoring for subjects who have withdrawn consent or are lost to follow-up. To investigate the impact of this assumption on the primary analysis, a 2-way tipping point analysis based on the approach described in Zhao et al. (2014)[4] is performed. In this analysis, subjects in the two treatment groups who have withdrawn or are lost to follow-up will have event times imputed from the conditional event distribution with a penalty in the sense that the risk (hazard) of MACE is changed following censoring compared to while under observation. Multiple imputed data sets are analysed with separate Cox regressions and results are combined using Rubin's rule. The tipping points are then defined as the combination of changes in penalties (in each of the treatment groups) needed to turn around the superiority conclusion.

Two additional sensitivity analyses will be performed by multiple imputation of event times for subjects who are withdrawn or lost to follow-up. If the imputed event time occurs after the subjects planned end-of-trial time the subject will be censored at the planned end-of-trial time

The first will be done by treatment arm using an estimated annual event rate from subjects who discontinue treatment permanently but remain in the trial. The event rate will be based on events and time while these subjects are permanently off-treatment. A time-point in the in-trial observation period is considered as belonging to the permanently off-treatment period if any dose of trial product has been administered more than 5 weeks (35 days) ago and the subject remains off-treatment for the remainder of the trial. This analysis condition on the future in the sense that subjects are only known to be permanently off treatment by the end of the trial.

The second analysis avoids conditioning on the future by using an estimated annual event rate for subjects who discontinue treatment at any point in the trial. The imputations are done by treatment arm. The event rate will be based on events occurring from the first time subjects are off treatment corresponding to when their first on-treatment period ends (section 2.2.2) and until end of the in-trial observation period. This may include time periods where the subjects actually went back on trial treatment.

Technically, the first of the two sensitivity analyses will be performed in the following steps:

1. For the purpose of estimating the off-treatment event rates, a set of retrieved dropouts are selected. The selection criteria are that the subject shall be a trial completer, have their date

of last dose during the trial reported as a treatment discontinuation, have ended the on-treatment observation period before the end of the in-trial observation period, and not having had an event before the end of the on-treatment observation period. For each selected subject, the off-treatment event time is calculated from a start date set to the day after the end of the on-treatment observation period. The event time is considered censored at the end of the in-trial observation period.

2. The off-treatment event time data are fitted within treatment arms to an exponential distribution using Bayesian analysis and accounting for censoring. A noninformative prior distribution is used for the rate parameter in each treatment arm. 500 replicates of the two off-treatment event rates are then randomly sampled from the posterior distribution.

3. To prepare the imputation, 500 copies of the original data set are created and linked to the corresponding replicate of the off-treatment event rates. For each subject who is censored due to withdrawal or being lost to follow up, the event time is imputed by adding a random variable to the original censoring date. The random variables are generated from an exponential distribution using the off-treatment event rate for the corresponding replicate and treatment arm, and rounded up to whole days. If the imputed event time lies beyond the planned date of end of trial for the subject, it is considered censored at this date. There will now be 500 complete data sets.

4. Each complete data set is analysed using the same Cox regression as in the primary analysis. The analysis gives the estimated log hazard ratio and associated standard error.

5. The log hazard ratios and standard errors from the 500 data sets are pooled using Rubin's rule to obtain a single point estimate, confidence interval and p-value.

The procedure for the second sensitivity analysis is identical to the first analysis except for step 1. The selection criteria for a retrieved dropout are instead that the subject shall have their date of last dose during the first on-treatment observation period reported as a treatment discontinuation, have ended the *first* on-treatment observation period before the end of the in-trial observation period and not having had an event during the first on-treatment observation period. The selection may include subjects who are later withdrawn or lost to follow-up. The off-treatment event time is calculated from a start date set to the day after the end of the first on-treatment observation period.

2.3.3 Supplementary analyses

The following supplementary analyses are planned:

- Absolute risk difference: Estimation of the absolute risk difference (and 95% CI) at week 156 between semaglutide 2.4 mg and semaglutide placebo based on the cumulative incidence function for each treatment group. If the trial is stopped early for superiority, week 104 will be used.

- On-treatment: Analysis addressing the secondary estimand using a Cox proportional hazards model using the first on-treatment period.
- Additionally, an analysis of non-CV death using the same Cox model as for the primary endpoint will be done to evaluate the influence of the competing risk non-CV-death on the primary results.

2.3.4 Subgroup analyses

The consistency in the treatment effect for the primary endpoint is explored by subgroup analyses based on the below baseline information:

- Sex: Females, Males
- Age: <55, [55,65[, [65,75[, ≥75
- Race: White, Black or African-American, Asian, Other
- Ethnicity: Hispanic/Latino, Not hispaninc/latino
- HbA_{1c} <5.7% (yes/no)
- BMI: <30, [30,35[, [35,40[, [40,45[, ≥45
- CV disease: MI alone, Stroke alone, PAD alone, any combination
- eGFR ≥60 ml/min/1.73 m^2 per CKD-EPI (yes/no)
- Region: Europe, North America Asia, Other where the regions are defined as follows:
    - **Europe**: Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Spain, Sweden, United Kingdom,
    - **North America**: Canada, , United States,
    - **Asia**: Australia, , India, Israel, Japan, Malaysia, , Taiwan, Thailand, Turkey,
    - **Other**: Algeria, South Africa, Russia, , Ukraine, Argentina, Brazil, Colombia, Mexico
- Chronic heart failure (yes/no)

The subgroup analyses are based on Cox proportional hazards models with an interaction between treatment group (semaglutide 2.4 mg, semaglutide placebo) and the specific subgroup as a factor.

2.3.5 Supplementary analyses evaluating impact of the COVID-19 pandemic

The following supplementary analyses will be made to assess the impact of the COVID-19 pandemic on the primary endpoint. The analyses address two scenarios: one where MACEs are impacted by an increased MACE rate and potentially a different treatment effect for events occurring concurrently with COVID-19 infection; the other with a reduced MACE rate due to concurrent COVID-19 infection leading to fewer CV deaths as the subjects die (prematurely) of COVID-19 infection and not their underlying atherosclerotic disease.

1. Time from randomisation to first MACE without concurrent COVID-19 SAE. The definition of MACE is modified so any MACE occurring concurrently with a COVID-19 SAE in a subject is not considered a MACE. The observation period and censoring are not changed. Any subsequent MACE can then qualify to be the first MACE for the subject.

2. Time from randomisation to first MACE without concurrent COVID-19 AE. The definition of MACE is modified so any MACE occurring concurrently with a COVID-19 AE in a subject is not considered a MACE. The observation period and censoring are not changed. Any subsequent MACE can then qualify to be the first MACE for the subject.

3. Time from randomisation to first MACE or non-CV death occurring concurrently with a COVID-19 SAE. The definition of MACE is modified to include non-CV deaths potentially related to COVID-19. The observation period and censoring are not changed.

The analyses will be done with the same Cox regression model as for the primary analysis. An event is considered concurring with a COVID-19 AE if the event occurs in the time period from the start day of the COVID-19 AE and until 30 days after the last of the following two dates: the stop date of the COVID-19 AE or the end of hospitalisation date for a hospitalisation reported together with the COVID-19 AE.

2.3.6 Supplementary analyses evaluating impact of co-participation in COVID-19 treatment or prevention trials

To assess the potential impact on the primary analysis of subjects being allowed to co-participate in trials with primary objective of evaluating an approved or non-approved investigational medical product for treatment or prevention of COVID-19 disease the following supplementary analysis will be done: An analysis of time to first MACE where all subjects co-participating in a COVID-19 treatment or prevention trial are censored at the day they receive the first trial treatment for preventing or treating COVID-19. This will reduce the observation time.

The analysis will be done with the same Cox regression model as for the primary analysis.

The analysis corresponds to the situation where patients withdraw from the trial when they start co-participation.

If less than 10 subjects have co-participated in COVID-19 treatment or prevention trials then this analysis will not be performed.

2.4 Secondary endpoints

Confirmatory secondary endpoints are analysed under multiplicity control.

2.4.1 Confirmatory secondary endpoints

If superiority is established for the primary endpoint, the superiority hypothesis stated in section 2.3.1 is tested for each of the confirmatory secondary endpoints under multiplicity control via a stagewise hierarchical testing scheme using the below order:

1. Time from randomisation to CV death.
2. Time from randomisation to first occurrence of a composite heart failure endpoint consisting of: heart failure hospitalisation, urgent heart failure visit or CV death
3. Time from randomisation to all-cause death.

For the type I error rate to be strongly controlled at one-sided level of 2.5%, a separate alpha spending function for the confirmatory secondary endpoints is applied as described in Glimm et al. (2010)[5]. The one-sided alpha spending function is given by

$$g(t) = \min\{\alpha * t^{0.7668}, \alpha\}$$

where t is the proportion of information included in the analysis for the primary endpoint and α is the overall one-sided alpha of 2.5%.

The testing procedure is stopped the first time an analysis fails to confirm superiority of the endpoint in question using the nominal significance level. No adjustments of results for the confirmatory secondary endpoints due to the group sequential design will be done.

Table 2-3 provides an example of the boundaries at interim and scheduled termination in the case where the interim is conducted at 2/3 of the planned number of primary endpoint events and where the number of events for the secondary endpoint at scheduled termination is 3/2 times the number of secondary endpoint events at the interim.

The actual nominal significance level will be based on the exact number of events available at the interim analysis.

Table 2-3 Nominal significance level for confirmatory secondary endpoints at interim and scheduled termination – an example

Stopping boundary scale	Interim	Scheduled termination
Nominal significance level	0.01832	0.01329

The confirmatory secondary endpoints are analysed using a Cox proportional hazards model as described for the primary endpoint and addressing the primary estimand. Supplementary analyses

described in section 2.3.3 for the primary endpoint, will also be done for the confirmatory secondary endpoints.

The two sensitivity analyses with imputation from subjects off treatment will be done for all confirmatory secondary endpoints. (section 2.3.2) Supplementary analyses described in section 2.3.5 with regards to the impact of the COVID-19 pandemic for the primary endpoint will also be done for cardiovascular death and the HF composite endpoint. The analysis assessing the potential impact of co-participation in COVID-19 trials (section 2.3.6) will be done for all confirmatory secondary endpoints.

Supplementary analyses for HF composite endpoint

For the HF composite endpoint a supplementary analysis will be done by replacing the CV death component with all-cause death.

Supplementary analyses for all-cause death – extended in-trial period

In addition, all-cause death is analysed using FAS and an extended in-trial observation period including the follow-up for vital status for subjects who withdraw consent or are LFTU. The relative risk for the binary endpoint death/alive will be compared between the two treatment groups using the likelihood ratio method. The model is chosen because it doesn't depend on the observation time which is only extended for subjects withdrawn or LTFU.

2.4.2 Supportive secondary endpoints

2.4.2.1 TTE supportive secondary endpoints

Each of the TTE supportive secondary endpoints are analysed using a Cox proportional hazards model as described for the primary endpoint and addressing the primary estimand.

For the eGFR components of the composite nephropathy endpoint, a persistent outcome in eGFR is defined as having two consecutive central laboratory assessments at least 4 weeks apart meeting the criteria. When classifying the events based on consecutive laboratory assessments, the date of the event is the date of the first sample meeting the criterion. If eGFR at baseline is below 15 ml/min/1.73m^2 the subject will still be included in the analysis as the subject still can experience one of the other four component events.

For the macroalbuminuria component a persistent outcome is defined as having 2 out of 3 consecutive central laboratory assessments of UACR at least 4 weeks apart meeting the criterion. When classifying the events based on consecutive laboratory assessments, the date of the event is the date of the first sample meeting the criterion.

Supplementary analyses for MI and stroke

For MI and stroke, supplementary analyses including fatal MI and fatal stroke are performed. Thus, the supplementary analysis will analyse endpoints defined as

- Time from randomisation to first MI (fatal or non-fatal)
- Time from randomisation to first stroke (fatal or non-fatal).

Supplementary analysis for 5-component MACE

For the 5-component MACE a supplementary analysis will be done by replacing the CV death component with all-cause death.

2.4.2.2 Continuous supportive secondary endpoints

The continuous supportive secondary endpoints (change from baseline to week 104) are analysed using multiple imputation for missing values.

The imputation model (linear regression) is done separately for each treatment arm and includes baseline value as a covariate and fitted to subjects having an observed data point (irrespective of adherence to randomised treatment) at week 104. The fitted model is used to impute values for all subjects with missing data (see section 2.2) at week 104 to create complete data sets. Subjects without a baseline measurement will not be part of the model. The complete data sets are analysed by an ANCOVA with treatment as fixed factor and baseline value as covariate. Rubin's rule is used to combine the results. Analyses of lipids and hsCRP are on logarithmic scale.

Additionally, analyses for body weight and HbA_{1c} are carried out at week 52, 156, 208 if less than 10% of subjects from FAS have missed the corresponding visit due to trial termination, see section 2.2.5.

Sensitivity analyses for body weight

Sensitivity analyses for body weight (week 52, 104, 156, 208) using a multiple imputation approach in which missing values in both treatment arms are imputed using an imputation model for the placebo group only (irrespective of adherence to randomised treatment at time-point). This approach is referred to as a jump to reference multiple imputation approach (J2R-MI).

Supplementary analysis for body weight

The change in body weight from randomisation to week 52 will additionally be analysed to address the secondary estimand (section 2.2.3) using a mixed model for repeated measurements (MMRM). The model will use assessments from the first on-treatment observation period restricted to the first

52 weeks, see section 2.2.2. Planned assessments up until and including the week 52 assesments that are within the first on-treatment period are included in the model. The MMRM is fitted with treatment (semaglutide 2.4 mg, semaglutide placebo) as fixed factor and baseline body weight (kg) as covariate all nested within visit. An unstructured covariance matrix for measurements within the same subject is employed.

2.4.2.3 Supportive secondary endpoints based on subsets of FAS

The following endpoint is defined only for subjects with a screening $HbA_{1c} < 5.7\%$

- Time from baseline to $HbA_{1c} \geq 5.7\%$

The TTE endpoint is analysed using a Cox proportional hazards model with treatment group (semaglutide 2.4 mg, semaglutide placebo) as fixed factor.

The following endpoints are defined only for subjects with a screening $HbA_{1c} \geq 5.7\%$

- $HbA_{1c} < 5.7\%$ (yes/no) at each visit where HbA_{1c} is assessed

The binary endpoints are analysed separately at week 52 and week 104 using logistic regression models with treatment (semaglutide 2.4 mg, semaglutide placebo) as fixed factors and baseline HbA_{1c} as covariate. Missing data are imputed using the same primary imputation model as for the supportive secondary endpoint change in HbA_{1c}. The imputation model will only include subjects with a screening $HbA_{1c} \geq 5.7\%$.

2.5 Exploratory endpoints

Smoking

Smoking (yes/no) is analysed separately at week 52 and week 104 using logistic regression models with treatment (semaglutide 2.4 mg, semaglutide placebo) and baseline smoking status (yes/no) as fixed factors. Missing data are handled by multiple imputation. The imputation model (logistic regression) is done separately for each treatment arm and includes baseline smoking status as fixed factor and fitted to subjects having an observed data point (irrespective of adherence to randomised treatment) at week 52 and week 104, respectively. The fitted model is used to impute values for all subjects with missing data (see section 2.2) at week 52 and week 104, respectively.

Glycaemic status

Deterioration from baseline to week 117 in glycaemic status as assessed by investigator (yes/no, where "yes" is determined by a change from normoglycaemia at baseline to pre-diabetes/diabetes at week 117 or from pre-diabetes at baseline to diabetes at week 117) is analysed using a logistic regression model with treatment (semaglutide 2.4 mg, semaglutide placebo) as fixed factor and baseline HbA_{1c} as covariate. Missing data post baseline are handled by multiple imputation based

on the value of the either observed or imputed HbA_{1c} value at week 104. The imputation of HbA1c values is described in section 2.4.2.2. Subjects with missing glycaemic status at baseline will not be included.

All-cause hospitalisations

Two exploratory endpoints are defined from all-cause hospitalisations. These are analysed as a recurrent events process with all-cause death as a competing risk (terminal event) and where events are having a duration, i.e. length of stay in hospital. Censoring of observations are done as for TTE endpoints, see section 2.2.4.

Total number of hospitalisations

Number of hospitalisations is analysed ignoring time periods where subjects are hospitalised, and acknowledging the fact that death precludes further hospitalisations [6, 7]. Mean number of hospitalisations is plotted as a function of study time and analysed using a marginal mean regression model for recurrent events with treatment group (semaglutide 2.4 mg, semaglutide placebo) as fixed factor and reported as mean ratio and corresponding 95% robust CI [8]. This is done for the full trial duration. Additionally, descriptive comparisons of treatment groups at year 1, 2, 3, and 4 are planned.

Total number of hospital days

Total length of stay (days) in hospital as a function of study time is estimated using methods for multi-state models. Specifically, the mean time spent in hospital (state 1 in Figure 2–4) per treatment group is estimated as the integral of the state occupation probability of being in hospital over duration of the in-trial observation period[9]. Comparisons of treatment groups are planned at year 1, 2, 3, and 4 separately using the method of pseudo observations[10].

Table 6-4 gives an overview of planned analyses for all endpoints.

Change from baseline to week 104 for WRSSM total score will be presented descriptively.

2.6 Other assessments

Adverse events

All systematically collected AEs, i.e. serious AEs and non-serious events requiring extra data collection are summarised as number of subjects with events, proportion of subjects with events, number of events and rate of events according to treatment group. Summaries of SAEs are categorised by severity, relation to treatment, and outcome.

Descriptive summaries of concomitant medication (lipid lowering, anti-hypertensive, glucose-lowering) are presented as well as descriptive summary of non-CV deaths by treatment group.

3 Interim testing

The trial design includes *one* pre-planned interim testing for superiority of the primary endpoint. The planned timing is when 817 events (two thirds of the planned total events) of the primary endpoint have been accrued. The interim testing is performed based on a locked snapshot of the study database. The date of the snapshot defines the interim analysis cut-off date for the interim analysis. Subjects without an EAC-confirmed primary endpoint event prior to the date of analysis cut-off are considered censored with the censoring date defined as the first of:

- in-trial observation period end-date
- interim analysis cut-off date

The same Cox model as described in section 2.3 is used for the interim testing addressing the primary estimand.

3.1 Role of DMC

Blinded and un-blinded data analyses during trial conduct are evaluated by the DMC, as described in the DMC charter. Trial integrity is ensured by using an external independent statistical service provider (independent of trial conduct and external to Novo Nordisk) to prepare these data and analyses for the DMC.

The DMC will evaluate the interim result and make recommendation to terminate the trial early for superiority if appropriate. The DMC evaluates the un-blinded interim results using the group sequential stopping boundary as guidance. Stopping the trial early for superiority is only allowed if the stopping boundary is crossed and the DMC makes the decision to recommend early trial termination based on this and other considerations as specified in the DMC charter.

If the DMC recommends to terminate the trial early due to efficacy a Novo Nordisk internal group referred to as the SELECT interim team (SIT)) will enter a dialogue with the DMC to facilitate the final decision to terminate or continue. This dialogue will be based on the unblinded results and output forming the basis for the DMC recommendation to terminate SELECT. The SIT will only see output/results that the DMC shows them during the dialogue. The SIT will comprise a limited number of Novo Nordisk personnel who have no direct involvement in the conduct of SELECT. For all other either at Novo Nordisk or any other party the recommendations from the DMC will exclude any details of the interim results as to maintaining trial integrity. Further details are outlined in the Data Access Management Plan.

3.2 Stopping boundary for superiority at interim

The exact number of primary endpoint events used for the interim testing is only known at the time of analysis, and the exact boundary is re-calculated using the Lan-DeMets alpha spending function.

3.3 Analysis on termination

If the trial is terminated early for superiority following the interim testing, definitive evaluation of superiority for the primary endpoint is performed based on all the available data at the end-of-trial, including overrun data. Overrun data include events happening between the cut-off date for the DMC interim analysis and end-of-trial as well as additional confirmed events that were undergoing adjudication at the interim analysis cut-off time point. If the trial is not terminated early for superiority following the interim testing, the analysis at scheduled termination is performed when the planned number of 1,225 events has been accrued. The exact number of primary endpoints events used for the analysis on termination is only known at the time of analysis, and nominal significance level is updated based on the exact number of total accrued events and the Lan-DeMets alpha spending function. Similarly, the significance level for the confirmatory secondary endpoints is updated based on the exact number of events and all available data at end-of-trial are used for analyses of both secondary and exploratory endpoints.

For reporting of results for the primary endpoint (p-value, HR and 95% CI), the analysis on termination (either early or at scheduled termination) is adjusted for the group sequential design using the likelihood ratio ordering.

4 Changes to the statistical analysis plan

In general, this SAP describes in more details the statistical analyses planned in the protocol.

SAP version 0.1 dated 27-Jun-2018

Analyses added in the SAP and not described in the protocol are

- Supplementary analyses for primary endpoint and confirmatory secondary endpoints (section 2.3.3)
  - estimation of risk difference at year 3
  - including out-of-trial observations
  - Secondary estimand (on-treatment)
- Supplementary analyses of MI and stroke using both fatal and non-fatal events in the endpoints (section 2.4.2.1)
- Analyses by year of change in body weight and HbA_{1c} (section 2.4.2.2)
- Supplementary analysis (MMRM) for change in body weight at week 52 addressing the secondary estimand (section 2.4.2.2)
- Analysis of smoking status at week 52 (section 2.5)

Analyses from protocol updated in the SAP

- Imputation model for continuous endpoints (section 2.4.2.2) is fitted to all subjects having observed values (irrespective of adherence to randomised treatment) at week 104 and not only to subjects being off-treatment for the first time.
- For subjects with screening ≥ 5.7% the analysis of presence of HbA_{1c}< 5.7% (yes/no) is done at week 52 and 104 and not at each visit where HbA_{1c} is assessed (section 2.4.2.3).

SAP version 1.0, dated 11-Mar-2019

The fixed design has been changed to a group sequential design with one pre-defined interim testing for superiority (sections 1.1.3, 1.2, 2.1, 2.3.1, 2.4.1, 3).

Section 2.1 reduced by excluding additional scenarios for the sample size considerations.

Removed the wording "cause-specific" (hazard) for the primary analysis to make it clear that a standard Cox model is used and to align with protocol wording (section 2.2.4).

Sensitivity analysis for the primary endpoint updated to a 2-way tipping point analysis (section 2.3.2).

Supplementary analyses included for 5-component MACE and 2-component HF by replacing CV death component with all-cause death (section 2.4.2).

Supplementary analysis "including out-of-trial observations" only planned for all-cause death and renamed "extended in-trial period".

In general, editorial changes for alignment with SAPs for trials EX9924-4473 (SOUL) and NN9535-4321 (FLOW).

SAP version 2.0, dated 31-Mar-2021
Author changed from [redacted] to [redacted].

The definition of baseline value has been updated (section 2.2).

It has been clarified how missing data from subjects who are LTFU or withdrawn are handled (section 2.2).

It has been clarified how subjects randomised more than once will contribute to the FAS (section 2.2.1).

The follow-up period has been changed from 7 weeks (49 days) to 5 weeks (35 days) in section 2.2.2 and throughout the document in alignment with protocol version 6.0.

A definition of the first on-treatment period has been added (section 2.2.2). The use of it has been added to supplementary analyses regarding on treatment (section 2.2.3, 2.3.3 and 2.4.2.2).

It has been clarified that tied event times are handled using the exact method and risk limits are based on the profile likelihood (section 2.2.4).

It has been clarified that it is less than 10% of subjects from FAS who can have missing visits due to early termination for imputations to be done (section 2.2.5).

hsCRP will be analysed using a log-normal distribution instead of a normal distribution (section 2.2.5 , 2.4.2.2, and 6).

A supplementary analysis of non-CV death has been added to evaluate the effect of competing risk on the primary endpoint (section 2.3.3).

In the specification of subgroup analyses EU has been changed to Europe and a description of which countries belong to each region has been added (section 2.3.4).

A section describing supplementary analyses assessing the impact of the COVID-19 pandemic on the primary endpoint has been added (section 2.3.5). The analyses will also be done for the confirmatory secondary endpoint CV death (section 2.4.1).

A section describing supplementary analyses assessing the impact of co-participation in COVID-19 trials on the primary endpoint has been added (section 2.3.6). The analyses will also be done for the confirmatory secondary endpoints (section 2.4.1).

For confirmatory secondary endpoints the significance level used in the hierachical testing procedure has been changed to follow a separate alpha spending function (section 2.4.1).

The supplementary analysis for all cause death has been changed to be a comparison of relative risks for the binary endpoint death/alive (section 2.4.1).

A statement regarding subjects with baseline eGFR below 15 ml/min/1.73m^2 being excluded from the analysis of the composite nephropathy endpoint has been removed, and a description on how the subject can meet the endpoint has been added (section 2.4.2.1).

Clarification of the exact definition of the different components in the nephropathy endpoint has been added (section 2.4.2.1).

Clarification as to how the ANCOVA for continuous secondary endpoints should be done has been added (section 2.4.2.2).

Clarification as to how the supplementary analysis of body weight addressing the secondary estimand should be done has been added (section 2.4.2.2)

For the analysis of smoking, details of the imputation model has been added (section 2.5).

It has been added that the glycaemic status of a subject is assessed by the investigator. Details on the imputation model for the analysis of glycaemic status has been added (section 2.5).

Change from baseline to week 104 for WRSSM total score has been changed from a supportive secondary endpoint to an exploratory endpoint (protocol v.6.0), and it has been added that it will be presented descriptively (section 2.5).

It has been added that the significance level for the confirmatory secondary endpoints will be updated based on the exact number of events and that all available data at end-of-trial are used for both secondary and exploratory endpoints (section 3.3).

The part describing that Novo Nordisk will replicate the interim analysis has been removed (section 3.3).

In general, editorial changes for alignment with SAPs for trials EX9924-4473 (SOUL) and NN9535-4321 (FLOW) has been made.

SAP version 3.0, dated 22-Apr-2022

The department name of the author has been updated

The composite HF endpoint has been inserted in the list of confirmatory secondary endpoints after CV death and before all-cause death in alignment with protocol version 7.0 (Section 1.1.2)

Details has been added to the description of baseline assesments (Section 2.2)

Two sensitivity analyses have been added. The analyses impute event times for those that are lost to follow-up or withdrawn, based on the observed event rates for subjects that either go permanently off treatment (first analysis) or at least go off treatment once. (Section 2.3.2 and 2.4.1)

For the subgroup analyses the following has been implemented: The wording of the ethnicity subgroups has been updated. Countries that aren't relevant have been removed from the Region subgroups, Mexico has moved from region "North America" to region "Other" and Serbia has moved from region "Other" to region "Europe". A chronic heart failure subgroup analysis has been added. (Section 2.3.4)

It has been added that if fewer than 10 subjects co-participate in COVID-19 trials the supplementary COVID-19 analyses will not be made. (Section 2.3.6)

The HF composite endpoint has been added in the testing hierarchy and where relevant in the following text. The supplementary analysis of HF composite with all-cause death has been moved from the section regarding secondary supportive endpoints. (Section 2.4.1 and 2.4.2.1)

It is clarified that for number of hospitalisations the comparisons at year 1,2,3 and 4 are descriptive. (Section 2.5)

It has been added that a small team at Novo Nordisk may be unblinded after the interim analysis if the recommendation from the DMC is to terminate the trial early for efficacy. (Section 3.1)

Where relevant the above changes is also reflected in the tables in the appendices (Section 6)

In general, small editorial changes to improve clarity of the text have been made.

5 References

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6 Appendix

Table 6-1 Handling of intercurrent events for the primary estimand and primary endpoint

Intercurrent event	Approach for estimand	MACE events available after intercurrent event	Statistical approach
Treatment discontinuations Medication modifying CV risk Bariatric surgery Initiation of chronic renal replacement therapy	Collect events irrespective of the intercurrent event	Yes	Use all available events irrespective of intercurrent event
Trial discontinuation (withdrawal and lost-to follow-up)	Attempts is made to collect vital events via indirect sources	Vital events potentially available	Censoring at time of discontinuation
Non-CV death	While alive perspective	No	Competing risks

Table 6-2 List of time-to-event endpoints

	Endpoint	Composite order/details *	EAC**	Competing risk
Primary				
	3-component MACE	- CV death - Non-fatal MI - Non-fatal stroke	Yes Yes Yes	Non-CV death
Confirmatory secondary				
	CV death	–	Yes	Non-CV death
	HF composite	- CV death - HHF or urgent HF Visit	Yes Yes	Non-CV death
	All-cause death	–	Yes	None
Supportive secondary				
	3-component MACE with all-cause death	- All-cause death - Non-fatal MI - Non-fatal stroke	Yes Yes Yes	None
	5-component MACE	- CV death - Non-fatal MI - Non-fatal stroke - Coronary revascularisation - Unstable Angina hospitalisation	Yes Yes Yes Yes Yes	Non-CV death
	Non-fatal MI	–	Yes	All-cause death
	Non-fatal stroke	–	Yes	All-cause death
	HHF or urgent HF Visit	–	Yes	All-cause death
	Coronary revascularisation	–	Yes	All-cause death
	Unstable angina hospitalisation	–	Yes	All-cause death
	$HbA_{1c} \geq 6.5\%$	Time to first $HbA_{1c} \geq 6.5\%$	No	All-cause death
	5-component nephropathy	- Renal death - Dialysis or transplantation - persistent eGFR < 15 ml/min/1.73m^2 - persistent ≥50% reduction in eGFR - Persistent macro albuminuria	Yes Yes No No No	Non-renal death
	Subjects with screening < 5.7% $HbA_{1c} \geq 5.7\%$	Time to first $HbA_{1c} \geq 5.7\%$	No	All-cause death
Exploratory				
	No of hospitalisations	Recurrent events	No	All-cause death
	No of hospitalisation days	Total length of stay in hospital	No	All-cause death

* For composite endpoints this defines the hierarchy of components when reporting events contributing to a composite endpoint in the situation of ties of date of events of the components

** EAC-confirmed event

Table 6-3 List of continuous and binary endpoints

Endpoint	Type	Details
Supportive secondary		
Subjects with screening ≥ 5.7% HbA_{1c} < 5.7% (yes/no)	Binary	At week 52, 104
Systolic BP	Continuous	Change from randomisation to week 104
Diastolic BP	Continuous	Change from randomisation to week 104
Pulse	Continuous	Change from randomisation to week 104
hsCRP	Continuous	Change from randomisation to week 104
Total cholesterol	Continuous	Change from randomisation to week 104
HDL	Continuous	Change from randomisation to week 104
LDL	Continuous	Change from randomisation to week 104
Triglycerides	Continuous	Change from randomisation to week 104
Body weight	Continuous	Change from randomisation to week 52, 104, 156, 208
Waist circumference	Continuous	Change from randomisation to week 104
HbA_{1c}	Continuous	Change from randomisation to week 52, 104, 156, 208
EQ-5D-5L index score	Continuous	Change from randomisation to week 104
EQ-5D-VAS score	Continuous	Change from randomisation to week 104
Exploratory		
Smoker (yes/no)	Binary	Smoker at week 52, 104
Glycaemic deterioration (yes/no)	Binary	Change from randomisation to week 117
WRSSM total score	Continuous	Change from randomisation to week 104

For analyses at visits later than week 52, the analysis will only be done if less than 10% of subjects from FAS have missed the relevant visit due to trial termination earlier than planned.

Table 6-4 Overview of planned analyses for all endpoints

Endpoint	Model/method	Summary measure	Sensitivity analysis	Supplementary analyses
Primary				
3-component MACE	Cox	Hazard ratio	Tipping point Analysis with imputations from subjects permanently off treatment Analysis with imputations from subjects off treatment	- Risk difference at year 3 - On-treatment - Subgroup analyses -non-CV death - Excluding MACEs concurrent with COVID-19 SAE -Excluding MACEs concurrent with COVID-19 AE -Including non-CV deaths with concurrent COVID-19 SAE -Censoring subjects who co-participates in COVID-19 trials
Confirmatory secondary				
CV death	Cox	Hazard ratio	–Analysis with imputations from subjects permanently off treatment Analysis with imputations from subjects off treatment	- Risk difference at year 3 - On-treatment - Excluding CV deaths concurrent with COVID-19 SAE -Excluding CV deaths concurrent with COVID-19 AE -Including non-CV deaths with concurrent COVID-19 SAE -Censoring subjects who co-participates in COVID-19 trials
HF composite	Cox	Hazard ratio	–Analysis with imputations from subjects permanently off treatment Analysis with imputations from subjects off treatment	- Risk difference at year 3 - On-treatment - Excluding HF composite events concurrent with COVID-19 SAE -Excluding HF composite events concurrent with COVID-19 AE -Including non-CV deaths with concurrent COVID-19 SAE -Censoring subjects who co-participates in COVID-19 trials Including all-cause death
All-cause death	Cox	Hazard ratio	–Analysis with imputations from subjects permanently off treatment Analysis with imputations from subjects off treatment	- Risk difference at year 3 - On-treatment - Relative risk extended in-tr period -Censoring subjects who co-participates in COVID-19 tria
Supportive secondary				

	3-component MACE with all-cause death	Cox	Hazard ratio	–	–
	5-component MACE	Cox	Hazard ratio	–	Including all-cause death
	Non-fatal MI	Cox	Hazard ratio	–	Including fatal MI
	Non-fatal stroke	Cox	Hazard ratio	–	Including fatal stroke
	HHF or urgent HF Visit	Cox	Hazard ratio	–	–
	Coronary revascularisation	Cox	Hazard ratio	–	–
	Unstable angina hospitalisation	Cox	Hazard ratio	–	–
	$HbA_{1c} \geq 6.5\%$	Cox	Hazard ratio	–	–
	5-comp nephropathy	Cox	Hazard ratio	–	–
	Screening $< 5.7\%$ $HbA_{1c} \geq 5.7\%$	Cox	Hazard ratio	–	–
	Screening $\geq 5.7\%$ $HbA_{1c} < 5.7\%$	Logistic regression	Odds ratio	–	Logistic regression at week 52
	Systolic BP	ANCOVA w MImp	Mean difference	–	–
	Diastolic BP	ANCOVA w MImp	Mean difference	–	–
	Pulse	ANCOVA w MImp	Mean difference	–	–
	hsCRP	Log-ANCOVA w MImp	-Geometric mean ratio	–	–
	Total cholesterol	Log-ANCOVA w MImp	Geometric mean ratio	–	–
	HDL	Log-ANCOVA w MImp	Geometric mean ratio	–	–
	LDL	Log-ANCOVA w MImp	Geometric mean ratio	–	–
	Triglycerides	Log-ANCOVA w MImp	Geometric mean ratio	–	–
	Body weight	ANCOVA w MImp	Mean difference	J2R-MImp	MMRM year 1. ANCOVA at week 52, 156* and 208*
	Waist circumference	ANCOVA w MImp	Mean difference	–	–
	HbA_{1c}	ANCOVA w MImp	Mean difference	–	ANCOVA at week 52, 156* and 208*
	EQ-5D-5L index score	ANCOVA w MImp	Mean difference	–	–
	EQ-5D-VAS score	ANCOVA w MImp	Mean difference	–	–
				–	–
Exploratory					
	Smoker	Logistic regression	Odds ratio	–	–Logistic regression at week 52
	Glycaemic deterioration	Logistic regression	Odds ratio	–	–
	Number of hospitalisations	Mean regression	Mean ratio	–	
	Number of hospitalisation days	Pseudo-observations	Mean ratio	–	Year 1,2,3,4

*Only if less than 10% of subjects from FAS have missed the relevant visit due to trial termination earlier than planned
On-treatment = Secondary estimand; ANCOVA w MImp = Analysis of covariance with multiple imputation;
log-ANCOVA w MImp = ANCOVA on log-transformed assessments with multiple imputation;
J2R-MImp= jump to reference multiple imputation; MMRM = mixed model for repeated measurements

Clinical Trial Report

Trial ID: EX9536-4388 (SELECT)

MedDRA searches for safety focus areas

Author

Table of contents

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List of abbreviations and definitions of terms

AE	Adverse event
HLT	High level term
MedDRA	Medical Dictionary for Regulatory Activities
NEC	Not elsewhere classified
NNMQ	Novo Nordisk MedDRA query
PT	Preferred term
SMQ	Standardised MedDRA query
SOC	System organ class

MedDRA searches for safety focus areas in project EX9536

The MedDRA search strings in this document (ordered alphabetically) were used for the EX9536 submission documents. The MedDRA version used was 26.0.

1 Abuse and Misuse

Custom query (NNMQ Abuse and Misuse):

- SMQ Drug abuse and dependence, all terms (note contains only narrow terms)
- HLT Intentional product misuses (contains only primary terms)
- Additional PTs:
    - Poisoning deliberate
    - Intentional dose omission
    - Performance enhancing product use
    - Completed suicide
    - Intentional self-injury
    - Suicide attempt
    - Assisted suicide
    - Suspected suicide attempt
    - Suspected suicide.

2 Acute renal failure

SMQ Acute renal failure, narrow terms only.

3 Allergic reactions

Custom Query (NNMQ Allergic reactions) – only narrow terms from the following:

- SMQ Anaphylactic reaction
- SMQ Angioedema
- SMQ Severe cutaneous adverse reactions
- SMQ Anaphylactic/anaphylactoid shock conditions
- SMQ Hypersensitivity

4 Appendicitis

Custom Query (NNMQ Appendicitis) – with the following PTs :

- Appendiceal abscess
- Appendicectomy
- Appendicitis
- Appendicitis noninfective
- Appendicitis perforated
- Appendix disorder
- Stump appendicitis
- Complicated appendicitis

5 Covid 19

SMQ Covid 19, narrow terms only.

6 Cardiovascular disorders

SOC Cardiac disorders, primary terms only.

7 Drug-related hepatic disorders

SMQ Drug related hepatic disorders - comprehensive search, all terms.

8 Eye disorders

SOC of Eye disorders, primary terms only.

9 Gallbladder-related disorders

Custom query (NNMQ Gallbladder-related disorders). Narrow terms from the following:

- SMQ Functional, inflammatory and gallstone related biliary disorders
- SMQ Infectious biliary disorders

10 Gastrointestinal disorders

Custom query (NNMQ Gastrointestinal disorders SOC):

- SOC Gastrointestinal disorders, primary terms only

11 Hypoglycaemia

SMQ Hypoglycaemia, narrow terms only.

12 Malignant neoplasms

SMQ Malignant tumours, all terms (note contain only narrow terms).

13 Medication errors

SMQ Medication errors, all terms.

14 Pancreatitis

Custom query (NNMQ Pancreatitis):

- SMQ Acute pancreatitis), narrow terms only

- HLT Acute and chronic pancreatitis, primary and secondary terms

15 Rare events

Custom query (NNMQ Rare events) excluding events that are included in other safety focus areas. The following is included:

- SMQ Agranulocytosis, narrow terms only
- SMQ Guillain-Barre syndrome, narrow terms only
- SMQ Haematopoietic cytopenias affecting more than one type of blood cell, broad and narrow terms
- SMQ Haematopoietic leukopenia, broad and narrow terms
- SMQ Haematopoietic thrombocytopenia, narrow terms only
- SMQ Interstitial lung disease, narrow terms only
- SMQ Neuroleptic malignant syndrome, narrow terms only
- SMQ Pseudomembranous colitis, narrow terms only
- SMQ Retroperitoneal fibrosis, narrow terms only
- SOC Congenital, familial and genetic disorders, (all terms are primary PTs)
- HLT Angioedemas, primary and secondary routed PTs
- HLT Glomerulonephritis and nephrotic syndrome, primary and secondary routed PTs
- HLT Nephritis NEC, primary and secondary routed PTs
- Additional PTs:
    - Disseminated intravascular coagulation
    - Hepatic lymphocytic infiltration
    - Multiple organ dysfunction syndrome

16 Suicide/self-injury

SMQ Suicide/self-injury, all terms (note contain only narrow terms).

17 Suspected transmission of an infectious agent

Custom Query (NNMQ Transmission). Primary terms from the following:

- HLT Infectious disorder carrier
- HLT Infectious transmissions