Cover Page for SAP

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FLOW – Effect of semaglutide versus placebo on the progression of renal impairment in subjects with type 2 diabetes and chronic kidney disease

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List of abbreviations

ANCOVA	analysis of covariance
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease - epidemiology collaboration
CV	cardiovascular
DBL	data base lock
DMC	data monitoring committee
EAC	event adjudication committee
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
EQ-5D-5L	five-level version of the EuroQol five-dimensional questionnaire
FAS	full analysis set
HbA_{1c}	glycosylated haemoglobin
HR	hazard ratio
LTFU	lost to follow-up
MACE	major adverse cardiovascular event
MALE	major adverse limb event
MI	myocardial infarction
MImp	multiple imputation
SAP	statistical analysis plan
s.c.	subcutaneously
TTE	time-to-event
UACR	urinary albumin-to-creatinine ratio

1 Introduction

1.1 Trial information

1.1.1 Rationale

Chronic kidney disease (CKD) and diabetes often co-exist and for most of cases, the kidney damage and/or reduced kidney function is caused directly by longstanding and poorly controlled diabetes. Improved glycaemic control has been suggested to reduce the progression of CKD in type 2 diabetes (T2D) and both glycaemic and blood pressure control are key recommendations in international treatment guidelines for CKD in T2D. Yet there remains a major unmet medical need to improve the treatment of CKD in subjects with T2D. The purpose of this trial is to demonstrate that semaglutide s.c. delays the progression of renal impairment and lowers the risk of renal and cardiovascular (CV) mortality in subjects with T2D and CKD.

1.1.2 Objectives, endpoints and estimand

The primary objective is to demonstrate that semaglutide delays the progression of renal impairment and lowers the risk of renal and cardiovascular mortality compared to placebo, both added to standard-of-care, in subjects with type 2 diabetes and chronic kidney disease.

The key secondary objectives are to compare the effect of treatment with semaglutide versus placebo, both added to standard-of-care in subjects with type 2 diabetes and chronic kidney disease with regards to cardiovascular morbidity, peripheral artery disease, glycaemic control, body weight, blood pressure and safety.

The primary endpoint is time to first occurrence of a composite endpoint consisting of: Onset of persistent ≥ 50% reduction in estimated glomerular filtration rate (eGFR) (CKD-EPI) compared with baseline, onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2, initiation of chronic renal replacement therapy (dialysis or kidney transplantation), renal death, or cardiovascular death.

The key secondary endpoints are annual rate of change in eGFR (CKD-EPI) (total eGFR slope), time to first occurrence of a composite major adverse cardiovascular event (MACE) endpoint (consisting of: non-fatal myocardial infarction, non-fatal stroke, or CV death) and all-cause death.

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

1.1.3 Overall design

This is a multi-centre, international, randomised, double-blind, parallel-group, placebo-controlled trial comparing semaglutide 1.0 mg versus placebo both administered s.c. once weekly and added to standard-of-care in subjects with T2D and pre-existing CKD. Subjects are randomised 1:1 to receive either semaglutide or placebo. Randomisation is stratified by use of sodium glucose cotransporter-2 (SGLT-2) inhibitors (yes/no) at baseline. The number of subjects with inclusion eGFR ≥ 60 mL/min/1.73 m^2 is capped at approximately 20%.

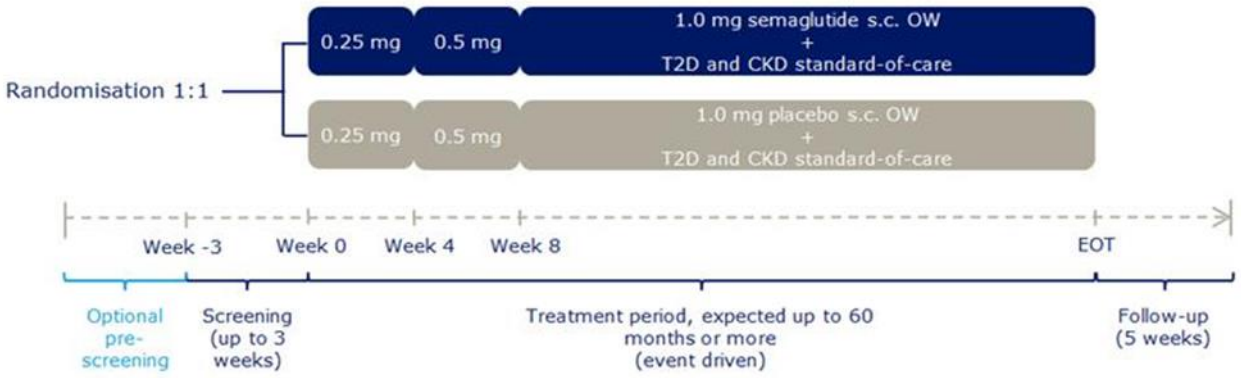
The trial is event driven; therefore, end of trial is scheduled according to accrual of events. The trial employs a group sequential design with one interim testing for superiority. Under the design assumptions, the trial duration is approximately 61 months following randomisation of the first subject and 3,508 subjects are planned to be randomly assigned to trial products.

If the trial is not stopped for superiority at the planned interim testing the trial is terminated when both of the following criteria are fulfilled:

- A minimum of 854 primary endpoint events
- A minimum of 515 primary renal endpoint events (components of the primary endpoint except CV death)

A schematic overview of the trial design is shown in Figure 1.

Figure 1 Trial design



1.2 Scope of the statistical analysis plan

The SAP includes elaborations on statistical analyses outlined in the protocol for the FLOW trial (NN9535-4321) as well as details on the interim testing for superiority. Any changes to the SAP after first subject first visit are 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 planned statistical analyses and in general reporting of data but will remain blinded to treatment allocations until data base lock (DBL). Additionally, another statistician independent of trial conduct, the DMC analyses, interim analysis, and external to Novo Nordisk will independently confirm the statistical analyses of the primary endpoint and secondary confirmatory endpoints. This statistician will also be blinded until 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 versus 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 0.80 a total of 854 primary endpoint events are required.

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

- annual primary endpoint rate in the placebo group of 7.5%
- uniform recruitment in 21 months
- annual lost to follow-up rate in both treatment groups of 1%
- trial duration of five years and five weeks

Under these assumptions, a total of 3,508 subjects are needed for randomisation.

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 1 provides the boundaries based on analyses performed after 570 (interim) and 854 (scheduled termination) events, along with the approximate hazard ratio estimates that correspond to those boundaries if the analyses are timed exactly to that schedule. The actual stopping boundaries will be based on the exact number of events available for the interim analysis.

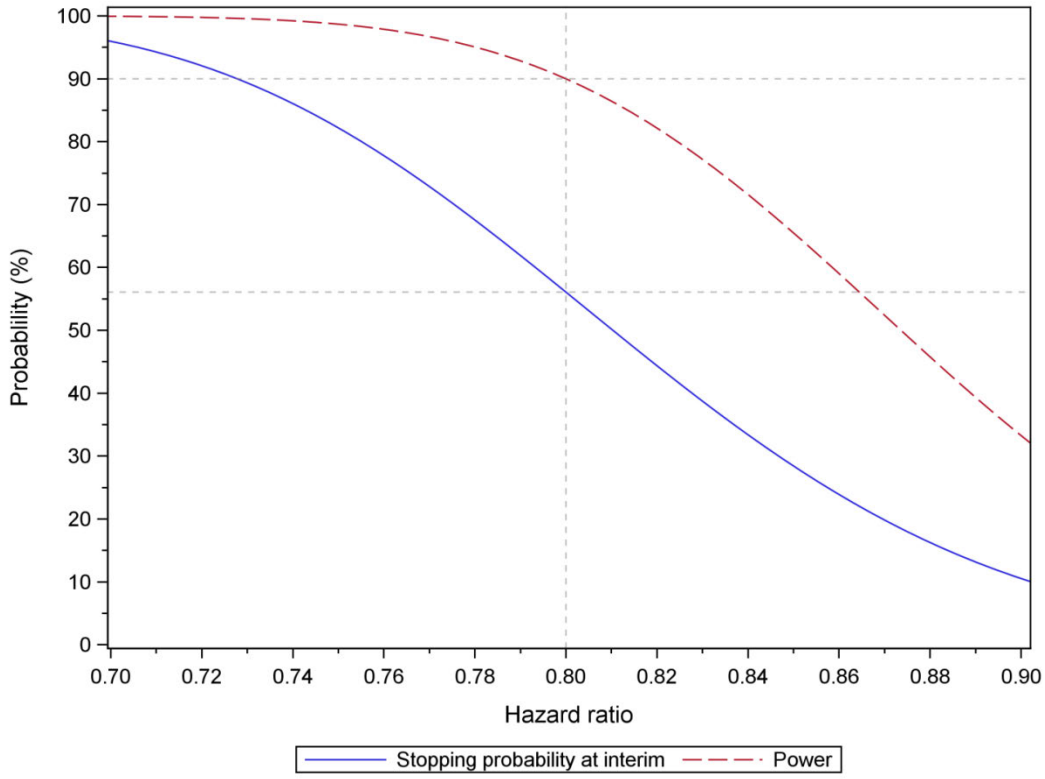
Table 1 Stopping boundary scales at interim and scheduled termination

Stopping boundary scale	Interim 570 events	Scheduled termination 854 events
Hazard ratio	0.8103	0.8725
Nominal significance level	0.00605	0.02314

Figure 2 below shows the probability of stopping the trial early at the interim (blue curve) and the overall power for confirming superiority for the primary endpoint (dashed red curve) as a function of alternative values for the true HR. The design HR of 0.80 is marked with a dashed vertical

reference line. The stopping probability at the interim and overall power for the design HR of 0.80 can be seen to be 56% and 90%, respectively.

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



Confirmatory secondary endpoints

If superiority is confirmed for the primary endpoint the below confirmatory secondary endpoints are controlled for multiplicity through a hierarchical testing strategy. The marginal powers below are calculated under the assumptions that the trial continues to the scheduled termination, a significance level of 2.5% (one-sided) and 3,508 randomised subjects.

The confirmatory secondary endpoint, annual rate of change in eGFR, is analysed using a linear random regression model. Under the assumptions of a difference in annual slope of 1 mL/min/1.73 m^2 between treatment groups, a between subject variance for the slope of 20 and a residual variance of 45, the marginal power is >99%. For an annual rate of decline in the placebo group of 4 mL/min/1.73 m^2, a difference of 1 mL/min/1.73 m2 corresponds to a 25% reduction in the annual decline with semaglutide versus placebo.

Assuming a hazard ratio of 0.8, an annual loss rate of 1% and an annual event rate of 7% in the placebo group for the confirmatory secondary MACE endpoint, the marginal power for confirming superiority is 89%.

With similar assumptions for hazard ratio and loss rate and assuming an event rate of 5% in the placebo group, the marginal power for the third confirmatory secondary endpoint, time to all-cause death, is 78%.

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 hypothesis of superiority. For reporting of results, the hazard ratio and the 95% CI are accompanied by the two-sided p-value.

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

Unless otherwise specified, baseline value is defined as the eligible measurement associated with the randomisation visit (V2), 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 the screening visit (V1) is used as the baseline assessment, if available. If more than one measurement is associated with the same visit, the earliest measurement is considered eligible. For eGFR, the baseline assessment is defined as the mean of the two assessments from the randomisation visit (V2) (if taken before or at the date of first dose) and the screening visit (V1). If only one of the assessments is available, this is used as the baseline assessment. For UACR, the baseline assessment is defined as the mean of the two assessments from the randomisation visit (V2) if these are taken before or at the date of first dose. If only one of the assessments is available, this is used as the baseline assessment. If no assessments are available from V2, then assessment from the screening visit (V1) will be used.

Missing data are defined as data that are planned to be collected and could have been collected 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 who 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.

Assessments of UACR or eGFR taken after initiation of chronic renal replacement therapy will not be used for analyses or summary tables.

2.2.1 Definition of analysis sets

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 who either attends the 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. Trial completion will be 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 and 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.

Secondary estimand (on-treatment)

This estimand covers the primary and confirmatory secondary 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. Intercurrent events

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

- randomised treatment adherence
- change in background medication modifying cardio-renal risk e.g. change in dose of current medication or initiation of additional medication
- 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 confirmatory endpoints is described in Table 4.

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

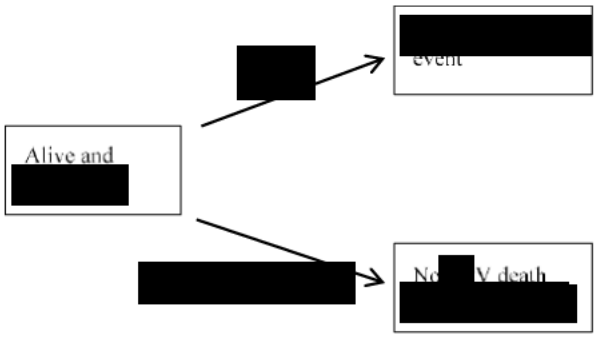
Time-to-event endpoints are in general time-to-first-event endpoints but are for simplicity denoted time-to-event (TTE) endpoints.

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 follow-up visit. For this reason, any event occurring after the in-trial observation period is not included in analyses, unless otherwise stated.

If a subject experiences 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, death not being of cardiovascular or renal aetiology is a competing risk terminating the observation for the event of interest. Figure 3 illustrates competing risk as a multi-state model for the primary endpoint. The hazard rate of interest is denoted by $\lambda(t)$, t being time since randomisation.

Figure 3 Multi-state model illustrating competing risk for the primary endpoint



Unless otherwise specified, the statistical analyses of TTE endpoints are done by using a stratified Cox proportional hazards model under the assumption of independent censoring. Stratification is use of SGLT-2 inhibitors (yes/no) at baseline. Terminated observations (due to competing risks) are technically treated as censored observations but are not part of the independent censoring

assumption. The population-level summary measure for TTE endpoints is the HR for semaglutide versus 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 competing risks.

Table 5 gives an overview of the TTE endpoints including any competing risk and whether the TTE endpoint is EAC-confirmed.

2.3 Primary endpoint

Time to first occurrence of a composite endpoint consisting of:

- Onset of persistent ≥ 50% reduction in eGFR (CKD-EPI) compared with baseline
- Onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2
- Initiation of chronic renal replacement therapy (dialysis or kidney transplantation)
- Renal death
- CV death

For the eGFR components, 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 definition.

When classifying chronic renal replacement therapy or kidney transplantation, the date of event is the EAC-confirmed date of initiation of the therapy or surgery, respectively.

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

In the case that only a single eGFR value fulfils the criteria of ≥50% reduction in eGFR compared with baseline or eGFR <15 mL/min/1.73 m^2 without any confirmatory sample Table 2 provides data handling rules for defining primary endpoint events. Any eGFR assessment made after initiation of chronic renal replacement therapy will not qualify as a confirmatory eGFR value.

Table 2 Data handling rules for eGFR components of the primary endpoint in the absence of a confirmatory test

Rule number	**Event:** One eGFR value fulfilling the criteria * with a subsequent event without any confirmatory eGFR value measured >=4 weeks after the first eGFR measurement being available.	**eGFR event**	**Date of event**
1	CV or renal death	No	Date of death
2	Non-CV and non-renal death	No	Not applicable
3	Initiation of chronic renal replacement therapy	No	Date of initiation
4	Lost-to-follow-up or withdrawal of consent	No	Not applicable

5	One eGFR value fulfilling the criteria* at the end of trial visit (V-FU)	No	Not applicable

* ≥50% reduction in eGFR compared with baseline or eGFR <15 mL/min/1.73 m^2

A persistent outcome in eGFR in the in-trial period is considered on-treatment if the first of the two consecutive measurements falls within the on-treatment period, irrespective of whether the confirmatory eGFR value falls within the on-treatment period or not.

2.3.1 Primary analysis

The primary analysis will address the primary estimand (intention-to-treat). The HR for comparing semaglutide versus placebo is estimated from a stratified Cox proportional hazards model with treatment (semaglutide, placebo) as fixed factor together with the 2-sided 95% confidence interval and one-sided p-value for hypothesis testing. Stratification is use of SGLT-2 inhibitors (yes/no) at baseline.

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 versus 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.

In the primary analysis missing data for scheduled central laboratory eGFR values due to e.g. missing blood samples while subjects are still being followed are not imputed, implicitly assuming no eGFR component events observed during the in-trial observation period with missing eGFR values.

Competing risk from non-CV, non-renal death is handled as censorings in the Cox analysis as described in section 2.2.4.

Please refer to Table 4 for handling of other intercurrent events.

2.3.2 Sensitivity analyses

Tipping point

If superiority is established for the primary endpoint, the following sensitivity analysis is 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)[1] 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 primary endpoint events 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 penalties (in each of the treatment groups) needed to turn around the superiority conclusion. A range of plausible penalties will be specified based on blinded data and before DBL.

Retrieved dropout

To further investigate the potential impact of missing data for subjects who withdraw consent or are lost to follow-up, two additional sensitivity analyses will be performed by multiple imputing event times for these subjects using the retrieved dropout approach as described in He et al (2022)[2].

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 (or death).

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 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:

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, 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.

The off-treatment event time data are fitted within treatment arms to a piecewise exponential model using Bayesian analysis and accounting for censoring. The event rate is modelled to be constant within 3 intervals that are chosen such that the intervals contain roughly the same number of events. A noninformative improper prior distribution is used for the rate parameters in each treatment arm. 500 replicates of the off-treatment event rates are then randomly sampled from the posterior distribution.

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 off-treatment event time is imputed by sampling from the corresponding piecewise exponential model conditional on being event-free from treatment discontinuation until the original censoring date. The imputed off-treatment event time is rounded up to whole days and added to the end of the on-treatment observation period. If it 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.

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

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 the selection of retrieved dropouts and the observation period during which the subjects are considered to be on treatment. 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 off-treatment event time is calculated from a start date set to the day after the end of the first on-treatment observation period.

Imputation of missing eGFR values

In the primary analysis, missing data for scheduled central laboratory eGFR values are not imputed. The following sensitivity analysis using multiple imputation is planned. Prior to analysis, missing data are imputed using multiple imputation generating 500 data sets to account for the inherent uncertainty. The imputation is performed separately for each treatment group. In the first step, intermittent missing values are imputed using the Markov Chain Monte Carlo method based on an assumption of multivariate normality. In the second step, imputation of monotone missing values is done within subject groups defined by the treatment group and based on a sequential univariate regression approach. At each scheduled visit starting with the first post-baseline visit the imputation model includes use of SGLT-2 inhibitors (yes/no) at baseline as fixed factor and baseline value and the previous post-baseline scheduled values (observed and imputed) prior to the visit being imputed as covariates. For each eGFR component of the primary endpoint it is evaluated whether an eGFR event has occurred (yes/no) within the in-trial observation period. Intermittent imputed data are excluded from this evaluation.

After imputation of missing eGFR data, the primary composite endpoint is derived, and the 500 multiple-imputed data sets are analysed with the primary stratified Cox proportional hazards model described above. Subjects that do not experience a primary endpoint event during the in-trial observation period are censored at the in-trial observation period end date. The resulting estimates of the log(HR) are combined using the methods of Rubin and back transformed to HR scale to draw inference.

Use of local laboratory serum creatinine values

This sensitivity analysis of the primary analysis will use all collected data of eGFR values including conversion of local laboratory creatinine values and central laboratory data. Conversion of local laboratory creatinine values will be performed based on availability of demographic factors necessary for the conversion. If race is not available for a subject, e.g. due to country specific requirements, local laboratory creatinine values will not be included in the analysis. No imputation of missing data is done in this analysis.

Only eGFR from scheduled visits as potential event times

For the primary analysis, subjects are supposed to have an eGFR measurement collected at an unscheduled visit in case a local laboratory creatinine value indicates a potential ≥50% reduction in eGFR or eGFR <15 mL/min/1.73 m^2. In order to investigate the impact of potential differences in when and how often eGFR is measured in the two arms, this sensitivity analysis of the primary analysis will only consider eGFR values from central laboratory collected in connection with scheduled visits as potential eGFR events. Any central laboratory value can serve as confirmatory test to confirm persistency but only data from scheduled visit can serve as the first of the two consecutive measurements.

2.3.3 Supplementary analyses

The following supplementary analyses are planned for the primary endpoint:

- Absolute risk difference: Estimation of the absolute risk difference (and 95% CI) at 2 and 3 years between semaglutide and placebo based on the Aalen-Johansen estimator for the cumulative incidence function. The risk difference will be estimated using a generalized linear regression model with identity link function on the pseudo-observations from the Aalen-Johansen estimate at the specified time point, as described in Andersen & Perme (2010)[3]. Treatment and use of SGLT-2 inhibitors (yes/no) at baseline will be included as fixed factors in the regression model.
- On-treatment: Analysis addressing the secondary estimand using a Cox proportional hazards model, and the first on-treatment observation period.
- Additionally, an analysis of non-CV, non-renal death using the same Cox model as for the primary endpoint will be done to evaluate the influence of the competing risk non-CV, non-renal 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: Female, Male
- Age < 65 years (yes/no)
- Age: <65, 65≤ to <75, ≥75 years
- Region: Europe, North America, Asia, Other. The regions are defined as
    - Europe: Belgium, Bulgaria, France, Germany, Greece, Hungary, Italy, Netherlands, Poland, Slovakia, Spain, United Kingdom
    - North America: Canada, United States
    - Asia: Australia, China, India, Israel, Japan, Malaysia, Thailand, Turkey
    - Other: Argentina, Brazil, Mexico, Russia, South Africa, Ukraine
- Race: White, Black or African-American, Asian, Other
- Duration of T2D < 15 years (yes/no)
- Ethnicity: Hispanic/Latino, Not Hispanic or Latino
- $HbA_{1c} \leq 8.0\%$ (yes/no)
- BMI ≤ 30 kg/m^2 (yes/no)
- Prior MI or stroke (yes/no)
- Metformin use (yes/no)

- Insulin use (yes/no)
- SGLT-2i use (yes/no)
- Chronic heart failure (yes/no)
- eGFR (≤45, 45-60, ≥60 mL/min/1.73 m^2 (CKD-EPI))
- eGFR: < 30, 30 ≤ to < 45, 45 ≤ to < 60, ≥ 60 mL/min/1.73m2 (CKD-EPI)
- UACR <300 mg/g (yes/no)

The subgroup analyses are based on stratified Cox proportional hazards models with an interaction between treatment group (semaglutide, placebo) and the specific subgroup as a factor and stratified for use of SGLT-2 inhibitors (yes/no) at baseline.

2.3.5 Supplementary analyses evaluating impact of the COVID-19 pandemic

The following supplementary analyses will be made to assess the potential impact of the COVID-19 pandemic on the primary endpoint:

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

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

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

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

2.3.7 Supplementary analysis using CKD-EPI equation not including race

The equation used for estimating eGFR (CKD-EPI) for the primary endpoint incorporates age, sex and race. To fight racial bias in clinical trials a new equation where race is not incorporated has been introduced, as described in Inker et al. (2021)[4]. A supplementary analysis will be made using this new equation where race is not included to estimate eGFR using the same model as for the primary analysis described in section 2.3.1.

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 three confirmatory secondary endpoints under multiplicity control via a stagewise hierarchical testing scheme using the following order:

1. Annual rate of change in eGFR (total eGFR slope)
2. Time to first occurrence of MACE
3. Time to occurrence of all-cause death

For the type I error rate to be strongly controlled at a one-sided level of 2.5% (Glimm et al (2010)[5]) the same alpha-spending function and information proportion *t* as for the primary endpoint (section 2.1) is used for the confirmatory secondary endpoints.
No adjustments of the results for the confirmatory secondary endpoints due to the group sequential design will be done.

Table 3 provides an example of the nominal significance levels at interim and scheduled termination in when the interim testing is conducted at exactly 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 3 Nominal significance level for confirmatory secondary endpoints at interim and scheduled termination – an example

Stopping boundary scale	Interim	Scheduled termination
Nominal significance level	0.00605	0.02314

Annual rate of change in eGFR (total eGFR slope)

The annual rate (slope) of change in eGFR is compared between treatment groups based on a linear random regression model on eGFR values with treatment, use of SGLT-2 inhibitors (yes/no) at baseline, time (as a continuous variable) and treatment time interaction as fixed effects, and including subject effect as a random intercept and time as a random slope. The random intercept and slope is assumed to be bivariate normal distributed with mean zero and an unstructured covariance matrix. The independent error term is assumed to be identical univariate normal distributed with mean zero. The model is fitted to observed scheduled central laboratory data from baseline and post-baseline, excluding data from confirmatory testing. The parameter of interest is the regression coefficient for the treatment and time interaction term, which measures the slope difference between semaglutide and placebo.

Two sensitivity analyses will also be done for the eGFR slope analysis.

The first analysis will be done using a joint model (shared parameter model as described in Vonesh et al (2006)[6]) with two submodels: a longitudinal model and a time-to-event model with time to first occurrence of either all-cause death or chronic renal replacement therapy. The longitudinal submodel will be similar to the random slope model described above and the time-to-event submodel will be a (proportional hazard) Weibull model with treatment and use of SGLT-2 inhibitors (yes/no) at baseline as covariates and with shared random effects added from the longitudinal model where each random intercept and random slope will be multiplied with a parameter respectively (random coefficients). As above, the random intercept(s) and random slope(s) by subject is assumed to follow a bivariate normal distribution with mean zero and a unstructured covariance matrix. The mean slopes derived from the longitudinal submodel may be thought of as the mean eGFR slope where eGFR trajectories have been hypothesized to be measured beyond death or renal replacement therapy through the association between the two submodels. The parameter of interest is the regression coefficient for the treatment by time interaction term in the longitudinal submodel. Effectively, the model will account for subjects with missing eGFR values due to death or renal replacement therapy having a steeper eGFR decline compared to subjects who are still in the trial and contributing with eGFR values.

In the second analysis, unobserved eGFR values due to initiation of renal replacement therapy or death will be multiple imputed with unfavourable eGFR values (<15mL/min/1.73 m2) and the resulting treatment estimates will be combined using Rubin's rule.

A supplementary analysis using the first on-treatment period as for the primary endpoint will also be done.

To evaluate the impact of the COVID-19 pandemic and co-participation in COVID-19 treatment or prevention trials, the following supplementary analyses will be done:

1. Exclusion of all eGFR values measured concurrently with a COVID-19 SAE.
2. Exclusion of all eGFR values measured concurrently with a COVID-19 AE.
3. Exclusion of all eGFR values measured after first trial treatment for preventing or treating COVID-19 in subjects co-participating in a COVID-19 treatment or prevention trial. If less

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

An eGFR value is considered measured concurrently with a COVID-19 (S)AE if the measurement is taken in the time period from the start day of the COVID-19 (S)AE and until 30 days after the last of the following two dates: the stop date of the COVID-19 (S)AE or the end of hospitalisation date for a hospitalisation reported together with the COVID-19 (S)AE.

MACE and all-cause death

The confirmatory secondary time-to-event endpoints are analysed using the stratified Cox proportional hazards model as described for the primary endpoint.

For time to first occurrence of MACE, 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.

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 lost to follow-up. The relative risk for the binary endpoint death/alive will be compared between the two treatment groups based on confidence intervals calculated using the Mantel-Haenszel method and a p-value calculated based on the Cochran-Mantel-Haenszel general association statistic stratified by use of SGLT-2 inhibitor (yes/no) at baseline. The model is chosen because it does not depend on the observation time which is only extended for subjects withdrawn or LTFU.

For time to first MACE, a supplementary analysis will be done by replacing the CV death component with all-cause death.

The retrieved dropout sensitivity analyses and the supplementary analyses described in section 2.3.2 and 2.3.3 for the primary endpoint, will similarly be done for MACE and all-cause death, except the analysis assessing non-CV, non-renal death..

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 MACE. The analysis assessing the potential impact of co-participation in COVID-19 trials in section 2.3.6 will be done for both MACE and all-cause death. If less than 10 subjects have co-participated in COVID-19 treatment or prevention trials then this analysis will not be performed.

2.4.2 Supportive secondary endpoints

Each of the supportive secondary time-to-event endpoints is analysed with a similar stratified Cox proportional hazards model as for the primary endpoint, see also Table 5.

For the two time-to-event endpoints “Onset of persistent ≥50% reduction in eGFR” and “Onset of persistent eGFR <15 mL/min/1.73 m^2” an event of initiation of chronic renal replacement therapy acts as competing risk. For these two endpoints subject will be censored in the Cox model at time of initiation of chronic renal replacement therapy. In case of one eGFR measurement fulfilling the criteria and no available confirmatory test, the data handling rules are as described for the primary endpoint (Table 2).

For the endpoint "Onset of persistent ≥50% reduction in eGFR" only subjects with a valid baseline value will be included in the analysis.

Annual rate of change in eGFR (chronic slope) is analysed similarly to the total eGFR slope using only eGFR values from week 12 and onwards.

The continuous supportive secondary endpoints (change from randomisation) are analysed using multiple imputation for missing values. An imputation model (linear regression) is estimated separately for each treatment group including baseline value and use of SGLT-2 inhibitors (yes/no) at baseline as covariates and fitted to subjects having an observed data point (irrespective of adherence to randomised treatment) at the endpoint-time (12 weeks or 3 years). Subjects without a baseline measurement will not be a part of the model. . If 10% or more of subjects from FAS have missed the year 3 visit due to trial termination earlier than planned (stopping after interim testing or event rates higher than expected) these secondary endpoints will be evaluated as change to 2 years. The fitted model is used to impute values for all subjects with missing data (see section 2.2) at the endpoint-time to create 500 complete data sets. The completed data sets are analysed by an analysis of covariance model with treatment group and use of SGLT-2 inhibitors (yes/no) at baseline as fixed factors and baseline value as covariate. Rubin's rule is used to combine the results. Relative change in UACR is done on the logarithmic scale.

Table 6 gives an overview of the continuous endpoints.

Mean number of severe hypoglycaemic episodes is plotted as a function of study time and analysed using a marginal mean regression model for recurrent events accounting for competing risk of dying, as described in Ghosh & Linn (2000)[7] Ghosh & Linn (2002)[8]. Treatment group and use of SGLT-2 inhibitors (yes/no) at baseline are used as fixed factors and treatment effect is reported as mean ratio and corresponding 95% robust CI to account for the dependency of within-subject of recurrent events.

2.5 Exploratory endpoints

The exploratory endpoints are analysed like the continuous supportive secondary endpoints.

2.6 Other assessments

All systematically collected AEs, i.e. serious AEs and non-serious events requiring additional data collection as well as COVID-19 AEs 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.

3 Interim testing

The trial design includes *one* pre-planned interim testing for superiority of the primary endpoint. The planned timing is when 570 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 analysis cut-off date for the interim testing.

Subjects without a 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
- analysis cut-off date

The same stratified Cox model as described in section 2.3 is used for the interim testing addressing the primary estimand. Similarly, the data handling rules described in the same section applies.

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 above 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.

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.

Recommendations from the DMC back to Novo Nordisk and any other party will exclude any details of the interim results in order to maintaining trial integrity.

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 testing and end-of-trial as well as additional confirmed events that were undergoing adjudication at the 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 854 primary endpoint events and a minimum of 515 primary renal endpoint events have been accrued. If less than 515 out of 854 accrued primary endpoint events are renal events, the trial will continue until 515 renal events have been accrued. The exact number of primary endpoint 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 levels for the confirmatory secondary endpoints are 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) are adjusted for the group sequential design using the likelihood ratio ordering.

4 Changes to the statistical analyses plan

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

SAP version 1.0 dated 07-APR-2019

Changes and additions to protocol version 2.0 dated 07-Dec-2018:

- Primary analysis for the primary endpoint changed to not include multiple imputation for missing eGFR data. Instead multiple imputation is applied in a sensitivity analysis.
- Supplementary analyses for primary endpoint and confirmatory secondary endpoints:
  - Risk difference
  - Secondary estimand (on-treatment)
- The confirmatory analysis of annual change in eGFR is updated to be done on raw eGFR values (not log-transformed)
- Requirement of 60% renal events at interim analysis removed
- Tipping point analysis expanded to a two way tipping point analysis
- Supplementary analysis for MACE replacing CV death component with all-cause death
- Supplementary analysis of all-cause death using an extended in-trial observation period
- Supplementary analyses of MI and stroke using both fatal and non-fatal events
- Additional exploratory analyses listed in Table 8.
- Definition of eGFR components of primary endpoint in case of competing events added

SAP version 2.0 dated 13-APR-2022

Changes and additions to SAP version 1.0.

- Author has been deleted from front page
- It has been clarified that the independent statistician confirming the confirmatory analyses will also be blinded until DBL.
- The planned sample size has been updated in accordance with protocol version 4.0 (section 2.1)
- The definition of baseline value has been clarified (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 that assessments of UACR or eGFR taken after initiation of chronic renal replacement therapy will not be used for analyses or summary tables (section 2.2).
- It has been clarified how subjects randomised more than once will contribute to the FAS (section 2.2.1).
- 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, 2.4.1).
- 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).
- The definition of eGFR components of primary endpoint in case of competing events (section 2.3) has been adjusted and a description of on-treatment for eGFR components has been added.
- A sensitivity analysis for the primary endpoint using only scheduled eGFR measurements has been added (section 2.3.2).

- The absolute risk difference analysis has been further specified (section 2.3.3).
- A supplementary analysis of non-CV, non-renal 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. The subgroup analysis for RAAS blocker use at baseline (Y/N) has been removed due to low number of subjects not using RAAS blockers at baseline. The subgroup Hispanic or Latino, Other has been updated to Hispanic or Latino, Not Hispanic or Latino (section 2.3.4).
- Supplementary analyses evaluating the impact of the COVID-19 pandemic on the primary and confirmatory secondary endpoints have been added (section 2.3.5, 2.4.1).
- Supplementary analyses evaluating the impact of co-participation in COVID-19 trials on the confirmatory endpoints have been added (section 2.3.6, 2.4.1).
- A supplementary analysis using a new equation (CKD EPI) where race is not included to estimate eGFR has been added (section 2.3.7)
- For confirmatory secondary endpoints the significance level used in the hierarchical testing procedure has been changed to follow a separate alpha spending function (section 2.4.1 and 3.3)
- The analysis for all-cause death using the extended in-trial period (section 2.4.1) has been further specified.
- The requirement for when year 2 will be used instead of year 3 has been clarified (section 2.4.2) and the requirement has been added for the additional exploratory analyses in Table 8.
- The imputation model for the ANCOVA for continuous endpoints has been clarified (section 2.4.2).
- Section 2.6 has been added
- The part describing that Novo Nordisk will replicate the interim analysis has been removed (section 3.3).
- It has been clarified in the appendix that UACR, urea, bicarbonate, lipids and hsCRP are log-transformed prior to analysis.
- It has been specified in the appendix that change in insulin dose is analysed in subjects who are using insulin at baseline and that both absolute and relative change will be analysed.
- Various smaller editorial changes and corrections to ease reading or add clarification and ensure alignment with SAPs for trials EX9924-4473 (SOUL) and NN9536-4388 (SELECT) have been made.

SAP version 3.0 dated 07-FEB-2023

Changes and additions to SAP version 2.0.

- Sensitivity analyses using retrieved dropouts have been added for the primary and confirmatory secondary endpoints (section 2.3.2, 2.4.1 and Table 7)
- Subgroup analysis based on age: <65, 65≤ to <75, ≥75 years and eGFR: < 30, 30 ≤ to < 45, 45 ≤ to < 60, ≥ 60 mL/min/1.73m2 (CKD-EPI) have been added (section 2.3.4)
- The alpha-spending function on the confirmatory secondary endpoints (section 2.4.1) has been updated to the same alpha-spending function as for the primary endpoint.
- Two sensitivity analyses have been added for the confirmatory secondary endpoint annual rate of change in eGFR (total eGFR slope) (section 2.4.1 and Table 7)

- The supplementary analysis for the primary endpoint using the CKD-EPI eGFR equation without race was taken out of the equation (primary endpoint) has been added to Table 7.

5 Appendix

Table 4 Handling of intercurrent events for the primary analyses of the confirmatory endpoints for the primary estimand

Endpoint	Intercurrent event	Handling
Time to first occurrence of primary endpoint (5 component)	Treatment discontinuations Medication modifying cardio-renal risk	Events and follow-up time are collected after intercurrent events and used in the analysis
	Trial discontinuation (withdrawal of consent or lost to follow-up)	Censoring at time of trial discontinuation
	Non-renal, Non-CV death (competing risk)	Censoring at time of non-renal, non-CV death
Annual rate of change in eGFR	Treatment discontinuations Medication modifying cardio-renal risk	All measurements are collected after intercurrent events and used in the analysis
	Trial discontinuation (withdrawal of consent or lost to follow-up)	Censoring at time of trial discontinuation, i.e. no eGFR data available
	Initiation of chronic renal replacement therapy	Censoring at time of initiation, i.e. eGFR data after initiation are not used in the analysis
	Death	Censoring at time of death, i.e. no eGFR data available
Time to first occurrence of MACE	Treatment discontinuations Medication modifying cardio-renal risk Initiation of chronic renal replacement therapy	Events and follow-up time are collected after intercurrent events and used in the analysis
	Trial discontinuation (withdrawal of consent or lost to follow-up)	Censoring at time of trial discontinuation
	Non-CV death (competing risk)	Censoring at time of non-CV death
Time to occurrence of all-cause death	Treatment discontinuations Medication modifying cardio-renal risk Initiation of chronic renal replacement therapy	Events and follow-up time are collected after intercurrent events and used in the analysis
	Trial discontinuation (withdrawal of consent or lost to follow-up)	Censoring at time of trial discontinuation

Table 5 List of time-to-event endpoints

Endpoint	Composite order/details*	EAC**	Competing risk
Primary			
5-component composite	- Renal death - CV death - Initiation of chronic renal replacement therapy - Onset of persistent eGFR<15 mL/min/1.73 m^2 - Onset of persistent ≥50% reduction in eGFR	Yes Yes Yes No No	Non-CV, non-renal death
Confirmatory secondary			
MACE	- CV death - Non-fatal MI - Non-fatal stroke	Yes Yes Yes	Non-CV death
All-cause death	–	Yes	None
Supportive secondary			
CV death	–	Yes	Non-CV death
Renal death	–	Yes	Non-renal death
Initiation of chronic renal replacement therapy	–	Yes	All cause death
Onset of persistent ≥50% reduction in eGFR	–	No	All cause death and initiation of chronic renal replacement therapy
Onset of persistent eGFR<15 mL/min/1.73 m^2	–	No	All cause death and initiation of chronic renal replacement therapy
Non-fatal MI	–	Yes	All-cause death
Non-fatal stroke	–	Yes	All-cause death
MALE	- Acute limb ischemia hospitalisation - Chronic limb ischemia hospitalisation	Yes Yes	All cause death
Acute limb ischemia hospitalisation	–	Yes	All-cause death
Chronic limb ischemia hospitalisation	–	Yes	All-cause death
No of severe hypoglycaemic episodes	Recurrent events	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 List of continuous endpoints

Endpoint	Details
Confirmatory secondary	
Annual rate of change in eGFR (total eGFR slope)	From randomisation to end-of-trial
Supportive secondary	
Annual rate of change in eGFR (chronic eGFR slope)	From week 12 to end-of-trial
Change in eGFR	Change from randomisation to week 12
Change in eGFR (cystatin C)	Change from randomisation to year 3
Change in Diastolic BP	Change from randomisation to year 3
Change in Systolic BP	Change from randomisation to year 3
Change in UACR	Relative change from randomisation to year 3
Change in Body weight	Change from randomisation to year 3
Change in HbA_{1c}	Change from randomisation to year 3
Exploratory	
EQ-5D index score	Change from randomisation to year 3
EQ-5D VAS score	Change from randomisation to year 3

If 10% or more of subjects from FAS have missed the relevant visit due to trial termination earlier than planned, the endpoints will be evaluated as change to 2 years.

Table 7 Overview of planned analyses for all endpoints

Endpoint	Model/method	Summary measure	Sensitivity analysis	Supplementary analysis
Primary				
5-component CKD	Cox	Hazard ratio	- Tipping point - Imputation of missing eGFR - Use of local laboratory data -Use of scheduled eGFR only -Retrieved dropout analyses	- Risk difference - First on-treatment - Subgroup analyses -Non-CV, non-renal death - Excluding CKD events concurrent with COVID-19 SAE -Excluding CKD events concurrent with COVID-19 AE -Including non-CV, non-renal deaths with concurrent COVID-19 SAE -censoring subjects who co-participate in COVID-19 trials -Using CKD-EPI creatinine based eGFR equation without race.
Confirmatory secondary				
Total eGFR slope	Random regression model	Mean slope difference	-Joint modelling of slope and death or initiation of renal replacement therapy -Imputation of unfavourable values after death or initiation of chronic renal replacement therapy	- First on-treatment -Removing eGFR measurements taken concurrently with COVID-19 AE -Removing eGFR measurements taken concurrently with COVID-19 SAE -Removing eGFR measurements taken after participation in COVID-19 trial

	MACE	Cox	Hazard ratio	-Retrieved dropout analyses	- Risk difference - First on-treatment - Including all-cause 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-participate in COVID-19 trials
	All cause death	Cox	Hazard ratio	-Retrieved dropout analyses	- Risk difference - First on-treatment - Extended in-trial period (relative risk analysis) -Censoring subjects who co-participate in COVID-19 trials
Supportive secondary					
	CV death	Cox	Hazard ratio	–	–
	Renal death	Cox	Hazard ratio	–	–
	Initiation of chronic renal replacement therapy	Cox	Hazard ratio	–	–
	Onset of persistent ≥50% reduction in eGFR	Cox	Hazard ratio	–	–
	Onset of persistent eGFR<15	Cox	Hazard ratio	–	–
	Non-fatal MI	Cox	Hazard ratio	–	- Including fatal MI
	Non-fatal stroke	Cox	Hazard ratio	–	- Including fatal stroke
	MALE	Cox	Hazard ratio	–	–
	Acute limb ischemia hospitalisation	Cox	Hazard ratio	–	–
	Chronic limb ischemia hospitalisation	Cox	Hazard ratio	–	–
	No of severe hypoglycaemic episodes	Marginal mean regression	Mean ratio	–	–
	Chronic eGFR slope	Random regression model	Mean slope difference	–	–
	Change in eGFR	ANCOVA w MImp	Mean diff	–	–
	Change in eGFR (cystatin C)	ANCOVA w MImp	Mean diff	–	–
	Change in diastolic BP	ANCOVA w MImp	Mean diff	–	–

	Change in systolic BP	ANCOVA w MImp	Mean diff	–	–
	Change in UACR	Log-ANCOVA w MImp	Geometric mean ratio	–	–
	Change in body weight	ANCOVA w MImp	Mean diff	–	–
	Change in HbA_{1c}	ANCOVA w MImp	Mean difference	–	–
Exploratory					
	Change in EQ-5D-5L index score	ANCOVA w MImp	Mean diff	–	–
	Change in EQ-5D-VAS score	ANCOVA w MImp	Mean diff	–	–

ANCOVA w MImp = Analysis of covariance with multiple imputation; log-ANCOVA w MImp = ANCOVA on log-transformed assessments with multiple imputation; Mean diff = mean difference

Table 8 Additional exploratory analyses

Endpoint	Time frame	Unit	Analysis
Time to first occurrence of ESRD defined as a composite endpoint consisting of: - Initiation of chronic renal replacement therapy - Onset of persistent eGFR <15 mL/min/1.73 m2	From randomisation to end-of-trial	Months	Stratified Cox model as for the primary endpoint (primary analysis)
Time to first occurrence of a 4-component CKD endpoint consisting of: - Renal death - Initiation of chronic renal replacement therapy - Onset of persistent eGFR <15 mL/min/1.73 m2 - Onset of persistent ≥50 % reduction in eGFR			
Time to first occurrence of a composite endpoint consisting of: - Onset of persistent ≥57 % reduction in eGFR (doubling of serum creatinine) - Renal death - Initiation of chronic renal replacement therapy - Onset of persistent eGFR <15 mL/min/1.73 m^2			
Time to first occurrence of a composite endpoint consisting of: - Renal death - Initiation of chronic renal replacement therapy - Onset of persistent eGFR <15 mL/min/1.73 m2 - Onset of persistent ≥40 % reduction in eGFR			
Time to first occurrence of a composite endpoint consisting of: - All-cause death - Initiation of chronic renal replacement therapy - Onset of persistent eGFR <15 mL/min/1.73 m2 - Onset of persistent ≥50 % reduction in eGFR			
Time to first insulin initiation (in subjects who are insulin naïve at randomisation)			
Time to first occurrence of all-cause hospitalisation			
Change in total cholesterol		mg/dL	

Change in LDL cholesterol	From randomisation to year 3*.	mg/dL	ANCOVA (change in insulin dose) /log-ANCOVA (rest) as for the continuous supportive secondary endpoints
Change in HDL cholesterol		mg/dL	
Change in Triglycerides		mg/dL	
Change in Urea		mg/dL	
Change in bicarbonate		mmol/L	
Change in hsCRP		mg/L	
Change in insulin dose (for subjects using insulin at baseline) (absolute and relative change)		IU and IU/kg	

*If 10% or more of subjects from FAS have missed the relevant visit due to trial termination earlier than planned. the endpoints will be evaluated as change to 2 years.

6 References

1. Zhao Y, Herring AH, Zhou H, Ali MW, Koch GG. A multiple imputation method for sensitivity analyses of time-to-event data with possibly informative censoring. J Biopharm Stat. 2014;24(2):229-53.
2. He J, Crackel R, Koh W, Chen LW, Li F, Zhang J, et al. Retrieved-Dropout-Based multiple imputation for time-to-event data in cardiovascular outcome trials. J Biopharm Stat. 2022:1-19.
3. Andersen PK, Perme MP. Pseudo-observations in survival analysis. Stat Methods Med Res. 2010;19(1):71-99.
4. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737-49.
5. Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Stat Med. 2010;29(2):219-28.
6. Vonesh EF, Greene T, Schluchter MD. Shared parameter models for the joint analysis of longitudinal data and event times. Stat Med. 2006;25(1):143-63.
7. Ghosh D, Lin DY. Nonparametric analysis of recurrent events and death. Biometrics. 2000;56(2):554-62.
8. Ghosh D, Lin D. Marginal regression models for recurrent and terminal events. Statistica Sinica. 2002;12:663-88.