Title Page

Protocol Title:

A parallel-group, randomized, prospective, interventional, double-blind, multicenter global Phase 3 study to investigate the efficacy and safety of finerenone versus placebo, in addition to standard of care, in participants with chronic kidney disease and type 1 diabetes

Protocol Number: 22267

Compound Number: Finerenone (BAY 94-8862)

Short Title: Effects of ***fine***renone on the efficacy and safety in chronic kidney disease and type ***1*** diabetes

Acronym: FINE-ONE

Sponsor Name: Bayer AG

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Version History

SAP Version	*Date*	*Change*	*Rationale*
1.0	*18 APR 2024*	*Not applicable*	*Original version*
2.0	*15 SEP 2025*	*1. Remove sentence 'Multiple imputation methodology will be adapted for this to avoid underestimation of the standard error 'in section 1.1.*	*Administrative update:* *No need for this statement in the estimand definition - this belongs to the analysis.*
		2. Add specification of planned/actual treatment and handling per analysis set in section 4.1.	*Missing detail in SAP V1.0 – added to clarify text.*
		3. Updating the text on the UACR measurements reassessment in section 4.1.2.3.	*Clarification from medical that reassessment is allowed at all visits, not just screening.*
		4. Add definitions for 'End of study' and 'On-treatment' in section 4.1.2.3.	*Missing detail in SAP V1.0 – added to clarify text.*
		5. Clarify data handling for 'medication of interest' in section 4.1.2.3.	*Added to clarify text.*
		6. *Remove sentence 'to characterize the participant's baseline specific response over time' in section 4.2.2.*	*Administrative update: Removed as not required.*
		7. Update the text for missing data imputation in section 4.2.2.	*Text updated to clarify order of steps and provide further detail on methodology used.*
		8. Remove the sentence "Both steps of the missing …with the MNAR statement." in section 4.2.3.	*Explanation of process moved to section 6.2, Appendix 2.*

		9. Include sentence 'Missing data due to death or ESRD will then be imputed using a "worst case" approach.' for both control-based imputation and tipping point analysis in section 4.2.3.	*Missing detail in SAP V1.0 – added to clarify text.*
		10. Update the population to be used for section 4.5.1, 6.1.2, 6.1.3 and 6.1.4.	*There is only 1 subject that was randomized but never took study medication. Repeating all tables for FAS and SAF is not necessary as differences will be negligible.*
		11. Add text on summary for hyperkalemia and worsening of renal function in section 4.5.2.	*To clarify that both an overall summary and by PT summary will be provided.*
		12. Section 4.5.2 updated to use 2% instead of 5% for common AEs tables.	*Administrative update: Request from medical considering small sample size.*
		13. Section 4.5.2 updated to use 100 instead of 1000 participant years when considering the incidence rate and also clarifying the definition.	*Administrative update: Correction of typo in protocol which was not addressed in SAP V1.0 and clarify the text.*
		14. Add the eGFR line plot in section 4.5.3.1.	*Request from medical to have line plots for both MMRM results and mean change from baseline.*
		15. In section 4.6.1: *Add the forest plot with MMRM model.*	*Request from medical to have visualization of subgroup analysis results.*
		16. Update the medical history terms in section 6.1.3.	*Request from the medical.*
		17. Updates including how to identify medications of interest in section 6.1.4.	*Request from the medical.*

		18. Update section 6.2.	*Further detail the Primary/sensitivity analysis approaches.*
		19. Update section 6.3.	*Further detail the analysis for Alternative Estimands.*
		20. Correction of typos and / or grammar throughout the document.	*Administrative update.*
		21. Update of version history and Section 4.8 Changes to Protocol-planned Analyses.	*Administrative update.*

List of Abbreviations and Definitions of Terms

In general, abbreviations are not introduced in the text but are listed here only.

ACEI	Angiotensin-converting enzyme inhibitor
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitors
BMI	Body mass index
BP	Blood pressure
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case report form
CT	Clinical Trials
CYP3A4	Cytochrome P450 isoenzyme 3A4
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
EU	European Union
FAS	Full analysis set
FIDELIO-DKD	**FI**nerenone in reducing ki**D**n**E**y fai**L**ure and d**I**sease pr**O**gression in **D**iabetic **K**idney **D**isease (Study 16244)
FIDELITY	Preplanned pooled analysis of FIDELIO-DKD and FIGARO-DKD
FIGARO-DKD	**FI**nerenone in reducin**G** c**A**rdiovascular mo**R**tality and m**O**rbidity in **D**iabetic **K**idney **D**isease (Study 17530)
FINE-ONE	**FINE**renone in Type **ONE** diabetes
GLP1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
ICE	Intercurrent event
KDIGO	Kidney Disease Improving Global Outcomes
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Monte Carlo Markov Chain
MI	Multiple Imputation
MLG	MedDRA Labeling Grouping
MR	Mineralocorticoid receptor
PBMQ	Project-specific Bayer MedDRA Queries
RND	Randomization
SAE	Serious adverse event

SAF	Safety Analysis Set
SAP	Statistical analysis plan
SD	Standard deviation
SGLT2	Sodium-Glucose co-transporter-2
SoA	Schedule of activities
SoC	Standard of care
SOC	System organ class
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TIA	Transient ischaemic attack
UACR	Urinary albumin-to-creatinine ratio
ULOQ	Upper limit of quantification
US(A)	United States (of America)
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

The clinical course of CKD in patients with T1D is characterized by an increased urinary albumin excretion rate, which is the first sign of kidney damage and may progress to macroalbuminuria and decrease in eGFR in later stages (Groop et al. 2009). CKD affects up to 40% of people with T1D and 25% of those progress to ESRD. Finerenone is a non-steroidal, selective antagonist of the MR, which is activated by aldosterone and cortisol and regulates gene transcription. Finerenone blocks MR-mediated sodium reabsorption and MR overactivation in both epithelial (e.g., kidney) and nonepithelial (e.g., heart and blood vessels) tissues. Currently, finerenone (10 mg and 20 mg tablets) has been approved for CKD in T2D and is being marketed globally. Further details are provided in the Protocol Section 2.2.

This Statistical Analysis Plan (SAP) is based on:

- Clinical Study Protocol Amendment 1, Version 2.0, dated 23 OCT 2023.

The SAP describes the final statistical analysis of the study. No statistical interim analysis will be performed. Table, figure and listing specifications are contained in a separate document.

1.1 Objectives, Endpoints, and Estimands

Primary efficacy and **secondary safety objectives** are reported together with the respective **primary** and **secondary endpoints** and the **primary estimand** of the study (Table 1–1). This table also summarizes pre-specified **exploratory objectives (efficacy, biomarkers)** and the respective **other exploratory endpoints.**

Table 1–1: Study objectives and endpoints

Objectives	Endpoints
Primary	
Efficacy	**Primary endpoint**
• To demonstrate that finerenone in addition to SoC is superior to placebo in reducing UACR over 6 months in participants with CKD and T1D	• Change in UACR from baseline (ratio to baseline) over 6 months
The ***primary clinical question of interest*** is to demonstrate a difference between assigning finerenone and placebo including effects of death and ESRD and irrespective of treatment discontinuation. Assuming a beneficial effect of finerenone after 6 months of treatment, using the treatment policy strategy is considered to produce a conservative estimate of the average effect that might be seen in clinical practice. In detail, the attributes constituting the **primary estimand** are the following: o *Population:* Adults with a clinical diagnosis of CKD and T1D. o *Treatment:* Finerenone (10 mg or 20 mg) or placebo on top of protocol defined background therapy. o *Endpoint:* see primary endpoint above. o *Intercurrent events and strategy:* The most important ICEs are death and ESRD: These events are considered clinically relevant and will be handled using a composite strategy. Therefore, the treatment effects that are observed will be assessed on the primary outcome and the ICEs. A “worst case” approach will be implemented to handle the ICEs in terms of a composite strategy. For participants experiencing the ICE, their subsequent UACR values will be set to a “worst case” value. Given there is no upper limit for post-baseline UACR measurements, the values will be drawn from the distribution of the largest change in UACR from baseline values observed during the trial (e.g. worst 10% of change in UACR from baseline values). Treatment policy strategy relates to participants being followed up for the remainder of the study after discontinuing study intervention for reasons other than death or ESRD. Follow-up time after discontinuation of study intervention will be included in the analysis. o *Population-level summary:* Geometric mean ratio of treatment arm ‘ratios to baseline’ over the study period (i.e. average of geometric mean of treatment effect at Month 3 and Month 6 visits).	
Secondary	
Safety	**Secondary endpoints**
• To assess the safety of finerenone in addition to SoC compared to placebo	• Number of participants with o TEAEs, TESAEs o Hyperkalaemia (AESI)
Exploratory	**Other exploratory endpoints**
Efficacy	
• To further demonstrate the effect of finerenone in addition to SoC as compared to placebo	• Proportion of participants with ≥30% reduction of UACR from baseline at Month 6 • Proportion of participants with ≥50% reduction of UACR from baseline at Month 6 • Change in UACR from baseline to Month 3 • Change in UACR from baseline to Month 6

(continued)

Table 1–1: Study objectives and endpoints

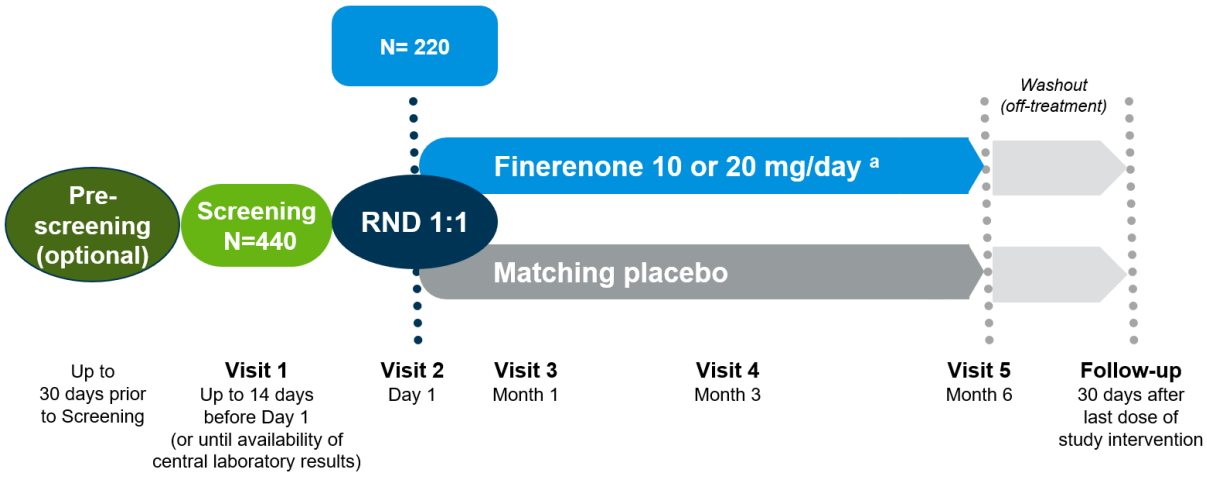
Objectives	Endpoints
Exploratory	**Other exploratory endpoints**
Biomarkers	
• To further investigate the study intervention (e.g., mode-of-action-related effects, safety) and to further investigate pathomechanisms deemed relevant to renal and cardiovascular disease - including diabetes - and associated health problems.	• Various biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

AESI = adverse event of special interest, CKD = chronic kidney disease, ICE = intercurrent event, SoC = Standard of care, T1D = type 1 diabetes, TEAE = treatment-emergent adverse events, TESAE = Treatment-emergent serious adverse event, UACR = Urinary albumin-to-creatinine ratio

1.2 Study Design

This is a double blind parallel-group intervention study in CKD and T1D participants (for an overview see the study scheme in Figure 1–1). UACR as the primary endpoint measure and serum potassium as the key safety parameter will be assessed according to the protocol specified visit schedule.

Figure 1–1: Study Schema



eGFR = estimated glomerular filtration rate, N = number of participants, RND = randomization

a Starting dose of finerenone:
10 mg/day for eGFR ≥25 to <60 mL/min/1.73 m² or
20 mg/day for eGFR ≥60 mL/min/1.73 m² at Screening visit

The overall design with specifics on screening, study intervention and follow-up are described in Protocol Section 4.1.

2. Statistical Hypothesis

The primary hypotheses to be tested for the primary estimand are provided below:

$$H_0: \mu_1 / \mu_2 = 1$$

$$H_1: \mu_1 / \mu_2 \neq 1$$

or equivalently

$$H_0: \log(\mu_1) - \log(\mu_2) = 0$$

$$H_1: \log(\mu_1) - \log(\mu_2) \neq 0$$

where μ_1 and μ_2 are the mean ratios to baseline of UACR over 6 months for finerenone and placebo, respectively. Here, μ_1 is defined as the geometric mean of the mean ratios to baseline of UACR at Month 3 (Visit 4) and Month 6 (Visit 5) in the finerenone group, and μ_2 is defined analogously for the placebo group. The null hypothesis (H_0) is defined as no difference in change in UACR between the treatment groups over 6 months. The alternative hypothesis (H_1) states that the two groups change in UACR over 6 months are different, where a ratio μ_1/μ_2 below 1 indicates superiority of finerenone over placebo.

The primary estimand will be tested under a confirmatory testing procedure. If the primary efficacy endpoint achieves the two-sided significance level of 0.05, the corresponding null hypothesis can be rejected.

2.1 Multiplicity Adjustment

No multiplicity adjustment will be applied.

3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Enrolled:	All participants who sign the Informed Consent Form.
Full analysis set (FAS):	All randomized participants.
Safety analysis set (SAF):	All randomized participants who have taken at least one dose of the study intervention.

All participants will be analyzed according to the planned treatment in the FAS (i.e. as randomized). All participants will be analyzed according to the actual treatment in the SAF.

The FAS is used to analyze endpoints/estimands related to the efficacy objectives and the SAF is used to analyze the endpoints and assessments related to safety.

Final decisions regarding the assignment of participants to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s).

4. Statistical Analyses

4.1 General Considerations

The statistical evaluation will be performed by using the software SAS (release 9.4 or higher; SAS Institute Inc., Cary, NC, USA).

A lognormal distribution for UACR is assumed, therefore the log-transformed values of UACR will be analyzed. Geometric statistics and ratios to baseline will be presented for UACR instead of arithmetic statistics with changes from baseline.

For all other continuous variables, a normal distribution is assumed. The distributional assumptions will be investigated. If necessary, nonparametric methods or transformation of the data will be considered.

All variables will be analyzed by treatment arm using descriptive statistical methods. The number of data available, mean, SD, minimum, median, and maximum, will be calculated for continuous data. The geometric mean and SD will be provided instead of the arithmetic mean and SD for the variables where lognormal distributions are assumed. Frequency tables will be generated for categorical data.

All participants will be analyzed according to the planned treatment group in the FAS. All participants will be analyzed according to the actual treatment in the SAF. If a participant receives both treatments in error, the treatment actually received for the majority of the time in the study will be used in SAF.

Only centrally analyzed samples will be considered for statistical analysis, unless otherwise specified.

In the event of repeated measurements for screening (Visit 1) and baseline (Visit 2), the closest measurement prior to randomization will be used for analysis instead of the scheduled measurements. At all visits post-randomization and, unless stated otherwise, only the values at scheduled measurements will be used for analysis.

All data will be presented in the participant data listing as they are recorded on the Case Report Form (CRF), i.e., partially missing data or fully missing data will appear as such.

For this study one month is defined as 28 days.

4.1.1 Handling of missing data

It is important to minimize the amount of missing data for the analysis of the primary estimand. Certain measures will be taken to guarantee the availability of all UACR values as far as possible.

Permanent study intervention discontinuation for any reason does not constitute withdrawal from the study and should not lead to the participant being withdrawn from the study (see Protocol Section 7.1.1), i.e. incomplete or missing values.

General rules

When appropriate, the following rules will be implemented so as not to exclude participants or observations from statistical analyses due to missing or incomplete data.

Concomitant medications with missing start and stop date but flagged as being ongoing at a participant's final visit will be considered to have started prior to study medication start and ended after stopping study medication. The start and end reference period will be imputed as "before" for the medication start and as "during/after" for the medication end.

In case of (partially) missing dates for interruptions or permanent stop of study medication intake, a "worst-case" approach will be applied to impute the start and end dates of study medication intake as the minimum and maximal possible dates, i.e.:

- first month of the year, and/or first day of the month for a partially missing start date, and
- last month of the year, and/or last day of the month for a partially missing end date.

If a participant died earlier than the imputed worst study medication end date, the death date will be taken as the study medication end date. However, if these imputations lead to a temporal overlap between different exposure date records, the imputed dates will be adjusted so that no overlap exists and the time on the higher dose is maximized. The date of first exposure to treatment is not expected to be missing as the participants are instructed by the investigator to take their first dose of study intervention directly at Visit 1, but in the very rare case that this date is not recorded, it will be imputed according to the rules outlined above for missing start dates, but not earlier than the randomization date.

When only partial dates are available for clinical events in the efficacy analysis, a median imputation rule will be used:

- For example, if the day is missing and the month is July, then day 16 is chosen.
- If the number of potential values is even, the lower of the 2 middle numbers is taken. For example, if the day is missing and the month is June, then day 15 is imputed. The same rule applies if the day and month are missing, e.g. if the year is 2022 and the day and month are missing, 2nd July is taken.
- In case the range of possible values is further restricted, e.g. because a participant died in the month in which the day is missing, the median in the restricted set of possible values is calculated. For example, if the clinical event occurred in June 2022 and the respective participant died on 11th June 2022, 6th June 2022 is imputed as the clinical event's date.

The same principle also applies to partially missing death dates, e.g. if only the year of death is available, but there is a last contact in the given year, then the date of death is imputed as the median of this date and the end of the given year.

In case a death date is completely missing, it will be imputed based on the last known contact when the participant was still alive and the first known contact when the participant was dead (e.g., from the participant's health status follow-up page) as the median of these two dates. As above, if the number of potential values is even, the lower of the two middle numbers is taken.

In case both a non-fatal clinical event and death have partially missing dates, then death takes precedence and will be imputed first according to the rules outlined above.

4.1.2 Data rules

General data rules are described in this section, further data rules for specific parameters or analyses are specified in the respective subsections of Section 4.

4.1.2.1 Baseline

Baseline values will be defined as the last non-missing measurement before or on the day of randomization. If the last observation available prior to randomization is the measurement from the Screening Visit, this would be used as the baseline value. This also includes assessments from a local laboratory, if no assessment from the central laboratory prior to first intake of study drug is available. Otherwise, baseline will be missing.

If more than one measurement was planned for a scheduled time point, for example blood pressure measurements and heart rate, the mean value of the last set of measurements per time point prior to randomization will be used for the calculation of the baseline value. This rule will not be applied for UACR, see Section 4.1.2.3 for the definition of analysis values for this parameter.

4.1.2.2 Change from Baseline

In general, change from baseline will be displayed as an absolute change from baseline defined as the difference from baseline, i.e.:

Absolute change = Post baseline value – baseline value

Some parameters will be additionally analyzed as relative change from baseline defined as:

Relative change = 100 * [(post baseline value – baseline value) / baseline value].

4.1.2.3 Other Data Handling

Only the data provided by the central laboratory will be used for analysis except for the baseline period. Values from local laboratories will only be used in the statistical analyses if there are no values from the central laboratory available for baseline, i.e. no central laboratory results are available prior to or on the date of randomization. Post-baseline only central laboratory results will be used with an exception made for eGFR and potassium where local laboratory values will be used if no central laboratory values are available.

In case of retests for Screening visits, the closest measurement prior to randomization will be used for analysis instead of the scheduled measurements. At all visits starting at Screening, Visit 1, and if not stated otherwise, only the values at scheduled measurements will be used for analysis. In the unexpected case that more values than planned are available for a scheduled visit, only the first valid value will be used.

For those laboratory values, which are <LLOQ (Lower limit of quantification), half the value of the LLOQ will be used for analysis. Differences between 2 values <LLOQ will be assigned values of 0. Ratios between 2 values <LLOQ will be assigned a value of 1. For values which are >ULOQ (Upper limit of quantification), the ULOQ will be used for analysis.

In case of log-normally distributed data, descriptive statistics other than minimum, maximum and median will only be calculated if at least 2/3 of the individual data were measured and were above LLOQ. In tables showing descriptive statistics, where values below LLOQ are included, these descriptive statistics will be marked.

Urinalysis is assessed 3 times per visit according to SoA (Protocol Section 1.3). For all visits (except the optional pre-screening) three first morning urine samples will be collected at the participant's home on the 2 consecutive days before each scheduled visit, and on the morning of the respective visit. At screening, collection of 3 morning void samples is also allowed on 3 consecutive days after the Screening visit. If one of the 3 UACR measurements is invalid but the other 2 are valid, these values can be used to assess participant's eligibility for this study. If only 1 sample is achieved, collection of another 3 consecutive samples for reassessment is needed.

The End of Study will be defined as the last subject visit either in person, at site, or via telephone contact.

On-treatment will be defined as the time from first intake of study intervention until 3 days after permanent end of study intervention.

For all groups of medications of interest as defined in the previous section in which the end date for a medication belonging to this group is on the day of randomization and there is

another medication belonging to the same group starting on the day after randomization, both medications are also considered as ongoing at baseline.

4.2 Primary Efficacy Endpoint/Estimand Analysis

4.2.1 Definition of Endpoint(s)

The primary efficacy variable of interest is change in UACR from baseline (ratio to baseline) over 6 months, which will be determined at Month 3 and Month 6.

The UACR will be assessed by the Central laboratory, and the geometric mean of 3 samples will be calculated at each visit.

The primary analysis of UACR is stated in Section 4.1. And a descriptive summary of UACR values over time will be presented by treatment group and visit. This will include descriptions of absolute and relative changes from baseline.

The population-level summary is geometric mean ratio of treatment arm 'ratios to baseline' over the study period (i.e. average of geometric mean of treatment effect at Month 3 and Month 6 visits).

4.2.2 Main Analytical Approach

The primary analysis of the primary efficacy variable will be performed according to participants' randomized intervention and will be based on the FAS.

The primary efficacy analysis will be performed on the primary efficacy estimand described in Table 1–1 and the study will be considered positive when the corresponding null hypothesis is rejected.

The analysis of UACR will be performed on the log-transformed UACR values, followed by a back transformation to the original scale. Accordingly, arithmetic means on the log scale correspond to geometric means on the original scale. The log-transformed ratio of UACR to baseline up to Month 6 (Visit 5) will be analyzed by a mixed model for repeated measures (MMRM) with the factors treatment group, visit, treatment by visit interaction, log-transformed baseline value as covariate and log-transformed baseline value by visit interaction. Pairwise ratios between the finerenone and placebo group will be calculated for each visit and corresponding two-sided 95% confidence intervals and p-values will be computed. The primary estimand will be estimated by the geometric mean of the pairwise ratios between the finerenone and placebo group over 6 months and the corresponding two-sided 95% confidence intervals and p-value will be provided. The study will be considered successful if the p-value is statistically significant (i.e. below 0.05). Covariance patterns within participants to adjust for the within subject variance will be estimated. For each treatment group a separate covariance pattern will be estimated based on an unstructured covariance. In case of convergency issues, an alternative covariance matrix will be used, with Toeplitz matrix as first choice alternative.

The mixed model for pairwise ratios between the finerenone and placebo group at Month 3, Month 6 and overall study is defined as follows:

$$Y_{ikj} = \mu + \beta x_i + v_j + t_k + (tv)_{kj} + a(xv)_{ij} + \epsilon_{ijk}$$

Where,

μ is the intercept,

Y_{ikj} is the log-transformed ratio of UACR to baseline for subject *i* with treatment *k* at visit *j*,

β is the baseline covariate effect (baseline coefficient),

x_i is the log-transformed baseline value for subject *i*,

t_k is the fixed effect of treatment *k (k=finerenone, placebo)*,

v_j is the fixed effect of month *(j=3&6),*

$(tv)_{kj}$ is the interaction effect of treatment *k* by visit *j*,

α is the covariate effect for the interaction (xv),

$(xv)_{ij}$ is the interaction effect of log-transformed baseline value of subject *i* by visit *j*,

ϵ_{ijk} denote within-participant residuals.

Intermittent missing values are considered missing at random (MAR) and will be imputed using a Monte Carlo Markov Chain (MCMC) MI method for imputation of non-monotone missing data.

Missing data due to death or ESRD will then be imputed using a "worst case" approach. See further details in the next section and Section 6.2.2.

Remaining missing data will be imputed conditioning on visit-specific treatment discontinuation indicators, as proposed by Guizzaro et al. Since participants who discontinue study intervention are encouraged to remain in the study, the data obtained from the "off-treatment" period can be used for imputation of missing data after permanent discontinuation of treatment. Multiple imputation methodology will be applied for this purpose to address the inherent uncertainty and variability associated with missing values (see Section 6.2.1).

4.2.2.1 Intercurrent Event Strategy for the Primary Efficacy Estimand

To account for ICEs such as death and ESRD (for definition and recording refer to Protocol Section 8.2.1), a "worst case" approach will be applied, which represents a composite strategy. For participants experiencing the ICE, their subsequent UACR values will be set to a "worst case" value which reflects the seriousness of the event. The values will be drawn from the distribution of the largest changes in UACR from baseline observed during the trial (e.g. worst 10% of changes in UACR from baseline). Therefore, the participants who do not have complete UACR measurements due to death or ESRD can be included in the primary analysis (method see in Section 6.2.1).

Treatment policy strategy relates to participants being followed up for the remainder of the study after discontinuing study intervention for reasons other than death or ESRD. Data from the visits after discontinuation of study intervention will be included in the analysis.

4.2.3 Sensitivity Analyses

To assess the robustness of the results for the primary efficacy estimand with respect to the impact of missing data, 'Control-based multiple imputation' and 'tipping point analysis' will be performed utilizing multiple imputation methodology.

Control-based multiple imputation

For the control-based multiple imputation in a first step intermittent missing values will be imputed using the MCMC methodology which assumes a multivariate normal distribution

over all variables included in the imputation model. Variables included in the imputation model will be baseline UACR and post-baseline UACR values as measured over time until Month 6. This imputation will be done by treatment group. Missing data due to death or ESRD will then be imputed using a "worst case" approach. In a second step all the monotone missing values will be multiply-imputed using the imputation model built from the placebo treatment group, i.e., assuming the missing data in the finerenone treatment group will have a profile that equals the profile of the placebo group for all time points.

Technical details of this sensitivity analysis are provided in Section 6.2.2.

Tipping point analysis

For the tipping point analysis, a delta-adjusted pattern imputation method will be applied, using the same variables for the imputation model as for the primary analysis. In the first step, intermittent missing values will be imputed using the MCMC methodology, which assumes a multivariate normal distribution over all variables included in the imputation model. Variables included in the imputation model will be baseline UACR and post-baseline UACR values as measured over time until Month 6. This imputation will be done by treatment group. Missing data due to death or ESRD will then be imputed using a "worst case" approach.

For the other missing values, in a second step, it will be assumed that the mean of the missing outcomes in the finerenone group deviates a certain amount, delta, from their observed counterparts in the direction of worsening outcome, but the mean in the control group is the same between missing values and observed values. Thus, each treatment group's missing values will be imputed using the observed values in their respective treatment groups. After imputation, the imputed values in the finerenone group are shifted a certain amount in the direction of worsening outcome, but the placebo group's imputed values remain unchanged. Multiple shifts within a plausible range are applied. The shift that turns the conclusion from favoring the finerenone treatment group to a non-significant result will define the tipping point. The missing data imputation will be implemented using SAS procedure PROC MI with the MNAR statement together with the ADJUST option.

Technical details of this sensitivity analysis are provided in Section 6.2.3.

4.2.4 Supplementary Analysis

4.2.4.1 Supplementary Analyses with Alternative Estimands

Alternative estimands will be considered with different strategies for handling ICEs, which are very close to the primary estimand in order to assess the robustness of the primary efficacy estimand.

Alternative Estimand 1:

- Population: as defined for the primary estimand
- Treatment: as defined for the primary estimand.
- Endpoint: Hierarchical Composite Endpoint using the following ordered components:

  1. Death
  2. ESRD
  3. Ratio to baseline of UACR over 6 months (geometric mean of ratio to baseline at Month 3 and Month 6)
- Intercurrent events and strategies:

The most important ICEs are death and ESRD: all death and ESRD events are included as outcome events in the components of the hierarchical composite endpoint (composite strategy).

Treatment policy strategy relates to participants being followed up for the remainder of the study after discontinuing study intervention for reasons other than death or ESRD.

- Population-level summary: win ratio between treatment groups, i.e. the odds that a random subject in the treatment group has a better outcome than a random subject in the control group.

Technical details of 'win odd' estimate are provided in Section 6.3.1.

Alternative Estimand 2:

- Population: as defined for the primary estimand
- Treatment: as defined for the primary estimand.
- Endpoint: as defined for the primary estimand.
- Intercurrent events and strategy: The same three ICEs as for the primary estimand are considered:
    - Death
    - ESRD
    - Discontinuing study intervention for reasons other than death or ESRD

  For the ICEs of death and ESRD during the trial, a "while alive strategy" (i.e. until the ICE of death or ESRD occur) will be considered to assess the change in UACR while the participants are alive and have not experienced ESRD.

  For the ICE permanent treatment discontinuation a "while-on-treatment strategy" will be considered to assess the change in UACR while the participants were taking study intervention.

  Technical details are provided in Section 6.3.2.

- Population-level summary: Defined as for the primary estimand.

4.3 Secondary Analysis

4.3.1 Secondary Safety Endpoints

All safety analyses will be performed in the SAF.

The safety analysis encompasses the numbers of participants with TEAEs, TESAEs as well as hyperkalemia (AESI) that were pre-specified as secondary safety endpoints (Table 1–1). AEs that started or worsened after the first dose of study intervention up to 3 days after any temporary or permanent interruption of study intervention will be considered as TEAEs.

4.4 Exploratory Analysis

4.4.1 Other Exploratory Efficacy Endpoints Specified in the Study Protocol

The exploratory efficacy analyses will be performed on the following other exploratory efficacy endpoints listed in Table 1–1:

Frequency tables will be generated for the number of participants with a relative decrease in UACR of ≥30% from baseline UACR at Month 6.

At Month 6, the categorical variable of a relative UACR decrease of ≥30% from baseline will be analyzed for the presence or absence of the event using logistic regression including covariates for the treatment group and baseline UACR. The odds ratio between the finerenone and the placebo treatment group will be calculated, and corresponding two-sided 95% confidence interval and p-value will be presented.

These analyses will be repeated for the other exploratory efficacy endpoint of reduction ≥50% of UACR from baseline at Month 6.

Change in UACR from baseline at Month 3, and Month 6 will be analyzed as described for the primary analysis (Section 4.2.1).

4.4.2 Other Exploratory Endpoints not Specified in the Study Protocol

Other exploratory endpoints not specified in the study protocol are as follows:

- Number of participants with UACR decrease of at least 30% from baseline at any time post-baseline
- Number of participants with UACR decrease of at least 40% from baseline at any time post-baseline
- Number of participants with UACR decrease of at least 50% from baseline at any time post-baseline

4.5 Other Safety Analyses

4.5.1 Extent of Exposure

The analyses described in this section will be performed in the SAF (unless otherwise stated). All tables and figures regarding treatment duration, extent of exposure and compliance will be presented by treatment group and overall (unless otherwise stated).

Treatment duration, defined as time from start of study intervention to permanent stop of study intervention (in months) will be summarized using descriptive statistics by treatment group and overall. In addition, treatment duration will be categorized to < 1 month, 1 to < 3 months, 3 to < 6 months and ≥ 6 months. Cumulative treatment duration will be categorized to at least 1 dose, at least 1 month, at least 3 months, and at least 6 months. Cumulative treatment exposure over the study in person-years will be given. A table will be presented with the absolute and relative frequencies of participants still on study medication at each visit. Kaplan-Meier plots for “Time to end of study treatment” will be provided by treatment group.

The above analyses will be repeated for study duration, defined as time from the day of randomization to the participants’ final visit (in months) for the FAS only.

The extent of exposure to study intervention (total amount of intake in grams) and the average daily dose in mg during treatment will be summarized using descriptive statistics by treatment group.

The overall titration status, regardless of actual or sham up-titration, will be summarized with absolute and relative frequencies per treatment group, differentiated by participants starting on 10 mg or 20 mg:

- For participants starting on 10 mg: never up-titrated, up-titrated once, and up-titrated more than once.
- For participants starting on 20 mg: never down-titrated, down-titrated once, and down-titrated more than once.

The number of participants on 10 mg, 20 mg or on an interruption at Day 1, Month 1, Month 3, Month 6 will also be derived based on exposure information and presented by treatment group.

In addition, the number of participants with study intervention down-titrated to 10 mg or temporarily interrupted as well as associated reason will be summarized with absolute and relative frequencies per treatment group.

The compliance (as percentage) will be calculated as follows:

100 * Number of taken tablets / Number of planned tablets

The number of planned tablets is calculated as follows:

(Days from randomization to last intake of study intervention + 1) * Number of planned tablets per day.

All tablets, including the dummy placebo tablets, will be counted. For participants who withdraw prematurely from the study intervention, compliance will be calculated up to the time of last dose. The compliance will be summarized descriptively by treatment group and overall. In addition, percent of compliance will be categorized into 3 groups, less than 80%, 80 to 120% and greater than 120%, and the categories will be summarized by treatment group and overall.

4.5.2 Adverse Events

With the exception of hyperkalemia, which is collected as an adverse event (AE) of special interest, non-serious AEs are not mandatory to be collected in the eCRF. Instead, only the following AEs will be collected:

- AEs leading to permanent discontinuation of study intervention;
- AEs considered related to study intervention by the investigator;
- AEs considered related to protocol required procedures;
- Any other AEs should only be collected if deemed relevant by the investigator.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, latest version available prior to data base freeze). A listing will be provided linking the original investigator terms and the coded terms.

AEs that started or worsened after the first dose of study intervention up to 3 days after any temporary or permanent interruption of study intervention will be considered as treatment-emergent AEs (TEAEs).

A worst-case approach will be applied for determining whether an adverse event (AE) with partially missing dates is treatment-emergent or not, i.e. if it is possible that the AE start date is within a period of study drug intake +3 days (on or after study treatment start date and on or before study treatment end date + 3 days) then the AE is considered treatment-emergent.

An overall summary of all reported AEs and TEAEs will be generated by treatment group. The number of participants with TEAEs, pre-treatment AEs, post-treatment AEs occurring more than 3 days after any temporary or permanent stop of study intervention, treatment-emergent SAEs, treatment-emergent study drug-related AEs, treatment-emergent study drug-related SAEs, and TEAEs causing permanent discontinuation of study intervention, treatment-emergent non-serious AEs, non-serious AEs, TEAEs by maximum intensity, treatment-emergent SAEs by maximum intensity, drug-related TEAEs by maximum intensity, TEAEs by worst outcome and treatment-emergent SAEs by worst outcome will be summarized by treatment group using MedDRA terms grouped by Primary System Organ Class (SOC) and Preferred Term.

In case of the same events with different intensities within a participant, the maximum reported intensity will be used. If the intensity is missing, the event will be considered severe. If the same event is considered both unrelated and related to the study intervention within a participant, it will be reported as related to study intervention. If the drug relationship is missing, the event will be considered as being related to the study intervention.

The following will be analyzed/assessed for safety:

- SAEs and AEs leading to discontinuation of treatment with study intervention
- Number of participants with hospitalization for hyperkalemia
- Number of participants discontinuing study intervention permanently due to hyperkalemia
- Number of participants with hospitalization for worsening of renal function
- Number of participants discontinuing study intervention permanently due to worsening of renal function

Hyperkalemia includes AEs with MedDRA codes (preferred terms): 10020646 (Hyperkalaemia), 10005725 (Blood potassium increased).

Worsening of renal function includes AEs with MedDRA codes (preferred terms): 10069339 (Acute kidney injury), 10005483 (Blood creatinine increased), 10018358 (Glomerular filtration rate decreased), 10059345 (Postrenal failure), 10072370 (Prerenal failure), 10038435 (Renal failure), 10062237 (Renal impairment).

For Hyperkalemia and Worsening of renal function an overall and by preferred term TEAE summary will be provided.

These will be summarized by treatment group using frequency counts. For the number of participants with these events, the summary will be provided once for all events and once for all treatment-emergent events.

Separate tables summarizing TEAEs, study drug-related TEAEs, and SAEs that occurred in more than 2% of the participants will be provided.

Deaths, SAEs and AEs leading to permanent study drug discontinuation will be listed separately.

The number, incidence and incidence rates per 100 participant years of participants with (TE)AEs and (TE)SAEs will be summarized by treatment group and overall using MedDRA terms grouped by Primary System Organ Class and Preferred Term. The incidence rate is defined as the number of participants with an event divided by the total sum of the times a participant is at risk for the respective event, multiplied by 365.25*100. For AEs and SAEs, it is defined as either the time from randomization until the first event or end of study in case no such event is recorded. For TEAEs and TESAEs, it is defined as time from first dose of study drug until the first TE event or up to 3 days after last dose of study intervention, or death, if earlier, for those patients without a respective TEAE. Times with temporary treatment interruption will be excluded from the at risk period for TE events.

4.5.3 Additional Safety Assessments

4.5.3.1 Laboratory Data

The number of participants with treatment-emergent (until 3 days after any temporary or permanent interruption of study intervention) abnormal laboratory values above or below the normal range will be tabulated by the laboratory parameter and treatment group. For this analysis, laboratory values from scheduled and unscheduled visits will be considered.

Summary statistics including changes from baseline will be calculated by treatment group and visit for all quantitative laboratory parameters, e.g. for hormone, clinical chemistry and quantitative parameter from urinalysis. Geometric statistics and ratios to baseline will be presented UACR. For eGFR, the relative change will be displayed in addition to the absolute change from baseline.

The following special safety parameters related to laboratory measurements will be further assessed by displaying the number of participants with treatment-emergent safety events. The summaries will be performed for the number of participants with:

- Absolute value of serum potassium >5.5 mmol/L
- Absolute value of serum potassium >6.0 mmol/L
- Relative decrease from baseline in eGFR of ≥30%, ≥40%, ≥50% and ≥57%

For all central laboratory parameters: HbA1c, serum K^+, uric acid, serum sodium, serum creatinine, and eGFR, the following visualizations will be presented:

- Bar plots showing the proportion of participants with available and missing measurement at each visit.
- Analysis summary table and associated line plots of least square means and 95% confidence intervals based on an MMRM analysis of change from baseline. The mixed model will include factors treatment group, visit, treatment by visit interaction, baseline value of central laboratory parameter of interest, and baseline value by visit will be included as covariates.
- For eGFR a line plot of mean change from baseline by visit with 95% CIs for visits up to and including follow-up.

It is assumed that after study intervention discontinuation the acute drop in eGFR observed at the start of study intervention intake will be negated by a rebound of similar magnitude after

last intake of study intervention. A post treatment eGFR measurement will be taken for all participants 30 days after last dose of study intervention (at the Follow-up visit). An ANCOVA model will be fitted to summarize the treatment difference in the change from baseline value. The model will include treatment group as a factor and baseline eGFR as a covariate. Corresponding two-sided 95% confidence intervals and p-values will be produced.

4.5.3.2 Vital Signs

The analysis of vital signs includes blood pressure and pulse measurements. Averages of non-missing values will be calculated and used for the statistical analysis. If only 1 of the planned measurements is available, this value will be used.

Vital signs values will be summarized by treatment group and visit using descriptive statistics including absolute changes from baseline.

Systolic and diastolic blood pressure will be analyzed using an MMRM with factors treatment group, visit, treatment by visit interaction, baseline value (SBP or DBP), and baseline value by visit as covariates. Related line plots of least square means and 95% confidence intervals based on the MMRM analysis of change from baseline will be also provided.

4.5.3.3 Weight and BMI

The values and the absolute changes from baseline will be summarized by treatment group and visit using descriptive statistics for weight (kg) and BMI (kg/m²).

4.6 Other Analyses

4.6.1 Subgroup Analysis

Exploratory subgroup analysis will be performed for the primary efficacy endpoint. The list of key subgroups are specified below. Analyses will include descriptive statistics, estimated ratios to baseline with 95% CIs and forest plot for MMRM model including treatment, log-transformed baseline, study visit, subgroup, log-transformed baseline-by-visit interaction, and treatment-by-visit interaction and treatment group by subgroup interaction fitted.

If the result for a subgroup cannot be calculated due to a small sample size or number of events, then this subgroup will be dropped.

Subgroups are:

- eGFR category at baseline (eGFR < 45, 45 to < 60, ≥60 mL/min/1.73 m²)
- UACR category at baseline (< 300 mg/g, 300 to ≤ 1000 mg/g, > 1000 mg/g)
- Region (North America, Europe, Asia)
- Race (White, Black, Asian, other)
- Sex (male, female)
- Age group (< 65, ≥ 65 years)
- Serum K^+ (<4.0 mmol/L, 4.0 - 4.8 mmol/L, > 4.8 mmol/L)
- Systolic BP at baseline (<130, ≥130 mm Hg)
- HbA1c (≤7.5%, >7.5%)

4.7 Interim Analyses

No formal interim analysis is planned for this study.

4.8 Changes to Protocol-planned Analyses

- Per 100 patient years rather than 1000 patient years, that is the correction of protocol typo.
- The explanation for missing data imputation has been extensively re-written to improve and clarify the imputation process. This is not considered a protocol change.

5. Sample Size Determination

UACR ratio will be analyzed assuming a lognormal distribution. Assumptions for the UACR ratios to baseline at 6 months are based on the FIDELITY UACR mixed model analysis restricted to participants with UACR ≥200 mg/g and eGFR between 25 and 90 mL/min/1.73 m^2. We shall assume the effect of placebo on UACR is non-existent, so for sample size calculation we will assume a UACR ratio to baseline after 6 months of 1.00 for the placebo group.

In the FIDELITY restricted population, the UACR ratio to baseline after 4 months was 0.61 and 0.53 after 12 months in the Finerenone group. The value, using interpolation, at 6 months was estimated to be 0.59. As a conservative approach, we will assume the treatment ratio (finerenone/placebo) over 6 months to be 0.7 (i.e., the relative difference in UACR ratio to baseline between finerenone and placebo to be 30%). The standard deviation of the change from baseline of log-transformed UACR was calculated to range from 0.75 and 1.0 between month 4 and 12. Using linear interpolation, at Month 6 it was assumed to be approximately 0.8.

A sample size of 214 (107 per group) achieves 90% power at a two-sided significance level of 5%, to reject the null hypothesis of treatment ratio equal to 1 assuming the true treatment ratio of 0.7 and the standard deviation to be 0.8. To account for the potential loss of information in applying the “worst case” approach for the primary estimand, the sample size will be increased by 2.6% (the calculated cumulative incidence of death and kidney failure from the pool of FIDELIO-DKD and FIGARO-DKD) to ensure the desired power is achieved. Therefore, the sample size is increased to 220 participants (110 per group).

6. Supporting Documentation

6.1 Appendix 1: Population Characteristics

Population characteristic analyses will be performed for the FAS, if not stated otherwise.

6.1.1 Participant disposition

The number of participants enrolled, screen failures, randomized and valid for the FAS and SAF will be summarized overall and by treatment group, region, and country.

The number of sites will be summarized by country.

The number of participants with important protocol deviations will be summarized by deviation category, overall and by treatment group.

The number of participants with validity findings will be presented by treatment group and overall.

A disposition summary for each period will be presented summarizing the number of participants starting and completing the respective study period, the number of participants discontinuing it and the primary reason for discontinuation. This will be presented overall and for each treatment group. The number of participants completing the study intervention and the number of participants completing the overall study will be provided by study arm and overall. Participants who completed the study are those who were followed for the duration of the study irrespective of discontinuation of study intervention.

6.1.2 Demography and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment arm and all participants for FAS only.

Variables according to KDIGO categories will also be displayed:

- eGFR category at baseline, KDIGO category (eGFR <15, 15 to < 30, 30 to <45, 45 to < 60, 60 to < 90, ≥ 90 mL/min/1.73 m²)
- UACR category at baseline, KDIGO category (< 30 mg/g, 30 to ≤ 300 mg/g, > 300 mg/g). NB. < 30 mg/g category is not applicable for FINE-ONE due to inclusion criteria: UACR > 200 mg/g

6.1.3 Medical History

Medical history will be coded using the MedDRA dictionary. Medical history will be presented for each MedDRA Primary SOC and Preferred Term by treatment group and overall in a summary table. Additional medical history terms by the following Project-specific Bayer MedDRA Queries (PBMQs), Bayer MedDRA Labeling Groupings (MLGs), or selected Preferred Terms will also be presented, including the following:

- Hyperlipidemia (MLG)
- Hypertension (MLG)
- Atrial fibrillation/flutter (PBMQ)
- Ischaemic Stroke/TIA (PBMQ)
- Myocardial Infarction (MLG)
- Coronary Artery Disease (PBMQ)
- Myocardial Ischaemia and Angina pectoris (MLG)
- Peripheral Artery Disease (PBMQ)
- Cardiac Failure (MLG)
- Coronary Artery Bypass Graft (CABG) (PBMQ)
- Percutaneous coronary intervention (PCI) (PBMQ)
- Carotid endarterectomy (Preferred Term)

- Renal failure acute (MLG)
- Diabetic neuropathy (PBMQ) and Neuropathy peripheral (Preferred Term) should be presented as Diabetic neuropathy
- Diabetic retinopathy (Preferred Term) and Diabetic retinal oedema (Preferred Term) should be presented as Diabetic retinopathy
- Diabetic Ketoacidosis (Preferred Term)

The medical history tables will be presented for FAS only.

6.1.4 Prior and Concomitant Medications

The prior and concomitant medication tables will be presented for SAF only. For prior and concomitant medications, the following definitions apply:

- Prior medication: Medication taken before start of the study intervention intake, (regardless of when it ended).
- Concomitant medication: Medication taken during treatment period, i.e., between first and last study intervention intake (regardless of when it started or ended).

Prior and concomitant medication will be coded to Anatomical Therapeutic Chemical (ATC) classification codes according to the World Health Organization Drug Dictionary (WHO-DD, current version at the time of analysis). The number of participants taking prior and concomitant medication will be presented by study arm and overall using ATC classes and subclasses. The concomitant medication tables will be repeated summarizing the number of participants with medications in the Standard or Bayer Drug Groupings of interest:

- ACEIs
- ARBs
- Beta-blockers
- Diuretics
- Loop diuretics
- Thiazide diuretics
- Potassium-sparing diuretics
- Potassium supplements
- Potassium lowering agents (including binders)
- Alpha blocking agents
- Alpha and beta blocking agents
- Calcium channel blockers
- Centrally acting antihypertensives
- Oral anticoagulants
- Nonsteroidal anti-inflammatory drugs (NSAIDs) (excluding acetylsalicylic acid and its salts)
- Acetylsalicylic acid and its salts
- Statins
- Erythropoietin stimulating agents

- Angiotensin receptor neprilysin inhibitors (ARNI)
- Platelet aggregation inhibitors (excluding heparin)
- Glucocorticoids
- SGLT2 inhibitors
- Strong CYP3A4 inhibitors
- Moderate CYP3A4 inhibitors
- Weak CYP3A4 inhibitors
- Strong CYP3A4 inducers
- Moderate CYP3A4 inducers
- Weak CYP3A4 inducers
- Trimethoprim and derivatives
- Insulin and analogues
- DPP4 inhibitors
- GLP1 RA
- Biguanides
- Thiazolidinediones

A participant will be counted only once within each ATC class / subclass or Standard drug grouping, respectively.

The following table provides details on how to identify each of the above medications of interest:

Drug Grouping	**Definition**
ACEIs	Use of Study drug grouping, DGCODEL2 (Group ID lowest level)=53 *DGNAME2 (Group name lowest level)=Antihypertensive angiotensin converting enzyme (ACE) inhibitors*
ARBs	DGCODEL2=54 *DGNAME2= Antihypertensive angiotensin II receptor antagonists*
Alpha blocking agents	DGCODEL2=50 [exclude DGCODEL2 IN (553 554 555)] *DGNAME2=Antihypertensive adrenergic receptor antagonists* *Excluding* *DGNAME2=Antiarrhythmic selective beta blocking drugs, Antiarrhythmic non-selective beta blocking drugs, and* Antiarrhythmic alpha and beta blocking drugs
Beta-blockers	DGCODEL2 IN (553 554) *DGNAME2= Antiarrhythmic selective beta blocking drugs, and Antiarrhythmic non-selective beta blocking drugs*
Alpha and beta blocking agents	DGCODEL2 IN (555) DGNAME2= Antiarrhythmic alpha and beta blocking drugs
Diuretics	Merge the following, indented 4 rows to obtain an overall diuretics group
Other Diuretics **(*Programming note: excluding loop diuretics, thiazide diuretics, and potassium-sparing diuretics which are given on the next 3 rows)***	Use of Study drug grouping, DGCODEL2 IN (57 59 1377 1378 1478) DGNAME2= *Diuretic carbonic anhydrase inhibitors* *Osmotic diuretics* *Vasopressin antagonists* *Other diuretics* *Low-ceiling diuretics, excluding thiazides*
Loop diuretics	Use of Study drug grouping, DGCODEL2=58 DGNAME2=*Loop or high-ceiling diuretics*
Thiazide diuretics	Use of Study drug grouping, DGCODEL2=1477 DGNAME2= *Low-ceiling diuretics, thiazides*
Potassium-sparing diuretics	Use of Study drug grouping, DGCODEL1=1473
Potassium supplements	ATC="A12BA"

Drug Grouping	**Definition**
Potassium lowering agents (including binders)	DGCODEL2='B_000002' *DGNAME2=Potassium binding agents*
Calcium channel blockers	DGCODEL2 IN (556 770 771) *DGNAME2= Calcium channel blockers with antiarrhythmic effects, Antihypertensive dihydropyridine derivative calcium channel blockers, and Other antihypertensive calcium channel blockers*
Centrally acting antihypertensives	DGCODEL2 IN (51) *DGNAME2= Antihypertensive adrenergic receptor agonists*
Oral anticoagulants	DGCODEL2 IN (127 131 152) *DGNAME2= Antithrombotic vitamin K antagonists, Antithrombotic direct-acting thrombin inhibitors, and Antithrombotic direct-acting factor Xa inhibitors*
Nonsteroidal anti-inflammatory drugs (NSAIDs) (excluding acetylsalicylic acid and its salts)	DGCODEL1=1761 and exclude DTOI: DGCODEL2='S_000001' *DGNAME1=Nonsteroidal anti-inflammatory drugs (NSAIDs) used in pain therapies* *Excluding* *DGNAME2=Acetylsalicylic acid and its salts*
Acetylsalicylic acid and its salts	Use of DTOI: DGCODEL2='S_000001' *DGNAME2=Acetylsalicylic acid and its salts*
Statins	DGCODEL2=96 *DGNAME2=Statins*
Erythropoietin stimulating agents	DGCODEL1=529 *DGNAME1=Erythropoiesis stimulating drugs*
Angiotensin receptor neprilysin inhibitors (ARNI)	Use of DTOI: DGCODEL2='S_000002' *DGNAME2=Sacubitril and sacubitrilat containing drugs*
Platelet aggregation inhibitors (excluding heparin)	DGCODEL1=126 and DGCODEL2=129 DGNAME1= Antithrombotic drugs, *DGNAME2=Platelet aggregation inhibitors, excluding heparin*
Glucocorticoids	DGCODEL2=10 *DGNAME2=Corticosteroids*

Drug Grouping	**Definition**
SGLT-2 inhibitors	DGCODEL2=291 *DGNAME2=SGLT2 inhibitors used in diabetes*
Strong CYP3A4 inhibitors	DGCODEL2=253 *DGNAME2=Strong CYP3A inhibitors*
Moderate CYP3A4 inhibitors	DGCODEL2=234 *DGNAME2=Moderate CYP3A Inhibitors*
Weak CYP3A4 inhibitors	DGCODEL2=221 *DGNAME2=Weak CYP3A Inhibitors*
Strong CYP3A4 inducers	DGCODEL2=265 *DGNAME2= Strong CYP3A inducers*
Moderate CYP3A4 inducers	DGCODEL2=225 *DGNAME2= Moderate CYP3A inducers*
Weak CYP3A4 inducers	DGCODEL2=210 *DGNAME2=Weak CYP3A Inducers*
Trimethoprim and derivatives	DGCODEL2=907 *DGNAME2=Trimethoprim and derivatives used as antibacterials*
Insulins and analogues	DGCODEL2=100 *DGNAME2= Insulins and analogues used in diabetes*
DPP-4-inhibitors	DGCODEL2=107 *DGNAME2=Dipeptidyl peptidase-4 inhibitors used in diabetes*
Glucagon-like peptide-1 receptor agonists (GLP1 RA)	DGCODEL2=168 *DGNAME2= Glucagon-like peptide-1 (GLP1) agonists used in diabetes*
Biguanides	DGCODEL2=101 *DGNAME2= Biguanides used in diabetes*
Thiazolidinediones	DGCODEL2=106 *DGNAME2=Thiazolidinediones used in diabetes*

6.2 Appendix 2: Technical Details for Primary/Sensitivity Analysis

6.2.1 Imputation in primary estimand analysis

The following notation will be used in this and following sections:

SUBJECT	unique participant identifier
TRT	study intervention (=1 for FINERENONE and =2 for PLACEBO)
AVISITN	Visit identifier (1.5=baseline, 4=visit 4/month 3 and 5=visit 5/month
ADT	UACR assessment date
UACR	geometric mean UACR
LOG_BASE	log UACR value at baseline
R2BASE	Post-baseline UACR / baseline UACR
LOG(R2BASE)	Log(R2BASE) or LR2BASE
LOG_R2BASE_4	Log(R2BASE) at visit 4/month 3
LOG_R2BASE_5	Log(R2BASE) at visit 5/month 6

For multiple imputations steps 1000 imputed datasets will be generated (nimpute=1000) and seeds based on the study number, 22267, plus increments of 1 will be used, i.e. 222671, 222672, … to ensure the reproducibility of the results.

Step 1: Data selection

From the source data ADLB (laboratory analysis dataset) extract the records representing the required parameter UACR, and AVISITN (baseline, visit 4/month 3, and visit 5/month 6) to create VDATA dataset. Add additional dummy records, as required, so that each randomised subject has 3 rows, one for each AVISITN (baseline, visit 4/month 3, and visit 5/month 6).

Illustrative data:

SUBJECT	TRT	RANDDT	ADT	AVISITN	LOG_BASE	R2BASE	DEATH DATE
PPD	FIN	PPD	PPD	Baseline	6.12271	1	
	FIN			Visit 4/month 3	6.12271	0.58912519	
	FIN			Visit 5/month 6	6.12271	0.89344442	
	PBO			Baseline	6.21481	1	PPD
	PBO			Visit 4/month 3	6.21481	.	
	PBO			Visit 5/month 6	6.21481	.	
	FIN		PPD	Baseline	5.80272	1	
	FIN			Visit 4/month 3	5.80272	.	
	FIN			Visit 5/month 6	5.80272	0.74094203	
	PBO			Baseline	4.51961	1	
	PBO			Visit 4/month 3	4.51961	.	
	PBO			Visit 5/month 6	4.51961	.	

The illustrative data represents different cases that require different missing data handling:

Subject P: Subject did not die or experience ESRD. No missing data.

No imputation required.

Subject P: Subject died. Visit 4/month 3 prior to death, visit 5/month 6 after death.

Visit 4/month PPD imputation, visit 5/month 6 "worst" imputation.

Subject P: Subject did not die or experience ESRD. Intermittent missing data at visit 4/month 3.

Non-monotone missingness, MCMC imputation.

Subject P: Subject did not die or experience ESRD. Visit 4/month 3 and visit 5/month 6 missing.

Visit 4/month 3 and visit 5/month 6 retrieved dropout imputation.

If no ADT is provided, i.e. UACR assessment is missing, add additional variables for the lower and upper dates of visit 4/month 3 and visit 5/month 6 assessment relative to the date of randomisation (the planned visit window). Allow +/- 7 day visit windowing and define 1 month = 28 days, as specified in the protocol:

- M3_LOWER = Lower range for visit 4/month 3 = date of randomisation + 3x28 days – 7days

- M3_UPPER = Upper range for visit 4/month 3 = date of randomisation + 3x28 days + 7days
- M6_LOWER = Lower range for visit 5/month 6 = date of randomisation + 6x28 days – 7days
- M6_UPPER = Upper range for visit 5/month 6 = date of randomisation + 6x28 days + 7days

Illustrative data:

SUBJECT	TRT	RANDDT	AVISITN	ADT	M3_LOWER	M3_UPPER	M6_LOWER	M6_UPPER
PPD	FIN	PPD	Baseline	PPD	PPD			
	FIN		Visit 4/month 3					
	FIN		Visit 5/month 6					
	PBO		Baseline					
	PBO		Visit 4/month 3					
	PBO		Visit 5/month 6					
	FIN		Baseline	PPD				
	FIN		Visit 4/month 3					
	FIN		Visit 5/month 6					
	PBO		Baseline					
	PBO		Visit 4/month 3					
	PBO		Visit 5/month 6					

Step 2: Set indicator variables

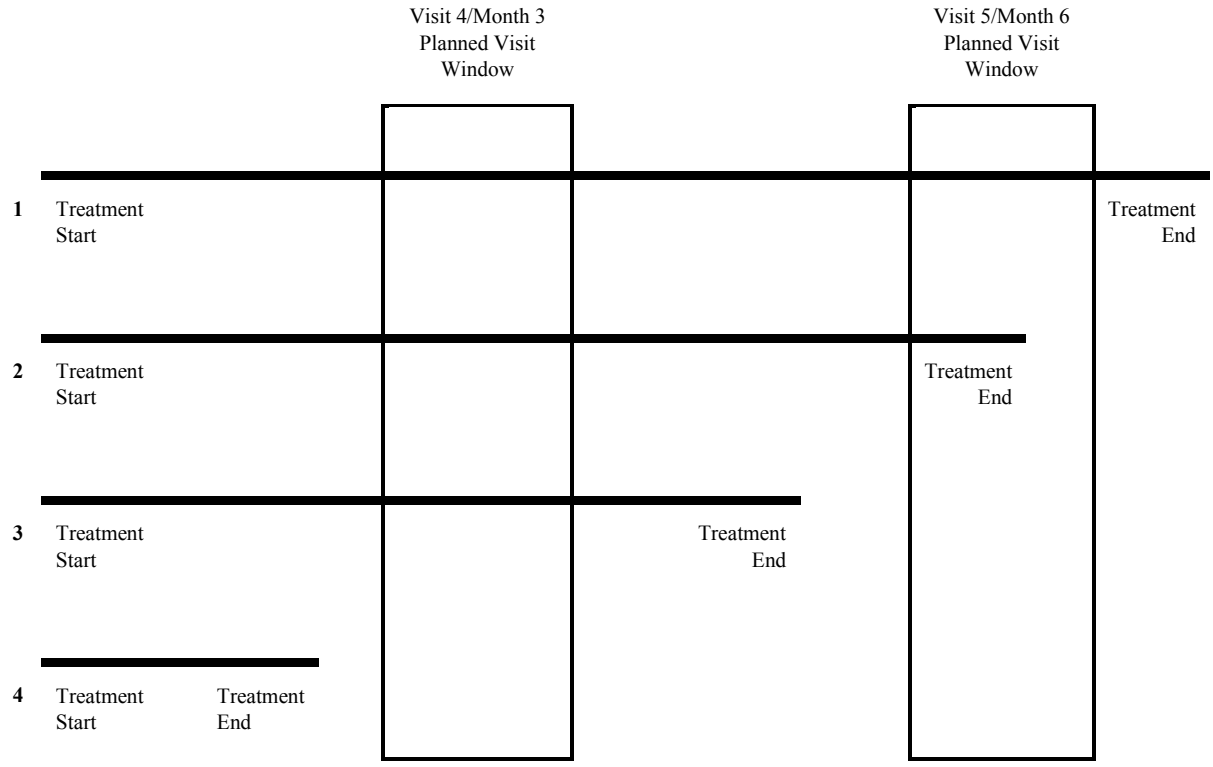
Add an indicator variable (DEATH_ESRD) which denotes whether or not a visit 4/month 3, and/or visit 5/month 6 UACR assessment is non-existing due to an ICE of death or ESRD (= 1 for assessments after the occurrence of the ICE, 0 otherwise).

Add an indicator variable (ON_TRT) which denotes whether or not each visit 4/month 3, and/or visit 5/month 6 UACR assessment is on or off-treatment. For non-missing ADT it will be compared to the overall start of study intervention and (end of study intervention) + 3. For

missing ADT, the visit window dates (M3_LOWER, M3_UPPER, M6_LOWER, M6_UPPER) will be compared to the overall start of study intervention and (end of study intervention) + 3. If the window for visit 4/month 3 and/or visit 5/month 6 is completely or partially after the start of study intervention and prior to the end of study intervention + 3 the assessment will set to on-treatment, see diagram below illustrating potential cases.

ON_TRT will be set to 1 if an individual is on-treatment, or 0 if they are off-treatment. This variable is needed for implementation of the data imputation for lost to follow-up participants outlined in the next section.

The following diagram illustrates different cases:



Case 1: Visit 4/month 3: ON_TRT=1, and visit 5/month 6: ON_TRT=1

Case 2: Visit 4/month 3: ON_TRT=1, and visit 5/month 6: ON_TRT=1

Case 3: Visit 4/month 3: ON_TRT=1, and visit 5/month 6: ON_TRT=0

Case 4: Visit 4/month 3: ON_TRT=0, and visit 5/month 6: ON_TRT=0

Illustrative data:

SUBJECT	AVISITN	ADT	DEATH DATE	M3_LOWER	M3_UPPER	M6_LOWER	M6_UPPER	TRTSDT	TRTEDT	DEATH_ ESRD	ON TRT
PPD	Visit 4/ month 3	PPD		PPD						0	1
	Visit 5/ month 6									0	1
	Visit 4/ month 3		PPD							0	0
	Visit 5/ month 6									1	0
	Visit 4/ month 3	PPD								0	1
	Visit 5/ month 6									0	1
	Visit 4/ month 3									0	0
	Visit 5/ month 6									0	0

Step 3: Transpose the data

Transpose VDATA, from the above vertical format (1 row per AVISITN for each subject, each subject has multiple rows) to horizontal format, HDATA (1 row per subject, with one column per AVISITN).

Illustrative data:

SUBJECT	DEATH_ESRD_4	DEATH_ESRD_4	ON_TRT4	ON_TRT5	LR2BASE_4	LR2BASE_5
PPD	0	0	1	1	-0.52912	-0.11267
	0	1	0	0	.	.
	0	0	1	1	.	0.29983
	0	0	0	0	.	.

Step 4: Assess the pattern of missingness within the data

Example SAS Code

```
proc mi data=HDATA nimpute=0;
    var TRT LOG_BASE LR2BASE_4 LR2BASE_5;
run;
```

Example output:

GROUP	TRT	LOG_BASE	LR2BASE_4	LR2BASE_5
1	X	X	X	X
2	X	X	X	.
3	**x**	**x**	**.**	**x**
4	X	X	.	.

Step 5: Address non-monotone missingness

For intermittent missing values (GROUP 3 in the example output above) LR2BASE_4 the LOG(R2BASE at visit 4/month 3 is missing but visit 5/month 6, LR2BASE_5 is not missing. The missing visit 4/month 3 LOG(R2BASE) will be imputed using the Markov Chain Monte Carlo (MCMC) methodology, which assumes a multivariate normal distribution over all variables included in the imputation model.

Example SAS Code

```
proc mi data=HDATA out=HDATA_IMP seed=222671 nimpute=1000;
   var  TRT LOG_BASE LR2BASE_4 LR2BASE_5;
   mcmc impute=monotone chain=multiple;
run;
```

Example *HDATA_IMP* data (for one imputation):

SUBJECT	DEATH_ESRD_4	DEATH_ESRD_4	ON_TRT4	ON_TRT5	LR2BASE_4	LR2BASE_5
PPD	0	0	1	1	-0.52912	-0.11267
	0	1	0	0	.	.
	0	0	1	1	**IMP1=0.09378**	0.29983
	0	0	0	0	.	.

IMP1 = value imputed in this step

Step 6: Impute missing data, prior to ICE, for individuals who experience an ICE of death or ESRD

For SUBJECTs who experienced an ICE of death or ESRD and have visit 4/month 3 LOG(R2BASE) missing and prior to the date of the ICE a monotone imputation model will be used to impute missing data prior to the ICE. Such a SUBJECT will have DEATH_ESRD_4=0 and DEATH_ESRD_5=1. The following code will be run to impute the missing LR2BASE_4:

Example SAS Code

```
proc mi data=HDATA out=HDATA_IMP_SPECIAL seed=222672 nimpute=1000;
   class TRT;
   var TRT LOG_BASE LR2BASE _4;
   monotone reg (LR2BASE _4 = TRT LOG_BASE);
run;
```

Retain only the LOG(R2BASE) imputed values that relate to DEATH_ESRD=0 records at visit 4/month 3 from *HDATA_IMP_SPECIAL_SUBSET*, and merge back into *HDATA_IMP, to create new dataset HDATA_IMP2*.

Example *HDATA_IMP2* data (for one imputation):

SUBJECT	DEATH_ESRD_4	DEATH_ESRD_4	ON_TRT4	ON_TRT5	LR2BASE_4	LR2BASE_5
PPD	0	0	1	1	-0.52912	-0.11267
	0	1	0	0	**IMP2=-0.40207**	.
	0	0	1	1	**IMP1=0.09378**	0.29983
	0	0	0	0	.	.

IMP2 = value imputed in this step

Step 7: Impute missing data, after ICE, for individuals who experience an ICE of death or ESRD

For participants experiencing an ICE of death or ESRD, missing LOG(R2BASE) after the occurrence of the ICE will be set to a "worst case" value which reflects the seriousness of the event. The values for imputation will be drawn from the worst 10% of the distribution of LOG(R2BASE) observed during the trial. NB. Higher values in LOG(R2BASE) indicate worsening UACR.

From the original data, VDATA, sort the data in descending order of LOG(R2BASE) for post-baseline, non-missing records. Select the worst 10% from the available data [i.e. largest 10% of LOG(R2BASE) values] to create the WORST_POOL dataset.

```
proc sort data=VDATA(where=(AVISITN in(4,5) and LR2BASE ne .);
    by descending LR2BASE;
run;
```

CREATES A MACRO VARIABLE, worst_obs, WHICH THE NUMBER OF RESULTS WHICH EQUATE TO 10% OF THE AVAILABLE LOG(R2BASE) VALUES

```
data _null_;
   if 0 then set VDATA nobs=num_obs;
   call symputx('worst_obs', ceil(num_obs * (0.1)));
run;

data WORST_POOL(keep=dummy_id lr2base);
    set _ VDATA;
    if _N_ <= &worst_obs;
   dummy_id=_n_;   [NEEDED FOR LATER MERGE]
run;
```

Evaluate the number of records which need worst imputation, K, which equals the number of records were DEATH_ESRD=1, in VDATA, multiplied by the number of imputations (i.e. 1000).

```
data NEED_WORST(keep=SUBJECT AVISITN);
   set VDATA(where=(DEATH_ESRD=1));
run;

data NEED_WORST_IMP0 (rename=(i=_imputation_);
    set NEED_WORST;
    do i=1 to &nimpute;   [NB. &nimpute=1000]
       output;
    end;
run;
data NEED_WORST_IMP;
     set NEED_WORST_IMP0;
    dummy_id=_n_;   [NEEDED FOR LATER MERGE]
run;
```

Evaluate the number of records which need to be imputed, K, which equals the number of records were DEATH_ESRD=1, in VDATA, multiplied by the number of imputations (i.e. 1000).

```
proc sql noprint;
    select count(*) into: N_NEED_WORST
        from NEED_WORST;
quit;

%let K=%sysevalf(&N_NEED_WORST*&nimpute);  [NB. &nimpute=1000]
```

Use random sampling with replacement to draw the required number (K) of LOG(R2BASE) values from WORST_POOL to form a dataset WORST_RANDOM_SAMPLE and add an ID variable to help with merging.

```
proc surveyselect data=WORST_POOL method=urs n=&K seed=222673
    out=WORST_RANDOM_SAMPLE outhits;
run;
data SCRAMBLED_WORST_RANDOM_SAMPLE;
   set _WORST_RANDOM_SAMPLE;
   call streaminit(222674);
   random_number = rand("uniform");
run;
proc sort data=SCRAMBLED_WORST_RANDOM_SAMPLE;
    by random_number;
run;
data WORST_RANDOM_SAMPLE (drop=random_number);
      set SCRAMBLED_WORST_RANDOM_SAMPLE;
      dummy_id=_n_;
run;
```

Merge the NEED_WORST_IMP and *WORST_RANDOM_SAMPLE* datasets by dummy_id to create NEED_WORST_IMP1. Transpose NEED_WORST_IMP1 to create HDATA_IMP_WORST which includes variables WORST_4 and WORST_5 for each _imputation_ and SUBJECT who has experienced the ICE of death or ESRD. Merge HDATA_IMP_WORST into HDATA_IMP2 by _imputation and SUBJECT, to create new

dataset *HDATA_IMP3*. If DEATH_ESRD_4=1 set LR2BASE_4 to WORST_4 [i.e. LOG(R2BASE) at visit4/month 3 to one of the worst 10% of LOG (R2BASE)], and if DEATH_ESRD_5=1 set LR2BASE_5 to WORST_5.

```
proc sort data=NEED_WORST_IMP1;
   by _imputation_ SUBJECT;
run;
proc transpose data=NEED_WORST_IMP1 out=HDATA_IMP_WORST(drop=_name_)
prefix=worst_;
    by _imputation_ SUBJECT;
    id AVISITN;
    var LR2BASE;
    format avisitn 8.;
run;
data HDATA_IMP3;
    merge HDATA_IMP2 HDATA_IMP_WORST;
    by _imputation_ SUBJECT;
    if death_esrd_4 eq 1 then do;
       if LR2BASE_4 eq . then do;
          if worst_4 ne . then do;
             LR2BASE_4=worst_4;
          end;
       end;
    end;
    if death_esrd_5 eq 1 then do;
       if LR2BASE_5 eq . then do;
          if worst_5 ne . then do;
             LR2BASE_5=worst_5;
          end;
       end;
    end;
run;
```

Example *HDATA_IMP3* data (for one imputation):

SUBJECT	DEATH_ESRD_4	DEATH_ESRD_4	ON_TRT4	ON_TRT5	LR2BASE_4	LR2BASE_5
PPD	0	0	1	1	-0.52912	-0.11267
	0	1	0	0	**IMP2=-0.40207**	**IMP3=0.42563**
	0	0	1	1	**IMP1=0.09378**	0.29983
	0	0	0	0	.	.

IMP3 = value imputed in this step

Step 8: Perform Missing data imputation for reasons other than death or ESRD

The remaining missing data for reasons other than death or ESRD will be imputed using an MI regression model that conditions on visit-specific treatment discontinuation indicators, as proposed by Guizzaro et al. (2021). The remaining monotone missing values will then be imputed with the MONOTONE REG method, each visit being modeled as a function of TRT, LOG_BASE and the ON_TRT indicator (as defined above) for missing visit 4/month 3 LOG(R2BASE) values, and TRT, LOG_BASE, ON_TRT indicators and LR2BASE_4 for missing visit 5/month 6 LOG(R2BASE) values. The ON_TRT indicator will only be included when at least 10 post-discontinuation observations are available at that AVISITN.

Example SAS Code

```
proc mi data=HDATA_IMP3 nimpute=1 seed=222675 out=HDATA_IMP4;
   by _imputation_;
   class TRT ON_TRT4 ON_TRT5;
   var TRT ON_TRT4 ON_TRT5 LOG_BASE LR2BASE_4 LR2BASE_5;
   monotone reg (LR2BASE_4= TRT LOG_BASE ON_TRT4);
   monotone reg (LR2BASE_5= TRT  LOG_BASE ON_TRT4 LR2BASE_4 ON_TRT5);
run;
```

Example *HDATA_IMP4* data (for one imputation):

SUBJECT	DEATH_ESRD_4	DEATH_ESRD_4	ON_TRT4	ON_TRT5	LR2BASE_4	LR2BASE_5
PPD	0	0	1	1	-0.52912	-0.11267
	0	1	0	0	**IMP2=-0.40207**	**IMP3=0.42563**
	0	0	1	1	**IMP1=0.09378**	0.29983
	0	0	0	0	**IMP4=-0.97113**	**IMP4=1.06988**

IMP4 = values imputed in this step

Transpose the *HDATA_IMP4* back to a vertical structure, VDATA_MI.

Step 9: Apply the mixed model to each complete dataset generated by PROC MI in previous steps. Let VDATA_MI:

Example SAS Code

```
ODS OUTPUT lsmeans=mi_lsmeans diffs=mi_diffs;
PROC MIXED data= VDATA_MI;
     BY _imputation_;
     CLASS TRT SUBJECT AVISITN;
     MODEL LR2BASE= TRT LOG_BASE AVISITN TRT*AVISITN LOG_BASE*AVISITN;
     REPEATED AVISITN/ subject=SUBJECT type=un group=TRT;
    TRT*AVISITN -0.5 -0.5 0.5 0.5/cl;
    LSMEANS TRT/diff cl;
    LSMEANS TRT*AVISITN/diff cl;
RUN;
```

Combine the results from mi_lsmeans and mi_diffs restricting to the rows needed for the primary analysis table to create mi_all.

Step 10: Use SAS PROC MIANALYZE to combine the results across the different _imputations_ using Rubins rule.

Example SAS Code

```
PROC MIANALYZE data=mi_all;
      by Label;
      MODELEFFECTS Estimate;
      STDERR StdErr;
      ods output ParameterEstimates=mi_results;
run;
```

6.2.2 Control-based Multiple Imputation – Sensitivity Analysis for Primary Endpoint

The general procedure for control-based pattern imputation as introduced by Little and Yau 1996, and later refined by Ratitch and O'Kelly 2011, is the following:

1) Impute intermediate, non-monotone missing data with the MCMC method and store the result of this partial imputation. In this study, the non-monotone data would represent those participants that miss some intermediate assessments who are able to come back at a later visit and complete the pertaining assessment.

2) Impute missing data after the occurrence of death or ESRD.
3) Impute the remaining missing data with control-based pattern imputation, example code below. Control-based imputation implies that the participants who are in the finerenone group and no longer receive finerenone will assume the same conditional distribution as those in the control group. We start with imputing monotone missing data at Month 3. This step is repeated for Month 6 sequentially. Thus, data filled for Month 3, will be used for predictor variables in the next call to PROC MI (for Month 6).

   Example SAS Code

   proc mi data=HDATA_IMP3 nimpute=1 seed=222675 out=HDATA_IMP4;

   by _imputation_;

   class trt;

   monotone regression;

   mnar model (lr2base_4 /modelobs=(trt="Placebo"))

   mnar model (lr2base_5 /modelobs=(trt="Placebo"));

   var log_base lr2base_4 lr2base_5;

   run;
4) Run the mixed-effects model for each of the imputed datasets.
5) Combine the results using PROC MIANALYZE.

Refer to Section 6.2.1 for further details and sample SAS code for the above steps

6.2.3 Tipping Point Analysis – Sensitivity Analysis for Primary Endpoint

The tipping point analysis will be performed applying the delta-adjustment method and will follow the second variant discussed in Ratitch, O'Kelly and Tosiello (2013).

The delta-adjustment method will be applied sequentially where at each iteration missing values of participants in the finerenone group are adjusted with a larger delta than at the previous iteration. This process continues until the difference between the experimental and control treatments is no longer statistically significant, i.e. the null hypothesis of no difference between finerenone and placebo is not rejected. This point is called a tipping point. The step by which delta parameters are increased at each iteration will be chosen based on the observed treatment difference from the primary analysis. No penalty in UACR will be applied in the placebo group. For participants with missing outcomes in the finerenone treatment arm, each imputed UACR value will be modified according to the required delta shift and thereby will be gradually increased until a p-value of 0.05 or higher is produced (beyond the tipping point). The actual penalty (taking the chosen step size of delta into account) that gives a p-value above and closest to 0.05 will then be identified.

The following steps are performed:

1) Impute intermediate, non-monotone missing data with the MCMC method and store the result of this partial imputation. In this study, the non-monotone data would

represent those participants that miss some intermediate assessments who are able to come back at a later visit and complete the relevant assessment.

2) Impute missing data after the occurrence of death or ESRD.

3) Next impute the monotone missing data with adjustment of imputed values in the finerenone arm (i.e. delta-adjustment method).

   The approach in this study will follow the second variant discussed in Ratitch, O'Kelly and Tosiello (2013) where a delta adjustment is applied at each visit starting with the first visit with missing data up to the end of the observation period. In addition to using previously delta-adjusted values as predictors it works under the assumption that discontinuation of active treatment is associated with a worsening process that persists throughout the whole time period after discontinuation.

Reference SAS code for this approach will be as follows:

```
PROC MI data= HDATA_temp seed=222675 nimpute=1 out=data_tpa;
      CLASS    TRT;
      VAR       TRT LOG_BASE LR2BASE_4 LR2BASE_5 ...;
      MONOTONE       regression (/details);
      MNAR ADJUST   (LR2BASE_4 /shift=delta adjustobs=(TRT='1'))
             ADJUST   (LR2BASE_5 /shift=delta adjustobs=(TRT='1'));
RUN;
```

A range of delta values will be considered starting with 0, with subsequent stepwise increases of delta by the chosen step size.

4) For each value of delta apply the mixed model to each of the iterations generated by PROC MI in step 3.

   For each fixed value of delta this step is identical to step 9 in Section 6.2.1.

5) For each fixed value of delta, use PROC MIANALYZE to combine the results. This step is identical to step 10, in Section 6.2.1.

6.3 Appendix 3: Alternative Estimands

6.3.1 Win Odds (alternative estimand 1)

The ordered components are the following: 1=Death; 2=ESRD; 3=ratio to baseline of UACR over 6 months.

Impute intermediate, non-monotone missing data with the MCMC method. Then impute missing data after the occurrence of death or ESRD.

See Section 6.2.1 for further details and sample SAS code. Then, proceed 'win odd' estimate and corresponding two-sided 95% confidence intervals and p-value will be provided.

In order to compare the treatment effect between the groups and to test the treatment effect difference, we define the win probability. The general procedure as introduced by Samvel et al 2021. Assume that the values of the variable of interest in the "Active" treatment group are

independently sampled from a random variable η, while the values of the "Placebo" group are independently sampled from the random variable ξ, where η and ξ are independent ordinal random variables. We need to estimate the win probability and the corresponding win odds for "Active" treatment against "Placebo", using the observed measurements in each treatment group. The win probability is defined as

$$\theta = P(\eta > \xi) + 0.5P(\eta = \xi), \qquad (1)$$

whereas the win odds is the odds of winning,

$$\kappa = \frac{\theta}{1-\theta} = \frac{P(\eta>\xi)+0.5P(\eta=\xi)}{P(\eta<\xi)+0.5P(\eta=\xi)}. \qquad (2)$$

In terms of win odds, a "win", a "loss" or a "tie" are, correspondingly, $\kappa > 1$, $\kappa < 1$ and $\kappa = 1$.

To estimate the win odds κ of the random variable η against the random variable ξ, under the assumption of independence of these random variables, we observe i.i.d. (independent, identically distributed) samples $Y = (Y_1,\ldots, Y_{n2})$ and $X = (X_1,\ldots, X_{n1})$ from their respective distributions.

The win probability θ can be estimated using the Mann-Whitney estimate:

$$\hat{\theta}_N = \frac{1}{n_1 n_2}\sum_{i=1}^{n_1}\sum_{j=1}^{n_2}\left(I\{Y_j > X_i\} + 0.5I\{X_i = Y_j\}\right), \qquad (3)$$

where $N = n_1 + n_2$ is the total sample size and the indicator function $I(.)$ takes the value 1 if the underlying condition is true, 0 otherwise. This estimator is consistent and asymptotically normal (Gasparyan et al. 2021).

The estimator for the win odds will be

$$\hat{\kappa} = \frac{\hat{\theta}_N}{1-\hat{\theta}_N} \qquad (4)$$

Equation (3) can also be written as

$$\hat{\theta}_N = \frac{1}{n_2}\sum_{i=1}^{n_2} p_j = 1 - \frac{1}{n_1}\sum_{i=1}^{n_1} q_i, \qquad (5)$$

Where

$$p_j = \frac{1}{n_1}\sum_{i=1}^{n_1}\left(I\{Y_j > X_i\} + 0.5I\{X_i = Y_j\}\right) \qquad (6)$$

is the *individual win proportion* of patient *j* of the "Active" group against the "Placebo" group. Correspondingly *qi* is the *individual win proportion* of patient *i* of the "Placebo" group against the "Active" group. Testing of the null hypothesis of no treatment effect, expressed as $\kappa = 1$ or, equivalently, $\theta = 1/2$, can be done using the following *Z* statistic (Gasparyan et al. 2021), which has a standard normal asymptotic distribution.

$$Z_N = \frac{\widehat{\theta_N} - \frac{1}{2}}{SE}, \; SE = \sqrt{\frac{Var(Y_2^0)}{n_2} + \frac{Var(Y_1^0)}{n_1}} \qquad (7)$$

Where $Var(Y_2^0)$ and $Var(Y_1^0)$ denote the estimates of the variances

$$Var(Y_2^0) = \frac{1}{n_2}\sum_{j=1}^{n_2}\left(p_j - \hat{\theta}_N\right)^2, Var(Y_1^0) = \frac{1}{n_1}\sum_{i=1}^{n_1}\left(q_i - \hat{\theta}_N\right)^2, \qquad (8)$$

Here we have denoted

$$Y_2^0 = (p_1, p_2, \ldots, p_{n2}), \; Y_1^0 = (q_1, q_2, \ldots, q_{n1}) \qquad (9)$$

According to Gasparyan et al. (2021) the CI for the win odds $\widehat{\kappa_N}$ can be constructed using the formula

$$\left[\widehat{\kappa_N} \cdot e^{-C_{1-\frac{\alpha}{2}}\cdot\frac{SE}{\hat{\theta}_N(1-\hat{\theta}_N)}}, \widehat{\kappa_N} \cdot e^{C_{1-\frac{\alpha}{2}}\cdot\frac{SE}{\hat{\theta}_N(1-\hat{\theta}_N)}}\right] \qquad (10)$$

where $C_{1-\frac{\alpha}{2}}$ is the $(1-\frac{\alpha}{2})$ quantile of the standard normal distribution, that is

$$P\left(\zeta < C_{1-\frac{\alpha}{2}}\right) = 1 - \frac{\alpha}{2}, \zeta \sim \mathrm{N}(0,1) \quad (11)$$

The win proportion and its asymptotic standard error (based on the theory of U-statistics) can also be obtained from Somer's D C/R statistic ($\sum_D$) as noted in Section 4.33 and Section 14.6 of Stokes et al. (2012).Indeed,

$$WP = \frac{\sum_D + 1}{2}, SE = \frac{ASE}{2} \quad (12)$$

where SE is the standard error based on the theory of U-statistics, while ASE is the asymptotic standard error of Somers' D C/R statistic. This means that in all software where this statistic is implemented (for example in PROC FREQ of the SAS software), the win odds and its CI can be derived (see also Carr et al. (1989) for related considerations with respect to Goodman-Kruskal gamma).
Since *Somers' C/R* is implemented in PROC FREQ (the measures option) of the SAS software, using Equation (12) we obtain the *SE* for the win proportion. The SAS code implemented as below for win odd and its confidence interval:

```
data resp0;
set resp;
if TRT = "FINERENONE" then TRT_ORD = 2 ;
else TRT_ORD = 1 ;
run;

proc freq data = resp0;
by _imputation_;
tables TRT_ORD * AVAL / measures;
ods output Measures = Measures0;
run;

data measures;
set measures0;
WP= (value + 1) / 2 ;
ASE = ASE / 2 ;
run;

Use PROC MIANALYZE to combine the results across imputed datasets:

PROC MIANALYZE data=measures
     MODELEFFECTS WP;
    STDERR ASE;
     ods output ParameterEstimates=WP_results (keep=estimate stderr tvalue probt);
  run;
```

According to formula (4) and (10), we can derive the WO and its 95%CI as below SAS code:

```
data WO_results;
   set wp_results;
   SE=stderr;
   WO=estimate/(1-estimate);
   C = PROBIT(0.975);
   Z=abs(estimate-0.5)/stderr;
   Pvalue=2*(1-PROBNORM(Z));
   WOLower= WO*exp(-C*SE/(estimate*(1-estimate)));
   WOUpper=WO*exp(C*SE/(estimate*(1-estimate)));
   p=2*(1 - PROBNORM (Z));
RUN;
```

6.3.2 MMRM (alternative estimand 2)

Prior to performing modeling with the MMRM, ICE will be handled in alignment with the estimand strategies in Section 4.2.4.1, Alternative Estimands 2. Missing values that occur while participants continue on their randomized treatment, that is, missed assessments will be assumed MAR. Such missing values are likely to be intermittent and will be imputed using a MCMC MI method.

6.4 Appendix 4: Region Grouping

For the subgroup analyses by region the participating countries will be pooled according to the following rule:

- Europe: Denmark, Germany, Italy, Spain, United Kingdom
- Asia: China, South Korea
- North America: Canada, United States of America

7. References

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