STATISTICAL ANALYSIS PLAN	
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MIRO-CKD:

A Phase IIb, Multicentre, Randomised, Double-Blind, Dose-finding Study to Evaluate the Efficacy, Safety and Tolerability of Balcinrenone in Combination with Dapagliflozin Compared with Dapagliflozin in Patients with Chronic Kidney Disease and Albuminuria

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LIST OF ABBREVIATIONS

List abbreviations and definitions of specialized or unusual terms, measurements, or units. Examples are provided below.

Abbreviation or Specialized Term	Definition
ACEi	Angiotensin-Converting Enzyme Inhibitor
AE	Adverse Event
AER	Albumin Excretion Rate
AESI	Adverse Events of Special Interest
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
ARB	Angiotensin II Receptor Blockers
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BP	Blood Pressure
CDF	Cumulative Distribution Function
CDL	Clinical Data Lock
CKD	Chronic Kidney Disease
CM	Concomitant Medication
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CYP	Cytochrome P450
DAE	Discontinuation due to Adverse Events
ECG	Electrocardiogram
EOT	End of Treatment
eGFR	Estimated Glomerular Filtration Rate

EOT	End of Treatment Visit
ESKD	End-Stage Kidney Disease
FAS	Full Analysis Set
FCS	Fully Conditional Specification
FUV	
GeoCV	Geometric Coefficient of Variation
GeoMean	Geometric Mean
GCP	Good Clinical Practice
HR	Hazard Ratio
ICE	Intercurrent Event
ICF	Informed Consent Form
IP	Investigational Product
IMP	Investigational Medical Product
IPD	Important Protocol Deviation
ITT	Intent-to-Treat
IXRS	Interactive Voice/Web Response System
KM	Kaplan Meyer
LLM	Lower Limit Normal
LLOQ	Lower Limit of Quantification
LTFU	Lost-to-follow-up
MAR	Missing at Random
MMRM	Mixed Model for Repeated Measures
MI	Multiple Imputation
MedDRA	Medical Dictionary for Regulatory Activities
MRA	Mineralocorticoid Receptor Antagonist
NR	Not Reportable
NS	No Sample
NQ	Not- quantifiable
PD	Pharmacodynamic

PMM	Pattern-Mixture Model
PK	Pharmacokinetics
PPS	Per Protocol Set
PT	MedDRA Preferred Term
RAASi	Renin-angiotensin-aldosterone system inhibitors
RDMS	Regulatory Document Management System
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SGLT2i	Sodium-Glucose Cotransporter-2 Inhibitor
SoA	Schedule of Activities
SOC	MedDRA System Organ Class
SoC	Standard of Care
T2DM	Type 2 Diabetes Mellitus
TA	Therapeutic Area
TFDD	Treatment First Dose Date
TLFs	Tables, Listing and Figures
UACR	Urine Albumin to Creatinine Ratio
ULN	Upper Limit Normal
ULOQ	Upper Limit of Quantification
WHO	World Health Organization

AMENDMENT HISTORY

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
N/A	NA	Initial approved SAP	N/A	N/A
Derivation of primary endpoint(s)	5/27/2025	Added description for analysing multiple UACR values: In case of more than 3 UACR values derived from the samples, for applicable visit windows, the geometric mean of all UACR values at each visit window will be computed and used for the analysis.	Yes	For certain subjects, there are more than 3 UACR values available within certain visit windows as defined in the SAP, the change is to specify the way to analyze the UACR under multiple UACR sample situation.
Data presentation	5/27/2025	Participants who are classified as having discontinued the study include: • Those who voluntarily withdrew consent, • Those who were lost to follow-up, • Those who were discontinued due to death, an adverse event, or a decision made by the study physician. • Other	Yes	The previous definition of "Participants who are classified as having discontinued the study" does not cover all the scenarios.

Data presentation	5/27/2025	Added note for stratification information: Note: The derivation of stratification factor eGFR information will be based on laboratory derived values; T2DM status is derived from collected medical history RAVE data; and SGLT2i status is derived from concomitant medication RAVE data.	Yes	To clarify the source of the stratification factor information used in the statistical analysis.
Data presentation	5/27/2025	Added footnote to Table 4: "Other" race category includes subjects who reported "Other", "American Indian or Alaska Native", "Native Hawaiian or other Pacific Islander", or "Multiple races".	Yes	To clarify the "Other" race category.
Exploratory endpoint	5/27/2025	Added additional exploratory analyses regarding CCI and serum potassium endpoints	No	Additional exploratory analysis added to better describe the effects of balcinrenone/dapagliflozin in CCI and serum potassium

1 INTRODUCTION

This SAP contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol of the Phase IIb study D6405C00002 and includes detailed procedures for executing the statistical analysis of the primary endpoint and other data.

The reader is referred to the CSP and the CRF for details of study conduct and data collection.

This SAP describes CSP-defined analyses that will be reported in the CSR. Exploratory objectives that are reported outside of the CSR are specified in the CSP (Table 3 of Section 3).

1.1 Study Design

This is a Phase IIb, multicentre, randomised, double-blind, dose-finding, parallel group, double-dummy study aiming to determine the effect on albuminuria, as well as safety and tolerability of balcinrenone/dapagliflozin compared with dapagliflozin, when given once daily on top of other SoC to patients with CKD and albuminuria.

At least 300 participants ≥ 18 years old, with eGFR ≥ 25 to < 60 mL/min/1.73 m^2, UACR > 100 to ≤ 5000 mg/g, with or without T2DM will be randomised. Participants are eligible both if they are treated or untreated with an SGLT2 inhibitor at screening/enrolment.

Participants will be randomised into one of 3 treatment arms in a 1:1:1 ratio:

- Balcinrenone/dapagliflozin 15 mg/10 mg
- Balcinrenone/dapagliflozin 40 mg/10 mg
- Dapagliflozin 10 mg

For each participant, the total duration of participation will be approximately 23 weeks: starting with an up to 3-week screening period followed by a 12-week treatment period, and an 8-week follow-up period after end of IMP treatment. An optional pre-screening visit may be scheduled. The day of the pre-screening visit will be at the discretion of the investigator.

The study will be conducted at approximately 113 sites in approximately 16 countries globally.

The primary endpoint is the relative change in UACR from baseline to Week 12. In the analysis of the primary endpoint, the effect of treatment (balcinrenone/dapagliflozin 15 mg/10 mg versus dapagliflozin 10 mg and balcinrenone/dapagliflozin 40 mg/10 mg versus dapagliflozin 10 mg) will be analysed assuming that the UACR over time follows a log-normal distribution, hence the observed values will be log-transformed for the analysis.

1.2 Randomization

Participants will be randomized to one of 3 treatment arms in a 1:1:1 ratio. Randomization will be stratified in IRT/RTSM based on participant's enrolment laboratory eGFR at screening (≥ 25 to < 45 and ≥ 45 to < 60 mL/min/1.73 m2) (using the eGFR equation developed by Inker et al. (2021)), SGLT2 inhibitor treatment at screening (yes/no) and T2DM status at screening (yes/no).

1.3 Primary Efficacy Hypothesis

The primary efficacy hypothesis of the study is that in adults with CKD and albuminuria, once daily dosing of balcinrenone/dapagliflozin (either 40 mg/10 mg or both 40 mg/10 mg and 15 mg/10 mg) is superior to dapagliflozin 10 mg in reducing albuminuria, as assessed by the relative change in UACR from baseline to Week 12. For all study objectives see Table 3.

1.4 Sample Size

The sample size determination assumes a 0.7 geometric mean ratio between balcinrenone/dapagliflozin and dapagliflozin for the relative changes from baseline to 12 weeks in UACR, and a standard deviation of 1.0 on log-transformed scale. It is expected that 100 evaluable participants (participants with baseline and one post-baseline measurements of UACR) per treatment group (300 participants in total) will provide a power of 80% for a one-sided Type I error rate of 5% to test the high-dose of balcinrenone/dapagliflozin against dapagliflozin.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

No change was made in the conduct of the study or in the planned analysis reported in this SAP with respect to the CSP version 1.0 (11 January 2024) and CSP version 2.0 (02 October 2024).

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

3.1.1 CCI [redacted] Final Analyses

Final analysis will be conducted after CDL. CCI [redacted]
CCI [redacted]

3.2 Outputs

Descriptive summary outputs will include:

- Participant Disposition and Completion Status
- Analysis Sets

- Important Protocol Deviations
- Demographics
- Baseline Characteristics
- Disease Characteristics
- Medical History
- Prior and Concomitant Medication
- Study Treatment Compliance

3.3 Analysis Populations

Three analysis populations are defined below: Enrolled, Randomised, and FAS. If no signed informed consent is collected, the patient will be excluded from all analysis sets defined below.

Table 1 Populations for Analysis

Population/analysis set	Description
Enrolled	All participants who sign the ICF. Not applicable to participants who only sign the optional pre-screening ICF (abbreviated).
Randomised	All randomised participants.
FAS	All participants who are randomised and receive at least one dose of any IMP. Participants are evaluated according to the treatment assigned at randomisation. The FAS will be used for all analyses (demography, safety, and efficacy).

The FAS will be used for all analyses, including demographic baseline characteristics, efficacy, and safety analyses (for both on-treatment and on-study analysis periods, described in Section 3.4.6. For the pharmacokinetic analyses the Pharmacokinetic Analysis Set is defined in Section 4.3.

3.4 General Study Level Definitions

In this Section general definitions that are applicable to more than one domain are provided.

3.4.1 Continuous Variables

Continuous data will be summarised in terms of number of non-missing observations, mean, SD, median, minimum and maximum; if not otherwise specified.

Log-normal variables, if not otherwise specified, will be summarised in terms of number of non-missing observations, mean, SD, median, minimum, maximum, GeoMean and GeoCV.

3.4.2 Categorical Variables

Categorical variables will be summarised using frequencies and percentages. Unless otherwise specified, the denominator for the calculation of percentages will be the total number of participants within the respective analysis set and treatment group, as applicable.

Percentages will be calculated using the number of participants within a treatment group as denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

3.4.3 Handling of Missing Data

In general, other than that for the below described, or where otherwise specified in the analysis, missing data will not be imputed.

3.4.3.1 Laboratory Missing Data

Laboratory assessment values of urine albumin and urine creatinine of the form of "< x" (ie below the LLOQ) will be imputed as x/2, and those of the form "> y" (ie above ULOQ) will be imputed as "y" in the calculation of summary statistics but displayed as "< x" or "> y" in the listings.

3.4.3.2 AE Data Imputation

Completely missing AE end dates are not imputed. Partial missing AE end dates are imputed as below:

- If the AE is ongoing, the AE end date should be missing
- If the AE is not ongoing, and
    - only the day part of the AE end date is missing, and year (YYYY) and month (MM) parts of the date are present, impute the AE end date as the last day of the collection month
    - both day and month parts of the AE end date are missing, and only the year (YYYY) part of the date is present, impute the AE end date as YYYY-12-31

After applying these rules, if the imputed AE end date is after the end of study date, the AE end date is imputed to be last visit date for the given participant.

Before proceeding with the AE start date imputation, the AE end date is imputed if missing, as described above. Only partial AE start dates are imputed (dates which are completely missing are not imputed).

If only the day part of the AE start date is missing and

- month (MM) and year (YYYY) parts of the AE start date are different from the month and year of the TFDD, then impute the AE start date as YYYY-MM-01
- month and year parts of the AE start date are the same as the month and year of the TFDD
    - and the AE end date is on or after (including ongoing/missing) the TFDD, then impute the AE start date as the TFDD
    - and the AE end date is prior to the TFDD, then impute the AE start date as the AE end date

If both the day and month parts of the AE start date are missing and:

- the AE start year (YYYY) is different from the year of the TFDD, then impute the AE start date as YYYY-01-01
- if the AE start year is the same as the year of the TFDD
    - and the AE end date is on or after (including ongoing/missing) the TFDD, then impute the AE start date as the TFDD
    - and the AE end date is prior to the TFDD, then impute the AE start date as the AE end date

After applying these rules, if the imputed AE start date is after a complete AE end date, then impute the AE start date as the complete AE end date; if the AE end date is missing and the imputed AE start date is after the end of study date then impute the AE start date as the study end date.

3.4.3.3 Concomitant Medication Date Imputation

Completely missing CM end dates are not imputed. Partial missing CM end dates are imputed as below:

- If the CM is ongoing, the CM end date should be missing
- If the CM is not ongoing
    - and if only the day of CM end date is missing, then set the CM end date as the last day of the collected month
    - and both the day and the month are missing, and only the year (YYYY) part of the CM end is present, then set the CM end date as YYYY-12-31

After applying these rules, if the imputed CM end date is after the end of study date, then impute the CM end date as the study end date.

Missing CM start dates are not imputed.

3.4.4 Software

All analyses will be either produced using SAS version 9.4 or later (SAS Institute, Cary, North Carolina, USA), or R (R Core Team 2023) version 4.3.1 or later.

3.4.5 Baseline and Change from Baseline

The *baseline* value for statistical analysis is the last non-missing value prior to or on randomisation visit. In case multiple measurements occur on the same date and the variable is quantitative, then the mean of these measurements will be considered as baseline value. In case multiple measurements occur on the same date and the variable is qualitative, the clinically least abnormal value will be taken as baseline.

Baseline definition of the primary endpoint is provided in the Section 4.2.1.

Change from baseline for quantitative endpoints will be defined as the post-baseline value minus the baseline defined for each timepoint.

Percent change from baseline will be calculated as:

$$change\ from\ baseline(\%) = \left(\frac{visit\ value - baseline\ value}{baseline\ value}\right) \times 100$$

The *baseline age* will be the collected age at screening. If the age is not collected at screening, the following algorithm will be used to derive the age from the birth date in case of only the partial birth date being collected. If only the year part of a date is available, then the date will be set to 01-July. If only the year and month is available, then the date will be set to day 15 of the collected month. The imputed birth date will be used to derive the age at screening (using the date of ICF).

3.4.6 Study Periods

On-study period

The on-study analysis (on-and-off-treatment) period starts on the date of randomisation visit and through end of the planned follow-up period or withdrawal from study, or death.

On-treatment period

The On-treatment analysis period starts on the date of first IMP dose and ends on the earliest of the date of last dose of IMP + 28 days, or withdrawal from study, or death.

3.4.6.1 Study Day

Study Day will be calculated from the date of randomisation. Day 1 is the day of randomisation, Day -1 is the day prior to the date of randomisation, there is no Day 0. Otherwise, the following rules will apply:

- If the date of interest is on or after the date of randomisation:
  Study Day = date of interest – date of randomisation + 1 day.
- If the date of interest is prior to the date of randomisation:
  Study Day = date of interest – date of randomization

When converting the number of days to years, the following conversion factor will be used: 1 year = 365.25 days.

3.4.7 Visit Window

Analysis visit windows have been constructed so that every observation collected can be allocated to a particular visit, including unscheduled assessments. No analysis visit windows will be defined for screening visits. Participant listings will include the actual visits.

Table 2 Analysis Visit Window Definition

Visit Name	Analysis Visit Number	Visit	Target Day	Day Range
Baseline (Randomization)	2	Visit 2 (Baseline)	1	-21 to 1
Intervention Period	3	Visit 3 (Day 8)	8	2 to 14
	4	Visit 4 (Day 29)	29	15 to 43
	5	Visit 5 (Day 57)	57	44 to 70
EOT/ET	6	Visit 6 (Day 85)	85	71 to 99
Safety Follow-up 1	7	Visit 7 (Day 113)	113	100 to 126
Safety Follow-up 2	8	Visit 8 (Day 141)	141	127 to 155

Note: The day range will be extended to include visits with a longer follow-up in the same way (equidistant limits from the target day).

If multiple values are recorded within a single visit window, the rules below will be applied (Note: this does not apply to the primary endpoint which is based on 3 UACR consecutive samples)

- If there are 2 or more observations within the same visit window, then the non-missing observation closest to the scheduled visit will be used in the analysis.

- If 2 observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.

  if 2 or more observations are collected on the same day, then the non-missing observation with the earlier collection time will be included in the analysis. If any observations' collection time is missing the mean of the observations will be used in the analysis. For baseline measurements see 3.4.5.

If a visit window does not contain any observations, then the data will remain missing.

3.4.8 Multiplicity/Multiple Comparisons

For the primary endpoint analysis, the type I error will be controlled at a CCI level for multiplicity by adopting a fixed sequence testing strategy. Statistical significance will be assessed in the pre-specified order of the comparison as specified below. The testing procedure will continue down in the hierarchy if the preceding null hypothesis is rejected at a CCI CCI and will stop if the null hypothesis for the preceding treatment comparison is not rejected at a CCI .

The fixed sequence testing between treatments will be performed in the following order:

1. Balcinrenone/dapagliflozin 40 mg/10 mg vs dapagliflozin 10 mg difference in relative change in UACR from baseline to 12 weeks,

2. Balcinrenone/dapagliflozin 15 mg/10 mg vs dapagliflozin 10 mg difference in relative change in UACR from baseline to 12 weeks.

3.4.9 Handling of Protocol Deviations in Study Analysis

Important protocol deviations

Deviations from the protocol will be assessed as *important* or *not important*. All protocol deviations will be discussed at the data review meetings and finalised prior to CDL.

The final list of IPDs will include but may not be limited to the following deviations:

- Violation of inclusion and/or exclusion criteria
- Participants who received the wrong IMP at any time during the study

- Administration of prohibited medications.

Protocol deviation will not imply exclusion from analysis.

4 STATISTICAL ANALYSIS

This Section provides information on definitions, derivation, and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers participant disposition, analysis sets, protocol deviations, demographics, baseline characteristics medical history, prior, concomitant, and prohibited medication and IMP compliance.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definition and Derivation

The following definitions are applied.

Participants enrolled
All participants who sign the ICF.

Participants not randomised
All participants who have not been randomised to an IMP.

Participants randomised
All participants who have been randomised to an IMP.

Participants who started IMP
All randomised participants who have received at least one dose of IMP.

Participants randomised and not treated
All randomised participants who have not received at least one dose of IMP.

Participants who completed IMP
All participants who have received at least one dose of IMP and who have not discontinued IMP.

A participant who dies during the study without having discontinued IMP prior to date of death, is considered to have completed treatment.

Subcategories of completers will include participants who died, participants who had temporary IMP interruption, or participants who did not have IMP interruption.

Participants who discontinued IMP
All participants who have permanently prematurely discontinued IMP.

Participants who are classified as having discontinued the study include:

- Those who voluntarily withdrew consent,
- Those who were lost to follow-up,
- Those who were discontinued due to death, an adverse event, or a decision made by the study physician.
- Other

Participants who completed the study
All participants who completed the FUV.

4.1.1.2 Presentation

Participant disposition of the enrolled population will be summarised overall and by treatment group and will contain the number of participants:

- enrolled/screened
- randomised (randomised to each stratum)/not randomised
- started treatment/randomised but not started IMP
- completed IMP treatment (death, with interruption, without interruption)/discontinued IMP (reason of discontinuation)
- completed study (dead, alive)/withdrew from study

Randomisation code and assigned IP kit ID will also be listed. A listing including all standardised disposition terms will be also provided.

4.1.2 Analysis Sets

4.1.2.1 Definition and Derivation

The analysis set for efficacy and safety is the FAS as defined in Table 1.

4.1.2.2 Presentation

The number of participants belonging to the FAS, as well as the number of randomised participants excluded from the FAS will be presented in a summary table overall and by IMP treatment group. The FAS will be summarised by the planned treatments of participants, which will be derived from the IRT/RTSM assigned treatments. The actual treatment of participants will be derived from the actual treatment kit they received. The actual treatment of participants will be listed using the FAS population.

Listings of all randomised participants excluded from the FAS population will be also provided including reason for exclusion from the population.

4.1.3 Protocol Deviations

4.1.3.1 Definition and Derivation

Protocol deviations will be captured during the study and will be discussed at the data review meetings and finalised prior to CDL. Some criteria for IPDs are defined in Section 3.4.9.

4.1.3.2 Presentation

The number and percentage of participants with at least one IPD will be summarised for each treatment group and overall, in the FAS population. All protocol deviations will be listed for all participants included in the FAS population.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographics variable will include:

- Age (years)
- Age Group (years) [≤65, > 65 to ≤ 75, >75]
- Sex
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiians or other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Region/Country

Regions are defined as follows:

- Americas (Brazil, Canada, Chile, USA)
- Asia (China, Japan, Malaysia, Taiwan, Turkey, Vietnam)
- Europe (Austria, Bulgaria, Italy, Poland, Spain, UK)

4.1.4.2 Presentation

Demographic variables will be summarised for each treatment group and overall, in the FAS population. Demographic variables will be also listed for all participants included in the FAS population.

4.1.5 Baseline Characteristics

4.1.5.1 Definition and Derivation

Baseline characteristics will include:

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BMI Group (kg/m^2):
    - Underweight (<18.5)
    - Normal weight (≥18.5 to < 25.0)
    - Overweight (≥25.0 to < 30.0)
    - Obese (≥30 to < 35, ≥35 to < 40 and ≥40)

Body Mass Index (kg/m^2) is calculated as: weight (kg) divided by the square of height (m).

4.1.5.2 Reporting

Baseline characteristics will be summarised for each treatment group and overall, in the FAS population. In general, continuous variables will be summarised using number of participants in the analysis (n), mean, median, SD, minimum, and maximum, and categorical variables will be summarised using number and percentage of participants.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Disease characteristics at baseline will include:

- T2DM (yes/no)
- SGLT2 inhibitors (yes / no)
- RAASi (yes/no)

  - ARB (yes/no)
  - ACEi (yes/no)

- Simultaneous use of SGLT2i and RAASi
- Diuretics (yes/no)
  - High ceiling diuretics (yes/no)
- eGFR (mL/min/1.73 m^2)
- eGFR Group (mL/min/1.73 m^2) [< 30 mL/min/1.73 m^2, ≥30 to < 45 mL/min/1.73 m^2; ≥45 mL/min/1.73 m^2]
- UACR (mg/g)
- UACR Group (mg/g) [< 300 mg/g, ≥300 to <1000 mg/g, ≥1000 mg/g]
- Haemoglobin (g/dL)
- Clinical Chemistry parameters:
  - Serum K^+ (mmol/L)
  - Serum Na^+ (mmol/L)
  - Serum Creatinine (mg/dL)
- Vital Signs
  - SBP (mmHg)
  - DBP (mmHg)
- HbA1c (%)
- Serum K^+ Group (mmol/L) [< 3.5 mmol/L, ≥ 3.5 to < 4.5 mmol/L, ≥ 4.5 to < 4.8 mmol/L, ≥ 4.8 mmol/L]

eGFR will be calculated using the CKD-EPI equation (Inker et al 2021

$$eGFR = 142 \times min(SCr/\kappa, 1)\text{^}\alpha \times max(SCr/\kappa, 1)\text{^}(-1.200) \times (0.9938)\text{^}Age \times 1.012[if\ female]$$

Where SCr is standardized serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of (SCr/κ) or 1, and max indicates the maximum of (SCr/κ) or 1.

Details for UACR calculation are provided in Section 4.2.1.

Note: The derivation of stratification factor eGFR information will be based on laboratory derived values; T2DM status is derived from collected medical history RAVE data; and SGLT2i status is derived from concomitant medication RAVE data.

4.1.6.2 Presentation

Disease characteristics will be summarised using the FAS, by treatment group and overall. Continuous variables will be summarised using n (number of participants in the analysis), mean, median, SD, minimum, and maximum, as well as Q1 and Q3 (first and third quartiles), and categorical variables will be summarised using number and percentage of participants.

4.1.7 Medical History

4.1.7.1 Definitions and Derivations

Medical and surgical history will include historic and current medical conditions. Medical history is coded in Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later.

4.1.7.2 Presentation

Medical history and surgical history will be presented in summary tables as number and percentages of participants by SOC and PT for each treatment group and overall. Participants with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Participants with events in more than one SOC/PT will be counted once in each of those SOC/PT. Tables will be sorted by international order for SOC and in alphabetical order for PT. The tables will be based on the FAS population.

4.1.8 Prior and Concomitant Medication

4.1.8.1 Definitions and Derivations

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of screening (Visit 1), or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start date and end date, if applicable
- Dosage information including dose and frequency

The medications listed below are prohibited during the study:

- MRAs or aldosterone antagonists (eg, eplerenone, finerenone, spironolactone).
- Potassium sparing diuretics (eg, amiloride, triamterene).
- Aldosterone analogue fludrocortisone.

The medications listed below are prohibited during the randomised treatment period:

- SGLT2 inhibitors, other than the IMP.
- Strong or moderate CYP3A4 inhibitors or inducers (see Appendix F in CSP for a list of relevant medications and substances).

The WHO Drug Dictionary March 2022 B3 Global or later is used to classify medications by WHO ATC classification of ingredients. The imputation method described in Section 3.4.3.3 is used in case of medication stop date partially missing. Completely missing stop dates will not be imputed. Both completely missing and partially missing CM start dates are not imputed.

After the end date imputation, the medications will be classified as concomitant if the stop date is on or after the randomisation date, or if the medication is ongoing at the study end. Medications with completely missing stop dates are classified as concomitant.

4.1.8.2 Presentation

For analysis of prior, concomitant and prohibited medications, the number and percentage of participants will be provided using the FAS population:

On at least one prior medication, by ATC level 4 (therapeutic group) and product name.

On at least one CM (excluding prohibited medications), by ATC level 4 (therapeutic group) and product name.

On at least one prohibited concomitant medication, by ATC level 4 (therapeutic subgroup) and product name.

4.1.9 Study Intervention Compliance

4.1.9.1 Definitions and Derivations

Compliance will be assessed by pill count and will be calculated as a percentage as follows:

$$Compliance(\%) = \frac{Number\ of\ capsules/tablets\ taken}{Number\ of\ capsules/tablets\ planned} * 100$$

The number of capsules/tablets planned is equal to the expected doses between first dose and end of planned treatment period or when IP is prematurely permanently discontinued, irrespective of temporary discontinuation of IP. All tablets/capsules, including the placebo capsules, are to be counted.

Study drug compliance will be summarised as:

- Compliance (%)
- Compliance Group (%) [< 80%, ≥ 80% to ≤ 120 %, > 120 %]

4.1.9.2 Presentation

Treatment compliance will be summarised using the FAS by treatment group and overall.

4.2 Endpoint Analyses

This Section covers details related to the endpoint analyses such as primary, secondary, exploratory, and other endpoints including sensitivity and supplementary analysis. Table 3 lists primary, safety, and exploratory efficacy objectives.

Table 3 Objectives and Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in Section
Primary					
To determine whether balcinrenone/dapagliflozin is superior to dapagliflozin in reducing albuminuria	Relative change in UACR from baseline to Week 12.	FAS	Treatment policy	Geometric mean	4.2.1
Safety					
To evaluate the safety and tolerability of balcinrenone/dapagliflozin compared with dapagliflozin	• Occurrence and time to first occurrence of AE, SAE, SAE with outcome death, AE leading to discontinuation of IMP and possibly related AE as assessed by the investigator • Observed laboratory values and changes from baseline	FAS	Treatment policy	KM%, HR	4.4

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in Section
	• Observed vital sign values (including BP and pulse rate) and changes from baseline • Observed ECG parameters and changes from baseline • Occurrence and time to first event of AESI (hyperkalaemia, renal events/AKI, and hypotension)				
Exploratory					
Objective 1:					
To explore the magnitude of albuminuria regression for balcinrenone/dapagliflozin compared to dapagliflozin	• A > 1-step regression in albuminuria stage (i.e, from A3 to A2; from A3 to A1; or from A2 to A1) from baseline • At least a 30% reduction in albuminuria from baseline • At least a 50% reduction in albuminuria from baseline	FAS	Treatment policy	Difference in proportions	4.2.3
Objective 2:					
To assess the effect of balcinrenone/dapagliflozin compared with dapagliflozin, on serum K+	Observed values and changes from baseline in serum K+ over time	FAS	Treatment policy	Mean	4.2.3
Objective 3:					

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in Section
To assess changes in eGFR over time from baseline to end of study	Observed values and changes in eGFR from baseline during randomised treatment period and after end of treatment	FAS	Treatment policy	Mean	4.2.3
Objective 4:					
To assess the pharmacokinetics of different doses of balcinrenone/dapagliflozin and of dapagliflozin in plasma	Plasma concentrations of balcinrenone and dapagliflozin over time	PK Set	Treatment policy	Geometric mean	4.2.3
Objective 5:					
To assess the effect of balcinrenone/dapagliflozin on BP compared with dapagliflozin	Observed values and changes from baseline in SBP and DBP over time	FAS	Treatment policy	Mean	4.2.3
The following analyses will be reported outside of the CSR					
Objective 6					
To assess changes in CCI over time from baseline to end of study in subgroups (see objective 3)	See objective 3	FAS	CCI [redacted]	Mean	4.2.3
Objective 7					
To explore the distribution of change in CCI from baseline to day 29 (Visit 4) in each treatment arm and by subgroups.	• Proportion of patients with a change in CCI from baseline to 29 days of CCI [redacted]	FAS	CCI [redacted]	Difference in proportions	4.2.3
Objective 8					
To assess the correlation between the acute change in CCI from baseline to day 29 (Visit 4) and the change in CCI from day 85 (EoT) to day 113 (Visit 8)	• Change in CCI from baseline to day 29 (Visit 4) • Change in CCI from day 85 (EOT) to day 113 (Visit 8)	FAS		Correlation	4.2.3

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in Section
Objective 9					
To assess the correlation between the acute change in CCI and change in CCI CCI from baseline to day 29 (Visit 4)	• Change in CCI from baseline to day 29 (Visit 4) • Change in CCI CCI from baseline to day 29 (Visit 4)	FAS		Correlation	4.2.3
Objective 10					
To assess the effect of balcinrenone/dapagliflozin compared with dapagliflozin, on CCI according to baseline CCI CCI	• Observed values and changes from baseline in CCI over time	FAS	CCI	CCI	4.2.3
Objective 11					
To determine whether balcinrenone/dapagliflozin is superior to dapagliflozin in reducing CCI in subgroups (See Primary objective)	Relative change in CCI from baseline to Week 12.	FAS	CCI		4.2.3
Objective 12					
To determine whether the effect of balcinrenone/dapagliflozin on CCI reduction is mediated by CCI	Relative change in CCI from baseline to Week 12 adjusted by change from baseline in CCI to Week 12.	FAS	CCI		4.2.3
Objective 13					
To determine whether the effect of balcinrenone/dapagliflozin on CCI reduction is mediated by CCI	Relative change in CCI from baseline to Week 12 adjusted by change from baseline in CCI to Week 12.	FAS	CCI		4.2.3

Note: For efficacy analyses intercurrent events of IMP discontinuation and initiation of concomitant medication are handled using the treatment policy strategy, while following death, initiation of dialysis, kidney transplant, WoC, and LTFU participants will be handled using the hypothetical strategy.

4.2.1 Primary

The primary efficacy hypothesis of the study is that in adults with CKD and albuminuria, balcinrenone/dapagliflozin (either 40 mg/10 mg or both 40 mg/10 mg and 15 mg/10 mg, once daily) is superior to dapagliflozin 10 mg in reducing albuminuria, as assessed by the relative change in UACR from baseline to Week 12.

4.2.1.1 Definitions and Derivations

The efficacy variable will be assessed through an estimand with the following attributes:

- **Population:** Participants with an established diagnosis of CKD, eGFR between ≥ 25 and < 60 mL/min/1.73 m^2, and UACR > 100 mg/g to ≤ 5000 mg/g. Participants should not be taking an MRA.
- **Endpoint:** relative change from baseline to 12 weeks in UACR.
- **Treatment**: once daily balcinrenone/dapagliflozin 15 mg/10 mg, balcinrenone/dapagliflozin 40 mg/10 mg, or dapagliflozin 10 mg, all given on top of other SoC medications for CKD.
- **Intercurrent events**:
    - Initiation or change in concomitant treatment, premature discontinuation of IMP and use of prohibited medication will be handled using a treatment policy strategy i.e. ignoring these intercurrent events, implemented by including all available data.
    - Death, initiation of dialysis, kidney transplant, withdrawal of consent, and lost-to-follow-up will be handled using the hypothetical strategy.

All efforts will be made to the extent possible to follow randomised participants and to collect data regardless of study intervention compliance and use of concomitant medications.

UACR Derivation

Central laboratory urine sample for the determination of albumin and creatinine and calculation of UACR will be collected at timepoints described in the SoA. See CSP for reference.

For screening (Visit 1), one random spot urine specimen should be collected during the visit and analysed centrally.

For baseline (Visit 2), UACR will be defined as the geometric mean of 3 UACR values derived preferably from first morning void samples collected at 3 consecutive days, the third being the randomisation date (prior to the first dose of IMP).

Similarly, for Visit 4, Visit 5 and Visit 6 participants will be instructed to collect a first morning void urine sample preferably on 3 consecutive days prior to the visit (preferably the day of visit and the preceding 2 days) which will be returned on the day of visit.

All efforts should be made to ensure morning void samples are properly collected. Only in exceptional circumstances where participant arrives to site without any morning void samples, a spot urine sample can be collected during the visit and reported as an extra urine sample for UACR analysis. Samples will be analysed centrally.

For applicable visits, the geometric mean of the triplicate UACR values will be computed and used for the analysis. The individual UACR from each triplicate urine sample will be calculated as follows:

$$UACR\ (mg/g) = \frac{Urine\ Albumin\ (mg/dL)}{Urine\ Creatinine\ (mg/dL)} \times\ 1000.$$

In case of missing values for UACR the geometric mean will be calculated considering the number of the available measurements, or last non-missing value prior to or on randomisation visit (i.e. in case there is not UACR collected at baseline, and most recent central laboratory UACR value that is obtained from screening can be used as baseline value.)

In case of more than 3 UACR values derived from the samples, for applicable visit windows, the geometric mean of all UACR values at each visit window will be computed and used for the analysis.

UACR transformations

The primary efficacy endpoint for this study is the relative change from baseline in UACR at the end of 12 weeks of study treatment. As UACR is assumed to follow a log-normal distribution, it will be log-transformed for statistical analysis purposes obtaining the ratio of geometric means.

Estimates from analysis of change from baseline in log-transformed UACR will be back-transformed to the relative change from baseline in UACR at $Visit_k, k\ in\ \{3,4,5,6\}$

$$\frac{GeoMean(UACR_{Visit_k})}{GeoMean(UACR_{Baseline})}$$

4.2.1.2 Handling of Dropouts and Missing Data

All available UACR values from all visit windows will be used regardless of any intercurrent events. Missing values will not be imputed. In this analysis it is thus assumed that any missing UACR values are missing at random (MAR).

4.2.1.3 Primary Analysis of Primary Endpoint

Mixed Model for Repeated Measures

The change from baseline in log transformed UACR at Week 12 (EOT) for each of the 2 doses of balcinrenone combined with dapagliflozin 10 mg and dapagliflozin 10 mg will be estimated in a MMRM including in the model the treatment group, visit, and the treatment by visit interaction as fixed effects, adjusting for baseline log-transformed UACR values, randomisation stratification factors (eGFR, SGLT2i and T2DM status), and a participant level random effect. Note that the derivation of stratification factor information eGFR will be based on laboratory-derived values. The estimated change from baseline for each treatment arm as well as the difference between the 2 dose arms and dapagliflozin 10 mg arm will be back-transformed onto the original scale to give relative changes from baseline and the relative difference between treatments.

An unstructured covariance structure will be used for the within-participant errors. The denominator degrees of freedom will be calculated according to the Kenward-Roger method. If the estimating algorithms do not converge, the following steps will be taken to simplify the model until convergence is achieved:

- The following covariance structures will be tried in order: Toeplitz, the first order autoregressive, compound symmetry. Stop as soon as convergence is achieved.

Least square mean estimates per treatment group and the difference between treatment groups as well as SEs and 90% CIs will be obtained. Estimates will be back-transformed to relative change from baseline.

4.2.1.4 Sensitivity Analyses of the Primary Endpoint

In addition to the model-based missing data approach of the MMRM model, a pattern mixture model (PMM) (Ratitch and O'Kelly, 2011) will be employed to handle the missing UACR values based on MNAR assumption. The imputation will be drawn exclusively from the control group rather than the entire study cohort. The rationale behind this is that participants who discontinue from the experimental treatment arm (no longer receiving the experimental treatment) are anticipated to undergo a similar disease progression trajectory as those in the control treatment arm (who are not exposed to the experimental treatment). Likewise, participants discontinuing from the

control arm are assumed to experience a disease progression in the same way as control participants who remain in the study.

4.2.1.5 Subgroup Analysis

To assess the consistency of the treatment effect of the primary endpoint, subgroup analysis will be conducted. For each of the subgroup categories, a separate MMRM model will be fitted. The MMRM model will include, apart from the visit and the treatment-by-visit interaction, the same variables used in the primary analysis and additionally the subgroup variable, the treatment-by-subgroup, and subgroup variable-by-treatment-by-time interaction term will be included.

The model will be first fitted by assuming different covariance matrices by subgroup, following the same procedure for selecting covariance structure as in the primary analysis. If the model will not converge a common covariance matrix will be then assumed for the subgroups.

P-values for interaction term and treatment difference least square estimates per subgroups will be presented. As these analyses are exploratory, p-values and CIs will not be adjusted for multiplicity and results will be interpreted exploratory. The subgroup levels based on baseline values are listed in Table 4:

Table 4 Baseline Subgroups

Subgroup	**Categories (Baseline)**
eGFR (mL/min/1.73m2)	< 30, ≥30 to < 45, ≥45
UACR (mg/g)	≥100 to < 300, ≥300
SGLT2 inhibitor treatment at screening (yes/no)	Yes, No
T2DM Status (history or HbA1c ≥ 6.5% at baseline)	Yes, No
Age (years)	≤ 65, > 65
Sex	Male, Female
Race	White, Black or African American, Asian, Other*

Geographic region*	Americas (Brazil, Canada, Chile, USA) Asia (China, Japan, Malaysia, Taiwan, Turkey, Vietnam) Europe (Austria, Bulgaria, Italy, Poland, Spain, UK)
Ethnicity	Hispanic or Latino/Not Hispanic or Latino
BMI (kg/m^2)	$< 30, \geq 30$
Systolic BP (mmHg)	$\leq$ median, > median

*Geographic region are based purely on geography, using regions and country allocations from the United Nations standard country or area codes for statistical use (M49 Standard for Geographic Regions: https://unstats.un.org/unsd/methodology/m49/).

"Other" race category includes subjects who reported "Other", "American Indian or Alaska Native", "Native Hawaiian or other Pacific Islander", or "Multiple races".

4.2.2 Secondary Endpoints

There are no secondary endpoints.

4.2.3 Exploratory Endpoints

This Section describes analyses of exploratory endpoints corresponding to exploratory objectives (see Table 3).

4.2.3.1 Definition

Exploratory endpoint 1

1. The > 1-step regression is defined as a reversion from a higher baseline status to a lower category of albuminuria measured at the end of the study (i.e. from microalbuminuria (A2) to normal (A1), or from macroalbuminuria (A3) to microalbuminuria (A2) or normal (A1)). (Jansson et al 2018)

2. At least a 30% reduction in albuminuria from baseline.

3. At least a 50% reduction in albuminuria from baseline.

Exploratory endpoint 2

Observed values and changes from baseline in serum K+ over time.

Exploratory endpoint 3

Observed values and changes in eGFR from baseline during randomised treatment period and after end of treatment.

Exploratory endpoint 4

Plasma concentrations of balcinrenone and dapagliflozin over time.

Exploratory endpoint 5

Observed values and changes from baseline in SBP and DBP over time.

The following analyses will be reported outside of the CSR

Exploratory endpoint 6

Observed values and changes in CCI from baseline over time in the subgroups defined in section 4.2.3.2.

Exploratory endpoint 7

Proportion of patients with a change in CCI from baseline of CCI at 29 days overall and in the subgroups defined in section 4.2.3.2.

Exploratory endpoint 8

Correlation between the change in CCI from baseline to day 29 (Visit 4) and the change in CCI from day 85 (EOT) to day 113 (Visit 8).

Exploratory endpoint 9

Correlation between the change in CCI from baseline to day 29 (Visit 4) and change in CCI CCI from baseline to day 29 (Visit 4).

Exploratory endpoint 10

Observed values and changes from baseline in CCI over time in patients with baseline CCI

Exploratory endpoint 11

Relative change in CCI from baseline to Week 12 (EOT) in the subgroups defined in section 4.2.3.2.

Exploratory endpoint 12

Relative change in CCI from baseline to Week 12 adjusted by change from baseline in CCI to Week 12.

Exploratory endpoint 13

Relative change in CCI from baseline to Week 12 adjusted by change from baseline in CCI to Week 12.

4.2.3.2 Analysis of Exploratory Endpoint

Exploratory endpoint 1

The number and proportion of individuals with regression from microalbuminuria (A2) to normal AER (A1), or regression from macro (A3) to microalbuminuria (A2) or normal AER(A1) will be presented by treatment groups. Difference in proportions of patients between two treatment arms and dapagliflozin alone may be analysed using the Cochran-Mantel-Haenszel test, stratified by eGFR, T2DM and SGLT2i use. The difference in proportion will be obtained along with 95% confidence intervals.

The number and proportion of individuals with at least a 30% or at least a 50% reduction in albuminuria from baseline will be presented by treatment groups and the between-group differences in proportion will be tested using the Cochran-Mantel-Haenszel test, stratified by eGFR, T2DM and SGLT2i use. The difference in proportion will be obtained along with 95% confidence intervals.

Exploratory endpoint 2

Observed values and changes from baseline in serum K+ level (central labs) will be summarized by visit and treatment. The change from baseline over time will be analysed by MMRM including all visits (including CCI follow up visits). The model will include treatment group and visit as fixed effects, the baseline value, cohort, and the stratifying factors eGFR, SGLT2i and T2DM, as covariates. Moreover treatment-by-visit interaction will also be included in the model. The analysis will be performed on the FAS.

Exploratory endpoint 3

Observed values and changes from baseline in eGFR (central labs) will be summarized by visit and treatment. The change from baseline over time will be analysed by MMRM including all visits

(including CCI follow up visits). The model will include treatment group and visit as fixed effects, the baseline value, cohort, and the stratifying factors eGFR, SGLT2i and T2DM, as covariates. Moreover treatment-by-visit interaction will also be included in the model. The analysis will be performed on the FAS.

Exploratory endpoint 4

The pre and post dose plasma concentration of balcinrenone and dapagliflozin over time will be summarised in terms of number of non-missing observations, mean, SD, median, minimum, maximum, GeoMean and GeoCV. The analysis will be performed on the FAS.

The details for assessing the pharmacokinetics of different doses of balcinrenone/dapagliflozin and of dapagliflozin in plasma are presented in Section 4.3.

Exploratory endpoint 5

Observed values and changes from baseline in SBP and DBP will be summarized by visit (including follow up visits) and treatment. The change from baseline over time will be analysed by MMRM including all visits. The model will include treatment group and visit as fixed effects, the baseline value, cohort, and the stratifying factors eGFR, SGLT2i and T2DM, as covariates. Moreover treatment-by-visit interaction will also be included in the model. The analysis will be performed on the FAS.

The following analyses will be reported outside of the CSR.

Exploratory endpoint 6

For each subgroup defined below, the observed values and changes from baseline in CCI will be summarized by visit and treatment, where CCI changes over time are analyzed using MMRM, incorporating treatment, visit, baseline values, stratification factors and treatment-by-visit interaction. The analysis will be performed on the FAS. (Details can be found in *Exploratory endpoint 3*).

The analysis will be conducted within the following predefined subgroups

- Baseline eGFR (mL/min/1.73m2) categories: < 45, ≥45
- SGLT2i use at screening: Yes vs. No
- T2DM Status (history or HbA1c ≥ 6.5% at baseline): Yes vs. No
- Baseline UACR (mg/g) categories: ≤300 vs. >300
- Systolic BP (mmHg): <130 vs. ≥130
- Diuretic use at baseline: Yes vs. No

Exploratory endpoint 7

The number and proportion of individuals with CCI [redacted] from baseline at 29 days (Visit 4) will be calculated for each treatment group.

Difference in proportions of patients between two treatment arms and dapagliflozin alone may be analysed using the Cochran-Mantel-Haenszel test, stratified by eGFR, T2DM and SGLT2i use. The difference in proportion will be obtained along with 95% confidence intervals.

The analysis will be conducted in overall population (*Exploratory endpoint 3*) and within the following predefined subgroups:

- Baseline eGFR (mL/min/1.73m2) categories: < 45, ≥45
- SGLT2i use at screening: Yes vs. No
- T2DM Status (history or HbA1c ≥ 6.5% at baseline): Yes vs. No
- Baseline UACR (mg/g) categories: <300 vs. ≥300
- Systolic BP (mmHg): <130 vs. ≥130
- Diuretic use at baseline: Yes vs. No

Note that when a subgroup variable is also a stratification factor, it will be excluded from stratification for the analysis for that specific subgroup.

Exploratory endpoint 8

The correlation between the change in CCI from baseline to day 29 (Visit 4) and the change in CCI from day 85 (EOT) to day 113 (Visit 8) will be assessed using Pearson (Spearman) correlation coefficients. A scatter plot with a linear regression line will be provided to visualize the relationship. For correlation analysis, the 95% confidence intervals (CIs) for the correlation coefficients will be reported.

Exploratory endpoint 9

The correlation between change in CCI and change in serum CCI from baseline to day 29 (Visit 4) will be assessed using Pearson (Spearman) correlation coefficients. A scatter plot with a linear regression line will be provided to visualize the relationship. For correlation analysis, the 95% confidence intervals (CIs) for the correlation coefficients will be reported.

Exploratory endpoint 10

Observed values and changes from baseline in serum CCI (central labs) will be summarized by visit and treatment in patients with CCI [redacted]

CCI [redacted]. The change from baseline over time will be analysed by MMRM including all visits (including CCI follow up visits). The model will include treatment group and visit as fixed effects, the baseline value, cohort, and the stratifying factors eGFR, SGLT2i and T2DM, as covariates. Moreover treatment-by-visit interaction will also be included in the model.

The analysis will be conducted within the following predefined subgroups

- CCI [redacted]
- [redacted]

Exploratory endpoint 11

The treatment effect of the primary endpoint – relative change in UACR from baseline to Week 12 (EOT) will be conducted in two additional baseline subgroups as follows:

- CCI [redacted]
- [redacted]

For each of the subgroup categories, a separate MMRM model will be fitted. The MMRM model will include, apart from the visit and the treatment-by-visit interaction, the same variables used in the primary analysis and additionally the subgroup variable, the treatment-by-subgroup, and subgroup variable-by-treatment-by-time interaction term will be included.

The model will be first fitted by assuming different covariance matrices by subgroup, following the same procedure for selecting covariance structure as in the primary analysis. If the model will not converge a common covariance matrix will be then assumed for the subgroups.

P-values for interaction term and treatment difference least square estimates per subgroups will be presented. As these analyses are exploratory, p-values and CIs will not be adjusted for multiplicity and results will be interpreted exploratory.

Exploratory endpoint 12

To assess the treatment effect on CCI [redacted] while accounting for CCI [redacted] from baseline to week 12, a MMRM model will be used where the dependent variable is the change from baseline in log transformed UACR at Week 12 (EOT). The model will include the treatment group, visit, and the treatment by visit interaction as fixed effects, adjusting for CCI [redacted], baseline CCI [redacted] values, randomisation stratification factors (eGFR, SGLT2i and T2DM status) as covariates, and a participant level random effect. The estimated change from baseline for each treatment arm as well as the difference between the 2 dose arms and dapagliflozin 10 mg arm will be back-transformed onto the original scale to give relative changes from baseline and the relative difference between treatments. Further details for the MMRM will follow section 4.2.1.3.

Exploratory endpoint 13

To assess the treatment effect on CCI while accounting for CCI at week 12, a MMRM model will be used where the dependent variable is the change from baseline in CCI at Week 12 (EOT). The model will include the treatment group, visit, and the treatment by visit interaction as fixed effects, adjusting for CCI from baseline (where the screening value will be used instead as no measurement is collected at baseline) to week 12, CCI values, randomisation stratification factors (eGFR, SGLT2i and T2DM status) as covariates, and a participant level random effect. The estimated change from baseline for each treatment arm as well as the difference between the 2 dose arms and dapagliflozin 10 mg arm will be back-transformed onto the original scale to give relative changes from baseline and the relative difference between treatments. Further details for the MMRM will follow section 4.2.1.3.

4.3 Pharmacokinetics

All participants in the FAS who have at least one quantifiable balcinrenone and/or dapagliflozin plasma concentration measurement after study start will be included in the pharmacokinetic analysis. The PK Analysis Set will be used for all pharmacokinetic (PK) assessments.

4.3.1 Primary Analysis of Pharmacokinetics Endpoint

Plasma balcinrenone and dapagliflozin concentrations will be summarised by descriptive statistics, by timepoint and treatment. Summary statistics for the PK concentrations will include number of observations, number of observations below the LLOQ, geometric mean, geometric coefficient of variation, arithmetic mean, arithmetic standard deviation, median, minimum, and maximum.

Any concentrations that are not reportable or where no sample is available will be excluded from the summary tables. Three observations > LLOQ are required as a minimum for plasma concentrations at a specific time point to be summarised. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as not calculated. For PK concentration summaries, at a visit where less than or equal to 50% of the values are below LLOQ, the LLOQ values at that visit will be set to the LLOQ/2, and all descriptive statistics will be calculated. Plasma concentrations of balcinrenone and dapagliflozin will be listed and summarised by treatment groups and visit, based on the PK Analysis Set.

A by-participant listing of drug concentration data of balcinrenone and dapagliflozin will be provided for all randomised participants. Individual concentrations below the LLOQ will be reported as nonquantifiable in the listings with the LLOQ defined.

Individual plasma concentrations that are Not Reportable will be reported as NR and those that are missing will be reported as NS (No Sample) in the listings.

4.4 Safety Analysis

Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory tests (clinical chemistry, haematology, and urinalysis), and ECG. In addition, extra evaluation will be done for the Adverse Events of Special Interest (AESI; i.e. Hyperkalaemia, Renal Events/AKI, and Hypotension); as defined in Section 4.4.8. Exposure to IMP will be described.

Table 5 Safety Endpoints

Type	Safety Endpoint	Details in Section
General Safety Objective: To assess the general safety and tolerability of balcinrenone/dapagliflozin compared with dapagliflozin alone.		
AEs	Occurrence and time to first occurrence of AE, SAE, SAE with outcome death, Adverse events leading to discontinuation of IMP, possibly related AE as assessed by investigator, possibly related SAE as assessed by investigator.	4.4.2
Laboratory samples	Observed laboratory value, change from baseline.	4.4.3 4.4.4 4.4.5
Vital signs	Observed vital sign value, change from baseline	4.4.6
ECG	Observed ECG parameter, change from baseline.	4.4.7
Other	Occurrence and time to first occurrence of AESIs: Hyperkalaemia, Renal Events/AKI, and Hypotension.	4.4.8

Safety Estimand definition

The general safety objective is evaluated in a scenario where IMP is not prematurely discontinued. Two analysis approaches are considered complementary for all safety endpoints:

- On-treatment: unbiased under the assumption that censoring following premature treatment discontinuation is non-informative.
- On-study: unbiased under the assumption that the risk for an event is independent of continued treatment. Note that this approach could also be described as handling premature treatment discontinuation with a treatment policy approach.

Hence, the general safety objective will be assessed through an estimand defined by the following attributes: On study and on treatment periods are defined in Section 3.4.6.

Population: Patients with CKD and albuminuria as defined by the inclusion criteria and exclusion criteria in the CSP. Implement through the use of the FAS.

Treatment: Balcinrenone/dapagliflozin 15 mg/10 mg or 40 mg/10 mg, and dapagliflozin 10 mg.

Intercurrent events:

- Premature IMP discontinuation: All analysis will be provided using two complementary approaches:
  - Hypothetical as if this ICE cannot happen, implemented by censoring data after premature IMP discontinuation, using the on-treatment analysis period (Section 3.4.6).
  - Treatment policy by ignoring this ICE, implemented by including all available data, using the on-study analysis period (Section 3.4.6)
- Initiation or change of concomitant medication: These ICEs will be ignored, that is, handled using a treatment policy approach.
- Death: this ICE will be handled hypothetically as if it cannot happen, implemented by censoring time-to-event data at death and not imputing any data after death.

Population level summaries and estimators for respective analysis:

Probability of the event (eg AE, lab abnormality) occurring before a predefined time point. Difference in these between the treatment arms, as well as the hazard ratio (over the whole period of interest). For repeated measurements (eg laboratory evaluations performed at several time points) the distributions of the measurements at the respective time point.

This estimand requires that to the extent possible, randomised subjects are followed up regardless of study intervention compliance and adherence to the protocol (for both planned treatment period and safety follow-up).

Analysis

Hazard ratio comparing treatment groups will be estimated based on a Cox proportional hazards regression model with a factor for treatment group, using the full defined analysis period (on-study and on-treatment respectively). For the HR estimate, 95% confidence interval will be obtained from the same model.

The cumulative distribution function of time to event of interest in the respective treatment group will be estimated by a Kaplan-Meier estimator. The probability of the event of interest occurring before predefined timepoint will be estimated by the Kaplan-Meier estimator at last day of planned treatment by treatment group for the defined analysis period (on-study and on-treatment respectively), and the treatment group difference will be estimated at the last day of planned treatment. For the estimate of difference in probabilities, 95% confidence interval will be obtained.

Subgroup analysis of adverse events and other safety events will be performed for only subgroup eGFR (< 30, ≥30), and SGLT2 inhibitor use at screening (Yes/No) with the same approach as for the overall study population but within each subgroup category.

Presentation

Adverse events and safety parameters will be presented based on the FAS by treatment group. Unless otherwise stated all outputs will be presented for both the on-treatment analysis period and the on-study analysis period.

For presentations using data cumulatively over a defined analysis period, comparisons between treatment groups will be presented with their associated 95% confidence interval. Since all safety analysis are descriptive, no p-values will be presented, and the confidence intervals are provided as illustration of precision of the estimate, and their coverage should not be interpreted as a proof of an existence, or an absence, of a safety signal.

SAEs reported before randomisation will be included in the listing of SAEs.

4.4.1 Exposure

4.4.1.1 Definitions and Derivations

The total exposure to IMP (Days) will be defined as the length of period on IMP calculated for each patient as

$$Duration\ of\ Exposure\ (Days) = Date\ of\ Last\ Dose - Date\ of\ First\ Dose + 1.$$

Actual exposure to IMP (Days): an alternative measure where days of interruption are removed will be calculated and termed actual exposure.

4.4.1.2 Presentation

Treatment exposure will be summarised using the FAS by treatment group and overall. Kaplan-Meier estimates for time to premature permanent investigational treatment discontinuation will be presented.

4.4.2 Adverse Events

4.4.2.1 Definitions and Derivations

Adverse events will be collected from randomisation throughout the study intervention period and including the CCI follow-up period. Serious AEs will be recorded from the time of signing of ICF.

All AEs will be classified by SOC and PT according to a MedDRA version 25.0 or later. Additional details on AE reporting are provided in the CSP Section 8.4.8.

The duration of an AE is calculated as the end date of the AE – start date of the AE + 1. Duration is calculated for complete dates only. Imputed dates should not be used. If one of the dates is missing or partially missing, the duration is missing.

Participants with any AE
Defined as *participants* with at least one reported AE with an onset date within the defined analysis period.

Participants with AE with outcome death
Defined as *participants* with at least one reported AE with a 'Fatal' outcome and with an onset date within the defined analysis period (note that there may be more than one AE with a fatal outcome for a given *participant* due to specifics of data collection). The onset date of the AE determines whether an AE belongs to the analysis period, irrespective of date of death.

Participants with AEs possibly related to IMP
Defined as participants with at least one reported AE with "reasonable possibility AE caused by IMP" marked as "Yes" and with an onset date within the defined analysis period.

Participants with AE leading to discontinuation of IMP
Defined as *participants* with at least one reported AE with action taken IMP permanently discontinued and with an onset date within the defined analysis period. The onset date of the AE determines whether the AE leading to discontinuation of IMP belongs to the analysis period, irrespective of date of discontinuation of IMP.

Participants with SAEs
Defined as *participants* with at least one reported serious AE, irrespective of outcome, with an onset date within the defined analysis period. The onset date of the premeditating AE determines whether the SAE belongs to the analysis period, irrespective of the date the AE becomes serious.

Intensity of AEs
Each AE will be classified by the reported maximum intensity, "Mild", "Moderate" or "Severe". Subjects with AEs of a certain intensity will then be defined as subjects with at least one AE of this intensity. If a subject has multiple AEs within the same category of different intensities, the more severe intensity will be considered in the presentations.

4.4.2.2 Analysis

For the distinct types of AEs, the following summaries/analyses will be provided based on the FAS using the on-treatment analysis period as well as using the on-study analysis period:

- Number and percentage of *participants* who experienced an event, by treatment group.
- Kaplan-Meier risk estimate in percent (KM%) by treatment group.

- Difference between treatment groups in KM% together with 95% confidence interval.
- Hazard ratio between treatment groups together with 95% confidence interval, based on a Cox proportional hazards regression model with factor for treatment group.

Missing data
Missing AE data will generally not be imputed. For example, AEs that have missing causality or missing intensity, after data querying, will be left as missing. If missingness in dates prevents a conclusion of treatment emergence of an observation, the safety event will be assumed to be treatment emergent, that is, the concerned date is imputed

4.4.2.3 Presentation

Outputs where AEs are presented by SOC or PT will be sorted by international order for SOC and alphabetical order for PT.

The following outputs will be presented:

Table 6 Safety Outputs

Brief Output Description
Overall summary of AE; KM% table [a] for each respective category: Any AE, Any SAE, Any SAE with outcome death, Any AE leading to discontinuation of IMP, Any AE leading to interruption of IMP, Any possibly related AE [b] , Any possibly related SAE [b]
Any AE by SOC and PT; Any AE per subgroup level by SOC and PT;
AEs with KM% > 5% by PT KM% table [a], including all PTs with a KM% higher than 5%, presented in descending KM% value of treatment group or total of treatment groups.
AE maximum intensity by SOC and PT and severity categories: Any severity, Mild, Moderate, and Severe. AE by decreasing frequency on PT level.

Brief Output Description
SAE with Outcome Deaths by SOC and PT; Any SAE by SOC and PT; Any SAE by SOC, PT and subgroup levels [c];
Key participant information; Tables with key information for participant, categories include: SAE, SAE with outcome death, AE leading to discontinuation of IMP.
Listings; - An AE listing will cover details for each individual AE.
Narratives; Will be produced for all deaths, AEs leading to discontinuation of IMP and SAEs.

a The KM% table presents number and percentage of participants with at least one event per treatment group, KM% per treatment group, difference in KM% between treatment groups, HR.
b Possibly related, as assessed by investigator.
c Only subgroups eGFR (< 30, ≥30), and SGLT2 inhibitor use at screening (Yes/No) will be considered.
AE, adverse event; HR, hazard ratio; IMP, investigational medical product; KM, Kaplan-Meier; PT, preferred term; SAE, serious adverse event; SOC, system organ class.

4.4.3 Clinical Laboratory, Blood Sample

4.4.3.1 Definitions and Derivations

Blood samples for determination of haematology and clinical chemistry will be performed by a central laboratory throughout the study. Clinical laboratory assessments of blood samples will be categorised into haematology (whole blood) and chemistry parameters (serum).

A treatment emergent abnormality is defined as: a switch in parameter from not-abnormal at baseline to abnormal at post-baseline assessments according to predefined criteria.

The predefined criteria for a parameter abnormality is based on reference ranges from the central lab and defined as >ULN or <LLN, where applicable. In addition, the following definitions of abnormalities will be used for specific parameters.

Hy's Law

Potential Hy's Law cases are collected. Potential Hy's Law within a defined analysis period is defined as AST≥ 3 x ULN or ALT≥ 3 x ULN and Total bilirubin ≥ 2 x ULN, where at least one-

time Total bilirubin ≥ 2 x ULN occurred on or after the date of the first occurrence of ALT≥ 3 x ULN or AST≥ 3 x ULN.

Table 7 Laboratory Abnormalities

	Test	Unit	Thresholds
Chemistry	ALP	µkat/L	> 1.5 × ULN, > 3 × ULN
	ALT	µkat/L	> 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
	AST	µkat/L	> 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
	Total bilirubin	µmol/L	> 1.5 × ULN, > 2 × ULN
	S/P-Na^+	mmol/L	< 120, < 130, > 150
	S/P-K^+	mmol/L	≤ 2.5, ≤ 3,>5.5,>6
Haematology	Haematocrit (Vol)	(Vol)	< 0.20 <0.25 > 0.55 > 0.60
	Haemoglobin	(g/L)	< 60 < 80 > 180 > 200

4.4.3.2 Analysis

For the distinct types of treatment emergent abnormalities and potentially clinically significant worsening from baseline respectively the corresponding summaries/analysis as specified for adverse events in Section 4.4.2.2 will be provided based on the FAS using the on-treatment analysis period as well as using the on-study analysis period; including both planned and unplanned assessments.

For the distinct types of laboratory parameters, the following summaries over time per timepoint will be provided after baseline based on the FAS for the on-treatment analysis period as well as for the on-study analysis period; scheduled assessments as per analysis visit windows in Section 3.4.7 will be used;

- For continuous parameters, for observed values and change from baseline:
  - Number of subjects who provided a measurement (n), Mean, SD, Min, Q1, Median, Q3, Max; by treatment group and timepoint.
- For categorical parameters, for observed class and simplified class change from baseline (Class decreased, Class no change, Class increased):
  - Number of subjects who provided any observed class value (n), percentage of subjects who provided a specific class level value based on n, by treatment group and timepoint.

Missing data

Missing data will not be imputed, with the following exceptions:

- If missingness in dates prevents a conclusion of treatment emergence of an observation, assume the assessment is treatment emergent in the concerned analysis.
- In analysis of occurrence of treatment emergent abnormalities, for subjects who have a non-missing post-baseline value and a missing baseline value for a parameter, the missing baseline value is assumed normal.
- Safety assessment values of the form of "< x" (that is, below the lower limit of quantification) or > x (that is, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings.

4.4.3.3 Presentation

The following outputs will be presented:

Table 8 Laboratory Outputs

Brief Output Description
Figure of mean with 95% CI of absolute value or change from baseline over time by treatment group at each planned timepoint.
Treatment Emergent Abnormalities.

Potential clinically significant worsening from baseline.
Potential Hy's law; Cross-tabulation of maximum on-treatment ALT and AST versus maximum on-treatment bilirubin, by treatment group.
Key subject information; Tables with key information for subjects with treatment emergent abnormalities or potential Hy's law.
Listings; Individual participant data including variables such as assessment date and value, change from baseline, LLN, ULN, reference range indicator.

a The KM% table presents number and percentage of participants with at least one event per treatment group, KM% per treatment group, difference in KM% between treatment groups, HR.
ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; HR, hazard ratio; KM, Kaplan-Meier; LLN lower limit normal; ULN, upper limit normal.

4.4.4 Clinical Laboratory, Urinalysis

4.4.4.1 Definitions and Derivations

Urine samples for determination of urinalysis will be performed by a central laboratory, as specified in the SoA of the CSP. The definitions and derivations will follow those of Clinical Laboratory, Blood Sample in Section 4.4.3.1.

4.4.4.2 Analysis

The analysis will follow the Clinical Laboratory, Blood Sample analysis in Section 4.4.3.2.

4.4.4.3 Presentations

The outputs will be presented as described in Clinical Laboratory, Blood Sample presentations in Section 4.4.3.3: Line plots of observed values or class and change from baseline, KM% tables of treatment emergent abnormalities, and listings of individual participant data.

4.4.5 Other Laboratory Evaluations

All other laboratory evaluations will be presented in participant level listings.

4.4.6 Vital Signs

4.4.6.1 Definitions and Derivations

Vital signs will be assessed according to the timelines specified in the SoA. blood pressure and pulse rate will be assessed at study site prior to blood collection for laboratory tests.

The definitions and derivations will follow those of Clinical Laboratory, Blood Sample in Section 4.4.3.1. In addition, the following definitions of abnormalities will be used for specific parameters:

Table 9 Vital Signs

Parameter	Unit	Level	Threshold	Change from baseline
Systolic BP	mmHg	High	≥ 160	Increase ≥ 20
		Low	< 100	Decrease ≥ 20
Diastolic BP	mmHg	High	≥ 90	Increase ≥ 10
		Low	< 60	Decrease ≥ 10
Pulse Rate	bpm	High	≥ 100	Increase ≥ 20
		Low	< 50	Decrease ≥ 20

4.4.6.2 Analysis

The analyses will follow the Clinical Laboratory, Blood Sample analysis in Section 4.4.3.2.

4.4.6.3 Presentations

The outputs will be presented as described in Clinical Laboratory, Blood Sample presentations in Section 4.4.3.3: Line plots of observed values and change from baseline, and KM% tables of treatment emergent abnormalities.

4.4.7 Electrocardiogram

4.4.7.1 Definitions and Derivations

12-lead ECGs (standard ECG with a paper speed of 25 to 50 mm/second covering at least 6 sequential beats) should be recorded after the participant has been resting for at least 5 minutes. ECG date, heart rate, heart rhythm, QT, and QTcF intervals will be recorded in the eCRF. All ECG source data should be retained in the participant records and made available to the monitor upon request. All timepoints for ECG recordings are specified in the SoA (see protocol Table 1). The following definitions of abnormalities will be used:

Table 10 ECG Endpoints

Electrocardiogram	Unit	Thresholds	Change from baseline
Heart rate	bpm	< 30 < 45	NA

		< 50 > 100 > 120 > 150	
QT	ms	< 300 < 320 > 450 > 480 > 500	> 30 > 60
QTcF	ms	< 300 < 320 > 450 > 480 > 500	> 30 > 60

4.4.7.2 Presentations

The outputs will be presented as described in Clinical Laboratory, Blood Sample presentations in Section 4.4.6.3: Line plots of observed class and change from baseline.

4.4.8 AESIs

4.4.8.1 Definitions

The following 3 AESIs are defined in the study:

- Hyperkalaemia,
- Renal events/AKI,
- Hypotension.

Hyperkalaemia

Hyperkalaemia will be analysed based on:

- Reported hyperkalaemia AEs, SAEs, and DAEs. Preferred terms selected as defining hyperkalaemia AESI are listed in Appendix 6.1.
- Observed values and change from baseline in serum potassium levels.
- Protocol-defined criteria for hyperkalaemia (See protocol Section 8.4.4).
    - Central laboratory post-baseline serum K^+ levels above the thresholds of 5.5 mmol/L and 6.0 mmol/L.
    - Investigator-reported local/central laboratory post-baseline serum or plasma K+ levels above the thresholds of 5.5 mmol/L and 6.0 mmol/L.

Outputs for confirmed values (by another central or local laboratory value, collected within up to 72 hours) and single (not confirmed values) will be presented separately.

Renal Events/AKI

Renal events/AKI will be analysed based on:

- Reported deteriorating renal function-related AEs, SAEs, and DAEs. Preferred terms selected as defining renal events/AKI AESI are listed in Appendix 6.1.
- Observed values and change from baseline in serum creatinine/eGFR levels.
- Protocol-defined criteria for renal events/AKI:

  Protocol-defined criteria for renal events related to ESKD

  - Maintenance dialysis for ≥ 28 days, or
  - Kidney transplantation, or
  - Investigator-reported sustained eGFR of < 15 mL/min/1.73 m^2 for ≥ 28 days

  Protocol-defined criteria for renal events related to AKI

  - Investigator-reported increase in serum creatinine ≥ 2 and < 3 times baseline known or presumed to have occurred in the last 7 days, OR
  - Investigator-reported increase in serum creatinine ≥ 3 times baseline known or presumed to have occurred in the last 7 days, OR
  - Use of temporary dialysis (up to 28 days).

Hypotension

Hypotension will be analysed based on:

- Any reported AEs, SAEs, and DAEs due to hypotension. Preferred terms selected as defining hypotension AESI are listed in Appendix 6.1.
- Observed values and change from baseline in BP.
- Protocol-defined criteria for hypotension as defined as:

  - Investigator reported systolic BP below the threshold 90 mmHg and associated symptoms.
  - Any post-baseline absolute systolic BP below the threshold 80 mmHg.

4.4.8.2 Analysis of AESI

The analyses will follow the Adverse Event analyses in Section 4.4.2.2.

Overview

AESIs reported as AEs will be summarised as number and percentage of participants with an event, by seriousness (and whether it resulted in death), whether it leads to IMP discontinuation, by intensity, and whether it is possibly related to IMP (as assessed by the investigator).

Hyperkalaemia

Hyperkalaemia based on the protocol-defined criteria for potassium values will be provided by treatment group. Outputs for both investigator reported and protocol-defined criteria based on central lab values are presented in two sections. The confirmed values (central laboratory values confirmed by another central/local lab value or local lab value confirmed by another central/local lab value, collected within up to 72 hours) and single (not confirmed values) will be presented separately:

Any investigator reported hyperkalemia events in AESI HYKAL (Hyperkalemia) form

- Any central lab serum or plasma K+ levels > 5.5 mmol/L and ≤ 6.0 mmol/L
    - Confirmed by a follow-up central/local lab value (collected and re-tested within up to 72 hours)
    - Not confirmed serum or plasma K^+ levels > 5.5 mmol/L and ≤ 6.0 mmol/L
- Any local lab serum or plasma K+ >5.5 mmol/L and <=6.0mmol/L
    - Confirmed by a follow-up central/local lab value (collected and re-tested within up to 72 hours)
    - Not confirmed serum or plasma K^+ levels > 5.5 mmol/L and ≤ 6.0 mmol/L
- Any central lab serum or plasma K^+ levels > 6.0 mmol/L
    - Confirmed by a follow-up local/central lab value (collected and re-tested within up to 72 hours)
    - Not confirmed serum or plasma K^+ levels > 6.0 mmol/L
- Any local lab serum or plasma K^+ levels > 6.0 mmol/L

- Confirmed by a follow-up local/central lab value (collected and re-tested within up to 72 hours)
- Not confirmed serum or plasma K^+ levels > 6.0 mmol/L

Central lab values meeting the CSP defined criteria

- Any central lab serum or plasma K+ levels > 5.5 mmol/L and ≤ 6.0 mmol/L
  - Confirmed by a follow-up central lab value (available within 7 days)
  - Not confirmed serum or plasma K^+ levels > 5.5 mmol/L and ≤ 6.0 mmol/L
- Any central lab serum or plasma K^+ levels > 6.0 mmol/L
  - Confirmed by a follow-up central lab value (available within 7 days)
  - Not confirmed serum or plasma K^+ levels > 6.0 mmol/L

Mean (+/- standard deviation) of observed values and changes from baseline in serum potassium levels will be summarised.

Renal Events/AKI

Reported renal events related to AKI and ESKD, and their components, will be summarised by treatment group. Time to the first AKI-related event and separately time to the first ESKD-related event will be reported.

Mean (+/- standard deviation) of observed values and changes from baseline in eGFR levels will be summarised.

Hypotension

Hypotension based on protocol-defined criteria for hypotension (Section 4.4.8.1) will be provided by treatment group.

Mean (+/- standard deviation) of observed values and changes from baseline in systolic BP levels will be summarised.

4.4.8.3 Presentations

The following outputs will be presented for AESIs, where applicable:

Table 11 AESI Outputs

Brief Output Description for AESIs
Overall summary of AESI overall and by subgroup.
AESI by SOC and PT.
Overall summary of AE; KM% table [a] per AESI.

a The KM% table presents number and percentage of participants with at least one event per treatment group, KM% per treatment group, difference in KM% between treatment groups, HR.
AE, adverse event; AESI, Adverse event of special interest; HR, hazard ratio; KM, Kaplan-Meier; PT, preferred term; SAE, serious adverse event; SOC, system organ class.

4.4.9 Other Safety Assessments

4.4.9.1 Pregnancy

If there are any positive pregnancy tests reported during the study, an individual participant listing including but not limited to the variables: type of pregnancy test (plasma, serum or urine), assessment date, date of last menstrual period, date of expected delivery will be presented.

4.4.9.2 Overdose

If any overdoses are reported during the study, these will be presented in a listing, including but not necessarily limited to the variables: total dose, if the overdose was intentional and if the overdose was associated with an AE.

5 REFERENCES

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6 APPENDIX

6.1 List of Preferred Terms Defining the Adverse Events of Special Interest

The PTs are based on MedDRA English version 27.0

Hyperkalaemia

- Hyperkalaemia
- Blood potassium increased

Renal events/AKI (based on narrow SMQ Acute renal failure, except for PTs marked with *)

- Acute kidney injury
- Acute phosphate nephropathy
- Anuria
- Azotaemia
- Blood creatinine increased*
- Continuous haemodiafiltration,
- Creatinine renal clearance decreased*
- Dialysis
- Foetal renal impairment
- Glomerular filtration rate decreased*
- Haemodialysis
- Haemofiltration
- Neonatal anuria
- Nephropathy toxic
- Oliguria
- Peritoneal dialysis
- Prerenal failure
- Renal failure
- Renal failure neonatal
- Renal impairment
- Renal impairment neonatal
- Subacute kidney injury

Hypotension

- Hypotension

- Diastolic hypotension
- Orthostatic hypotension
- Dizziness
- Dizziness postural
- Presyncope
- Syncope