STATISTICAL ANALYSIS PLAN	
Study Code	D6970C00009
Edition Number	3.0
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A Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Effect of Baxdrostat on Ambulatory Blood Pressure in Participants with Resistant Hypertension

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialized Term	Definition
ABPM	Ambulatory blood pressure monitoring
ACEI	Angiotensin converting enzyme inhibitors
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AESI	Adverse Event of special interest
AMEA	Asia Pacific, Middle East, and Africa
ANCOVA	Analysis of covariance
AOBPM	Automated office blood pressure measurement
ATC	Anatomic Therapeutic Chemical
BMI	Body mass index
BP	Blood pressure
CDF	Cumulative distribution function
CDL	Clinical data lock
CI	Confidence interval
CM	Concomitant medication
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
DBP	Diastolic blood pressure
Dipper	Participants who have ≥ 10% reduction in night-time BP compared to daytime BP
DMC	Data Monitoring Committee
DOT	Direct observed therapy
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EoS	End of study
EoT	End of treatment
FAS	Full analysis set
FU	Follow-up
HR	Hazard ratio
ICE	Intercurrent event
IMP	Investigational medicinal product
IPD	Important Protocol Deviation

IRT	Interactive response technology
KM	Kaplan-Meier
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LS	Least Squares
MAR	Missing at random
MCAR	Missing completely at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing not at random
MI	Multiple imputations
MI-RD	Multiple imputations – Retrieved dropouts
MI-WO	Multiple imputations – Washout
MRA	Mineralocorticoid receptor antagonists
NDR	Nocturnal dipping rate
PD	Pharmacodynamic
PK	Pharmacokinetics
PPS	Per protocol set
PT	Preferred term
QD	Quaque die (once daily)
QTc	Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle (c for corrected)
RAAS	Renin angiotensin aldosterone system
rHTN	Resistant hypertension
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SoA	Schedule of activities
SOC	System organ class
SOP	Standard operating procedure
ULN	Upper limit of normal
WHODD	WHO drug dictionary

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	29May2024	Initial SAP	Yes	N/A
Section 5.2.2, 5.2.3 secondary endpoints	13Mar2025	Adding PPS analysis for first two secondary endpoints.	Yes	To align with EU feedback and updated EU protocol.
Section 4.2 Endpoint Analyses	13Mar2025	Definition of mean seated BP updated to better align with study design.	Yes	For consistency in the program.
Section 3.3.1.1 Baseline	13Mar2025	Baseline definition aligned with study design.	Yes	Clarification
Section 3.3.1.4 Analysis Periods	13Mar2025	Removed analysis periods irrelevant to the analysis, on-study period covers 2w safety follow-up	Yes	Clarification and for consistency in the program
Section 3.3.2 Analysis Visit Windows	13Mar2025	Updated window for randomisation visit and W12 to account for ABPM	Yes	Align with baseline definition.
Section 3.3.5 Handling of PD	13Mar2025	Updated IPD categories per PD plan and study design.	Yes	Align with study PD plan, clarification.
Section 3.3.7.1 Handling of incomplete dates	13Mar2025	Included definition of CM dates and MH start dates.	Yes	Clarification
Section 3.3.8 Multiple Imputation	13Mar2025	Further clarification regarding the implementation of the multiple imputation methods	Yes	Clarification
Section 3.3.10 ABPM definition and general considerations	13Mar2025	Details added regarding 24 versus 25 hourly averages	Yes	Ensure comparability between patients, clarification.

Section 4.1.1 Subject disposition	13Mar2025	Added subject status per study design.	Yes	Clarification
Section 4.1.6 Disease Characteristics	13Mar2025	Correction of which disease characteristics to be presented	Yes	Correction
Section 4.1.7 Medical and surgical history	13Mar2025	Added specific medical and surgical history, as well as time since diagnosis for hypertension.	Yes	New details provided
Section 4.1.8 Prior and Concomitant Medications	13Mar2025	Updated the definition of prior medication to better align with study design; Updated to present for FAS instead of Safety analysis set.	Yes	Clarification, consistency in the program.
Section 4.1.10 Stratification factors	13Mar2025	Added summary of stratification factor	Yes	Clarification
Section 4.2.1.8 Subgroup analyses	13Mar2025	Analyses and presentation of subgroup variables clarified.	Yes	For consistency in the program.
Section 4.2.4.1 Primary analysis of secondary endpoint	13Mar2025	Added details on multiple imputation.	Yes	Clarification
Section 4.2.9 Secondary Endpoint – Change from baseline in seated DBP at Week 12	13Mar2025	Removed supplementary analysis of secondary endpoint	Yes	For consistency in the program.
Section 4.3 Pharmacodynamic Endpoints	13Mar2025	Removed text on categorical variable summary; updated analysis set for PD analysis.	Yes	Clarification
Section 4.4 Pharmacokinetic Endpoints	13Mar2025	Description of PK reports outside of CSR has been limited	Yes	Lean writing approach
Section 4.6 Safety Analyses	13Mar2025	Specific study day for calculating KM% added at Week 12.	Yes	New details provided

Section 4.6.2 Adverse Events	13Mar2025	Details for analyses and presentation corrected. Brief description of tables included in presentation of safety analyses updated. Removal of AE leading to temporary interruption of IMP. AE by subgroup analyses removed.	Yes	Clarification, for consistency in the program
Section 4.6.7 Electrocardiogram	13Mar2025	Definition of abnormalities Included; Brief description of tables included in presentation of safety analyses updated.	Yes	Clarification, new details provided.
Section 4.6.3 Clinical Laboratory, Blood Sample	13Mar2025	Text for ACTH simulation test added. Criteria for treatment abnormalities related to serum potassium and eGFR updated Clarified Potential Hy's law definition.	Yes	Clarification, for consistency in the program
Section 4.6.6.1 Vital Signs	13Mar2025	Removed treatment emergent for Weight	Yes	For consistency in the program
Section 4.6.7 Electrocardiogram	13Mar2025	Add bar chart for observed class of ECG	Yes	Clarification, for consistency in the program
Section 4.6.8 Other Safety Assessments	13Mar2025	Details regarding AESI added for contributing factors. Pregnancy and Overdose will not be presented and sections removed.	Yes	For consistency in the program
Section 6 References	13Mar2025	Hedman et al 2024 added as reference for details for safety analyses.	Yes	New details provided
N/A	29Jul2025	Changed "heart rate" to "pulse rate" throughout	Yes	Clarification

Section 3.3.2 Analysis visit window	29Jul2025	Revised analysis visit window footnote	Yes	Clarification
Section 3.3.6 Descriptive statistics	29Jul2025	Increased decimal place for pvalue presentation	Yes	Revised to ensure consistency across clinical program
Section 3.3.8 Multiple imputation	29Jul2025	Removed erroneous reference to monotone imputation where not applicable	Yes	Correction
		Removed section on retrieved dropouts	Yes	MI-RD was removed due to insufficient number of retrieved dropouts.
Section 3.3.8.3 Multiple imputation Washout	29Jul2025	Provided additional details for multiple imputation.	Yes	Clarification
Section 4.1.6 Disease Characteristics	29Jul2025	Removed orthostatic	Yes	Simplification, based on clinical input
Section 4.1.8 Prior and Concomitant medications	29Jul2025	Updated definitions of prior, concomitant, and disallowed medications	Yes	Clarification
Section 4.2 Endpoint analyses	29Jul2025	Added tipping point analysis	Yes	FDA request
Section 4.2.1.1 Primary endpoint, definitions	29Jul2025	Added death as a potential intercurrent event and handling strategy.	No	FDA request
Section 4.2.1.5 Primary endpoint, Sensitivity analyses	29Jul2025	Added handling strategy for ICE of death	No	FDA request
Section 4.2.1.5 Primary endpoint, Sensitivity analyses	29Jul2025	Provided additional details for multiple imputation.	Yes	Correction/Clarification
	29Jul2025	Removed MI-RD	Yes	MI-RD was removed due to insufficient number of retrieved dropouts.

Section 4.2.1.6 Supplementary analysis of the primary endpoint	29Jul2025	Added handling for ICE of death	No	FDA request
Section 4.2.1.6 Supplementary analysis of the primary endpoint	29Jul2025	Corrected imputation of other missing	Yes	Correction
		Removed erroneous mention of imputation		
		Added handling and imputation details of ICE of death		
Section 4.2.2 Secondary endpoint	29Jul2025	Updates to derivation	Yes	Clarifications
		Added integer rounding		
		Corrected estimand reference		
Section 4.2.4.1 Primary analysis of secondary endpoint	29Jul2025	Removed MI-RD	Yes	MI-RD was removed due to insufficient number of retrieved dropouts.
Section 4.4.1 Pharmacokinetics	29Jul2025	Added analysis by serum concentration quartiles	Yes	Additional analysis
	29Jul2025	Added text to assign values below LLOQ to LLOQ	Yes	Clarification
Section 4.4.2 Endpoint analyses	29Jul2025	Specified use of day 85 for AEs and day 89 for VS/ECG	Yes	Clarification
Section 4.6 Safety analyses	29Jul2025	Changed km% day	Yes	Clarification
	29Jul2025	Replace weight with BMI	Yes	Based on clinical input
	29Jul2025	Several clarifications and corrections to AESI, vital signs parameters, treatment emergent abnormalities, Hy's law definition.	Yes	Clarification/correction
Section 4.6.1 Exposure	29Jul2025	Added clarification that exposure is defined for both treatment groups	Yes	Clarification
Section 4.6.2 Adverse Events	29Jul2025	Added definition of temporary interruption	Yes	Additional safety analysis

Section 4.6.2.2 Adverse events, analysis	29Jul2025	Removed "possibly related" from presentation of overall ae table	Yes	Consistency across clinical program
Section 4.6.2.3 Adverse events, presentation	29Jul2025	Split eGFR baseline post/baseline	Yes	Clarification
Section 4.6.3 Clinical Laboratory, Blood Sample	29Jul2025	Updated abnormality categories	Yes	Correction
		Adjusted age subgroup to match rest of document		
		Added confirming lab assessments		New analysis
		Added extreme value analyses		
		Added listing of confirming central lab assessments		
		Added KM estimates of potassium above thresholds		
Section 4.6.7 Electrocardiogram	29Jul2025	Removed "heart rhythm"	Yes	Correction across clinical program
Section 4.6.8 Other Safety Assessments	29Jul2025	Added temporary interruptions	Yes	Clarification

1 INTRODUCTION

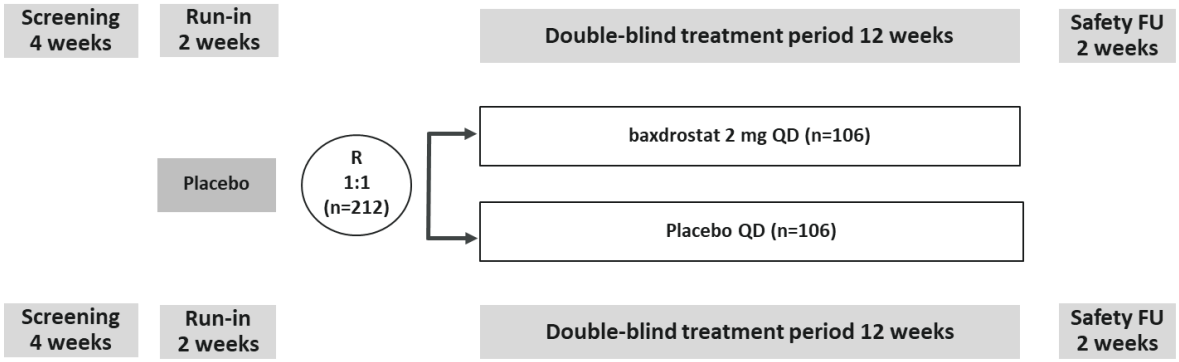
The purpose of this document is to provide details for the statistical analysis of study D6970C00009 supporting the CSR. The SAP is based on the CSP D6970C00009 version 2.0 and CSP EU version 3.0, both dated 29 May 2024.

1.1 Study Design

This is a Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel group study to evaluate the safety, tolerability and the effect of 2 mg baxdrostat versus placebo, administered QD orally, on the reduction of ambulatory 24-hour average SBP, measured by ABPM, in approximately 212 participants with rHTN (defined as seated SBP ≥ 140 mmHg at screening and mean ambulatory SBP ≥ 130 mmHg at baseline, despite a stable regimen of ≥ 3 antihypertensive agents, one of which is a diuretic).

The study is planned to be conducted globally in approximately 100 study centres and approximately 22 countries. For an overview of the study design, see Figure 1.

Figure 1 Study Design



FU = follow-up; QD = once daily; R = randomisation; n = number of participants in that category
Note: participants should remain on their background antihypertensive medication throughout the entire study duration.

Consenting participants will be screened within 4 weeks and will subsequently enter a 2-week single-blind (placebo) run-in period. Thereafter, approximately 212 eligible participants will be randomised in a 1:1 ratio to receive one of the following 2 treatments QD, during the 12-week double-blind treatment period:

- 2 mg baxdrostat
- Placebo

Randomisation will be stratified by mean ambulatory SBP at baseline (< 140 mmHg, ≥ 140 mmHg).

During the 12-week double-blind treatment period, participants should remain on their background antihypertensive medication. Doses of background medications should not be changed during this period unless participants experience SBP < 100 mmHg with symptoms of hypotension. Rescue therapy is permitted if the SBP or DBP exceeds 170 or 105 mmHg, respectively. The choice of rescue therapy is based on the Investigator's best clinical judgement; however, the use of potassium-sparing diuretics and MRAs is prohibited.

After completing the 12-week double-blind treatment period participants will complete a 2 -week safety FU period. The total duration of study participation will be approximately 20 weeks.

1.2 Sample Size

This study is planning to randomise approximately 212 participants using a 1:1 ratio to either receive 2 mg baxdrostat QD or placebo QD, in addition to a stable regimen of background antihypertensive medication in this double-blind treatment period of 12 weeks. The sample size takes into account the statistical power for the primary endpoint.

Assuming a treatment difference of 6 mmHg and a common standard deviation of 12 mmHg in change from baseline in 24-hour ambulatory SBP at Week 12, the planned sample size will provide 88% statistical power (accounting for 25% drop-out) for the comparison of baxdrostat 2 mg versus placebo, using a two-sample t-test at a 2-sided significance level of 0.05.

Due to lack of previous ABPM data on baxdrostat, the assumptions for the effect size for change in ambulatory SBP from baseline to Week 12 considered changes in SBP data from the Phase II studies BrigHTN (CIN-107-121) (Freeman et al 2023) and HALO (CIN-107-124, NCT06034743). The assumed standard deviation considers data from the PRECISION trial (Schlaich et al 2022) and AC-080A201 trial (Verweij et al 2020) for Aprocitentan.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

The ICE of death and its handling strategy have been added in the estimand definitions for the primary and secondary efficacy endpoints, with a hypothetical strategy applied as if the subject had not died.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

The CDL for writing the CSR will occur once all participants have completed their full study participation or have withdrawn from the study and the CDL database will be the source data for all analyses as indicated by the CSP and this SAP.

3.2 Analysis Populations

The following analysis populations will be used for this study:

Table 1 Populations for Analysis

Population/Analysis Set	Description
Randomised Set	Includes all randomised participants. This population will be used for the purpose of subject disposition.
FAS	All randomised participants who received at least one administration of IMP. Data from participants will be analysed according to the treatment group to which they were randomly assigned. Unless otherwise stated, the FAS will be used for the efficacy endpoints.
PPS	All participants in FAS who met the following criteria: 1) no permanent discontinuation of IMP 2) no rescue therapy initiated 3) pre-specified minimal exposure of IMP, defined as participants with compliance >= 80% 4) completed and valid ABPM assessment at Week 12 5) no IPDs Since receiving at least one dose of incorrect IMP will be an IPD, participants in the PPS will be analysed as randomised (which for this analysis set is identical to analysis by the actual study intervention received). Unless otherwise stated the PPS will be used for the sensitivity/supplementary analysis of the primary endpoint and key secondary endpoints, as specified in the CSP EU V3.0.
Safety Analysis Set	All randomised participants who received at least one administration of IMP. Treatment classification will be based on IMP that participants actually receive (ie, erroneously treated participants will be classified according to the treatment they actually received and not to the treatment they were meant to receive). Unless otherwise stated the safety analysis set will be used for the safety analyses.

Population/Analysis Set	Description
PK Analysis Set	All randomised participants who have at least one evaluable post-dose plasma concentration data for PK analysis and who received active treatment.

FAS, full analysis set; IMP, investigational medical product; PK, pharmacokinetic.

3.3 General Considerations

All statistical analyses will be performed using SAS® software (SAS Institute Inc., Cary, NC, USA).

3.3.1 General Study Level Definitions

3.3.1.1 Baseline

ABPM

Baseline 24-hour ABPM is defined as the last completed and qualified 24-hour ABPM recording obtained prior to randomisation and its average will be calculated by the sponsor based on final validated ABPM dataset provided by third party vendor (Clario). Baseline night-time (from 2200 to 0559) ambulatory BP and baseline daytime (from 0600 to 2159) ambulatory BP are defined analogously. Details of ABPM calculations are provided in Section 3.3.10.

Seated BP

Three seated BP measurements (each approximately 1 minute apart) should be obtained using the same arm and the AOBPM device at each clinical site visit. Mean seated BP is defined as the average of the last 2 seated BP measurements of the total 3 measurements, at any single clinical site visit as per CSP. If multiple mean seated BP readings are obtained during the baseline visit, the last mean seated BP will be used.

Other baseline values for statistical analysis are the last non-missing values prior to or on the date of randomisation unless otherwise specified.

3.3.1.2 Change from Baseline

Change from baseline to post-baseline is defined as measurement at post-baseline minus measurement at baseline.

Percent change from baseline to post-baseline will be calculated as, change from baseline to post-baseline divided by measurement at baseline, multiplied by 100.

3.3.1.3 Study Day

Study Day will be calculated from the date of randomisation. Study Day 1 is the day of the randomisation and Study Day -1 is the day prior to the randomisation. There is no Study Day 0.

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

3.3.1.4 Analysis Periods

Analysis periods will be used in reporting statistical analyses.

Double-blind period (Week 0 to Week 12 + 2 weeks of safety FU)

- On-study: The On-study analysis period starts on the date of randomisation (Visit 4) and ends on the date of the last visit in the study, unless the subject dies or withdraws consent, in which case the earliest of date of death or date of consent withdrawal will be used as the end of the period.
- On-treatment: The On-treatment analysis period starts on the date of randomisation (Visit 4) and ends on the earliest of 10 days following the date of last dose of IMP or the end of On-study analysis period.

The rationale of adding 10 days post last dose of IMP for the On-treatment period is to accommodate the half-life of approximately 29 hours for baxdrostat, which will require 7 days for the concentration to be below clinically relevant concentrations, and an additional estimated 3-4 days to accommodate for PD markers.

3.3.1.5 Treatment Groups

In efficacy analyses, participants will be analysed according to the treatment group to which they were randomly assigned, as defined by FAS in Table 1.

In safety analyses, treatment group classification will be based on the IMP that participants actually receive, as defined by Safety analysis set in Table 1. Specifically, a subject who on one or several occasions has received active IMP is classified as active and is accounted for the active IMP treatment group. Participants randomised to active treatment but only received placebo will be classified as having received placebo.

3.3.1.6 Stratification Factors

The randomisation will be stratified by mean ambulatory SBP at baseline (< 140 mmHg, ≥ 140 mmHg). The information on this stratification factor for the purpose of randomisation is provided by the site staff based on the preliminary report from ABPM device and captured in the IRT system.

3.3.2 Analysis Visit Window

For the purpose of by-visit analyses, the following analysis visits will be defined to map all assessments from visits to a specific analysis visit. Analysis visit windows will be defined in Table 2 in accordance with the SoA in the CSP. Analysis visit windows will use study day as defined in Section 3.3.1.3. The 2 sets of analysis visit windows defined below apply to most assessments. However, different visit windows may be necessary for assessments following a different schedule. Of note, analysis visit windows are not defined for the assessments performed at Visit 1 (Screening), Visit 2 and Visit 3 (Placebo run-in). These assessments will be summarised or analysed based on the recorded visit.

Table 2 Analysis Visit Windows

Visit number in CSP	Analysis Visit	Target Study Day	Study Day Range – All assessments except safety labs†	Study Day Range – Safety labs† only
1	Screening	N/A	N/A	N/A
2	Run-in	N/A	N/A	N/A
3	Run-in	-1	NA	NA
4	Randomisation	1	[-Inf,1]	[-Inf, 1]
5.1	Week 1	8	N/A	[2, 12]
5.2	Week 2	16	N/A	[13, 22]
6	Week 4	29	[2, 43]	[23, 43]
7	Week 8	57	[44, 70]	[44, 70]
8/9	Week 12/EoT *	84/85	[71, 92]	[71, 92]
SFU	Week 14	99	[93, +inf]	[93, +inf]

† Safety labs are defined in CSP V2.0 Section 8.3.4 Clinical Safety Laboratory Tests.
* For participants with Week 12 ABPM or AOBPM performed out of analysis window but still before Day 99, ie, [93, 98], the BP will be mapped to Week 12 analysis visit.

If there are multiple assessments within the same analysis visit window, the assessment that is closest to the target date will be selected. In case the assessments are equidistant from the target date, the earlier assessment will be selected.

3.3.3 Handling of Unscheduled Visits

If there is more than one assessment in the same time window, the assessment closest to the target day, without regard to whether visits were scheduled or unscheduled is selected for analysis. All scheduled and unscheduled assessments will be presented in the listings.

3.3.4 Multiplicity/Multiple Comparisons

A multiple testing procedure will be used to strongly control the familywise Type I error rate at 0.05 (two-sided), between the primary and secondary endpoints. In the first step of the confirmatory testing, the primary endpoint, change from baseline in ambulatory 24-hour

average SBP at Week 12, will be tested at two-sided alpha of 0.05. Thereafter, the hypotheses corresponding to the secondary endpoints will be tested in sequence until a test fails to reject the null hypothesis or until all the listed null hypotheses are rejected:

- Change from baseline in ambulatory night-time average SBP at Week 12
- Change from baseline in ambulatory daytime average SBP at Week 12
- Change from baseline in seated SBP at Week 12
- Achieving ambulatory 24-hour average SBP of < 130 mmHg at Week 12
- Change from baseline in ambulatory 24-hour average DBP at Week 12
- Change from baseline in ambulatory night-time average DBP at Week 12
- Change from baseline in ambulatory daytime average DBP at Week 12
- Change from baseline on seated DBP at Week 12
- Achieving a nocturnal SBP dipping of ≥ 10% at Week 12

The testing procedure will retain alpha for the next hypothesis in the sequence until a test fails to reject the null hypothesis or until all listed null hypotheses are rejected. The p-values from all endpoints in the testing procedure after the first non-rejected null hypothesis for the secondary endpoints will not be adjusted, thus will be nominal and considered explorative.

For exploratory endpoints no adjustment will be made for multiple testing and only nominal p-values will be presented. Similarly, for subgroup analyses no adjustment will be made for multiplicity and only unadjusted p-values of interaction will be presented. The p-values for treatment comparisons within subgroup categories will be presented where applicable.

3.3.5 Handling of Protocol Deviations in Study Analysis

IPDs are defined as protocol deviations which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a patient's rights, safety or well-being. They will include (but are not limited to):

1 Inclusion Criteria Deviations
2 Exclusion Criteria Deviations
3 Discontinuation Criteria for study product met but participant not withdrawn from study treatment
4 IP Deviation
5 Excluded Medications taken
6 Deviations to study procedure
7 Other IPDs

IPDs will not be used to exclude any participant or participant data from the FAS. However, IPDs will be used to exclude participants or participant data from the PPS.

All protocol deviations will be discussed at the data review meeting and finalised prior to CDL.

3.3.6 Descriptive Statistics

Study-collected data will be summarised with descriptive statistics to provide an overview of data. The type of descriptive statistic will depend on the variable being summarised. Generally continuous variables will be summarised with number of participants (n), mean, standard deviation (SD), minimum, 25% quartile (Q1), median, 75% quartile (Q3) and maximum. Geometric mean and coefficient of variance (CV) will be calculated in addition to arithmetic mean and SD, if appropriate. Generally categorical variables will be summarised with frequency and percentage of participants in each treatment group for each category. Participants with non-missing data will be included in the descriptive statistics. When appropriate, number of missing observations will be presented, and these will not be included in the denominator when calculating percentages. Total n and percentages will be reported for relevant variables and analysis sets when applicable.

Descriptive statistics (mean, SD, median, Q1, Q3) will generally be presented to 1 more decimal place than the collected values. The minimum and maximum values should be reported to the same number of decimal places as the individual values reported.

The ambulatory BP for 24-hour, night-time and daytime will be presented in integer, ie, with 0 decimal point. Same applies to the seated BP data.

The CI for data presentations is 95% by default if nothing else is specified. The p-values will be presented using 4 decimal places for all values ≥ 0.0001. For smaller values, the p-value will be presented as < 0.0001.

3.3.7 Handling of Missing Data

Unless otherwise noted, no imputation of missing data will be done. Efforts will be made to follow the participants and collect the data even after the participants discontinue the treatment.

For the primary analysis of the primary and secondary endpoints concerning ABPM, missing data will not be imputed. ABPM data will only be imputed for the sensitivity analysis and supplementary analysis of these endpoints. For the secondary endpoints concerning AOBPM, missing data will be handled using MI, as described in Section 3.3.8.

Approaches that will be used to handle missing data for other efficacy analyses will be described in the respective analysis sections.

3.3.7.1 Handling of Incomplete Dates

The following imputed dates will only be used for analysis purposes and will remain as reported (partially or completely missing) in subject listings.

Incomplete adverse event dates

Partially or completely missing AE onset dates will be imputed as follows:

- If only the day value of the AE onset date is missing, the first day of the month will be used; unless this occurs in the same month and year as the latest of randomisation (Visit 4) and date of first dose of IMP, then the latest of randomisation (Visit 4) and the date of first dose of IMP will be used.
- If the day and month values of the AE onset date are missing, January 1 will be used; unless this occurs in the same year as the latest of randomisation (Visit 4) and the date of first dose of IMP, then the latest of randomisation (Visit 4) and the date of first dose of IMP will be used.
- If the onset date is completely missing, the latest of randomisation (Visit 4) and the date of first dose of IMP will be used.

Incomplete concomitant medication dates

For CM started more than one year prior to study start the start date will not be imputed. The following applies to partially or completely missing medication start dates:

- Missing day – impute with the 1st of the month unless month is same as month of randomisation date, then impute with date of randomisation.
- Missing day and month – impute 1st January unless year is the same as randomisation date, then impute with date of randomisation.
- Completely missing – impute with date of randomisation unless the end date is prior to the randomisation date, in which case impute the 1st January of the same year as the end date.
- When imputing a start date, it will be ensured that the new imputed date is sensible, ie, is prior to the end date of the medication.

For the definition of a medication as concomitant (Section 4.1.8.1), the following applies to partially or completely missing medication end dates:

- If the medication is ongoing, the medication end date should remain missing.
- If the medication is not ongoing, partially missing end dates will be imputed as follows:

  - If only the day of medication end date is missing, then set the medication end date as the last day of the collected month.
  - If both the day and the month are missing, and only the year (YYYY) part of the medication end is present, then set the medication end date as YYYY-12-31.
  - After applying these rules, if the imputed medication end date is after the EoS date, then impute the medication end date as the study end date.
- Completely missing medication end dates are not imputed.

Incomplete medical/surgical history dates

The start date of medical history of hypertension will be used to calculate time since hypertension diagnosis. Partially or completely missing start dates of hypertension will be imputed as follows:

- If only the day value of the start date is missing, the first day of the month will be used; unless this occurs in the same month and year as the date of signing first ICF, then the date of signing first ICF - 1 will be used.
- If the day and month values of the start date are missing, January 1 will be used; unless this occurs in the same year as the date of signing first ICF, then the date of signing first ICF – 1 will be used.
- If the start date is completely missing, these will not be included in the summary.

No other imputation of start/end dates will be performed for medical/surgical history.

3.3.8 Multiple Imputation

MI will be applied to the sensitivity analysis/supplementary analysis of ABPM endpoints as well as the primary analysis/sensitivity analysis of the seated BP endpoints. Please refer to Section 4.2 for details.

3.3.8.1 Non-monotone Missing Data Patterns

Firstly, a distinction will be made between non-monotone and monotone missing data. Monotone missing data are defined as missing data after the last observation at time point t_1 to the end of FU, while non-monotone missing data means that there are observations made after the missing time point t_2. Since ABPM data are collected only at baseline and Week 12, non-monotone missing data are not expected for ABPM related endpoints. However, imputation of non-monotone missing data is expected to be applicable to seated BP. As the first step for any of the imputation methods described below, the non-monotone missing data will be imputed under the MAR assumption by using the MCMC method. This will generate partially imputed datasets with a monotone missing data pattern. A total of $m = 100$ datasets with monotone missing data pattern will be generated, using a seed of 10810.

The SAS procedure PROC MI will be used to perform the imputations, with the MCMC statement together with the options IMPUTE=MONOTONE. The imputation model will include baseline and post-baseline values at scheduled visits in chronological order where applicable. The imputations will be conducted separately for each treatment group. The datasets with monotone missing data pattern will be the starting point for implementing the imputation methods below.

3.3.8.2 Monotone Missing Data Patterns

Missing ABPM, including incomplete or non-valid ABPM will be multiple imputed to create a total of $m = 100$ datasets using a seed of 0520. Missing AOBPM will be multiple imputed to create a total of $m = 100$ datasets using a seed of 10810180.

Multiple imputation inference, under either the MAR or the MNAR assumption, involves the following three general steps:

1 The missing data are imputed with appropriate MI methods *m* times to generate *m* complete datasets.
2 The *m* complete datasets are analysed by appropriate method.
3 The results from the *m* complete datasets are combined for the inference using Rubin's rules.

Missing data not following not associated with intercurrent events of treatment discontinuation or initiation of rescue therapy will be assumed MAR and imputed using a regression method. The imputation model will include the same covariates as the imputation model above. The imputations will be conducted separately for each treatment group.

3.3.8.3 Multiple Imputation Washout

The MI-WO is a reference-based imputation method and assumes that the pattern of endpoint measurement in participants in the baxdrostat group who experience an ICE and subsequently do not have endpoint measurement at Week *t* is similar to the pattern in participants in the placebo group (reference group). The imputation will be conducted separately for baxdrostat and placebo.

For participants in the baxdrostat treatment group, missing endpoint measurements at Week *t* will be imputed based on observed endpoint measurements at Week *t* in participants in the placebo group assuming data pattern follows MNAR. The imputation model will include baseline endpoint value and endpoint value at Week *t* where applicable.

For participants in the placebo group, missing endpoint measurements will be imputed sequentially for each scheduled visit based on observed endpoint measurements in participants in the placebo group assuming MAR. Specifically, the imputations will be informed by all observed data from that visit and data from all prior visits (after imputation) in the placebo

group. The imputation model will include baseline endpoint value, and endpoint value at each post-baseline visit up to Week *t*.

MI-WO will be used for imputing ABPM data following treatment discontinuation or initiation of rescue medication in the sensitivity analysis and supplementary analysis of the primary endpoint. MI-WO will also be used for imputing seated BP data following treatment discontinuation or initiation of rescue medication in the primary analysis and supplementary analysis of the seated BP related secondary endpoints.

The SAS procedure PROC MI will be used to perform MI-WO, with the MONOTONE statement together with the REGRESSION option and, when appropriate, the MNAR statement.

3.3.8.4 Combining Results Based on Multiple Imputed Datasets

Continuous variables

An ANCOVA model will be used in each of the *m* imputed data sets to provide LS means, LS means differences and corresponding standard errors. These results are then combined according to Rubin's rules in the SAS procedure PROC MIANALYZE to provide the final estimates with 95% CIs as well as the p-value.

Categorical variables

A logistic regression model will be used to provide the parameter estimate and the corresponding standard error in each of the *m* imputed data sets. Rubin's rules assumes that multiple imputation estimates are asymptotically normal distributed. The following steps will be performed to estimate the odds ratio,

- Combine the log-transformed estimates from PROC LOGISTIC model using Rubin's rules in the SAS procedure PROC MIANALYZE to provide the combined parameter estimate, 95% CIs for the parameter estimate, as well as the p-value.
- Back transform the combined overall estimates using the exponential function to obtain odds ratio and 95% CIs for the odds ratio.

3.3.9 Geographic Regions

Geographic regions as defined in Table 3 will be used in the statistical analysis and reporting as applicable, such as recruitment summary by region and subgroup analysis by region.

Table 3 Geographic Regions

Region	Country
AMEA	Australia
	Malaysia
	Philippines
	Saudi Arabia
	South Africa
	Taiwan
	Thailand
	Vietnam
Americas	Argentina
	Canada
	United States
Europe	Belgium
	Bulgaria
	Czech Republic
	Germany
	Greece
	Hungary
	Poland
	Slovakia
	Spain
	Turkey
	United Kingdom

3.3.10 ABPM Definition and General Considerations

Ambulatory BP measurements will be performed for at least 25 hours; this will allow a minimum of 24-hour readings since the measurements recorded within the first hour - after placement and activation of the device - will not be used for analysis purposes.

Statistical analyses of the available ABPM recordings will be conducted independently from the ABPM report produced from ABPM device vendor.

The ABPM device will record BP measurements every 20 minutes during a 16-hour daytime period (from 0600 to 2159), more specifically, at the timepoints corresponding to the 00 minutes, 20 minutes, and 40 minutes of every hour; and every 30 minutes during an 8-hour night-time period (from 2200 to 0559), at the timepoints corresponding to the 00 minutes and 30 minutes of every hour. In the definitions in this section, 'hour' and 'hourly mean' refer to the hour based on clock time, not elapsed time. ABPM device will make up to two additional attempts if any ordinary measurement is a failure.

Data validity

If the ABPM 25-hour period is not completed, the assessment will be repeated at an unscheduled visit. The ABPM assessment will be considered completed and valid when all the following three criteria are fulfilled:

- $\geq$ 20 hours are recorded by the ABPM device.
- $\geq$ 70% of the ABPM readings are recorded.
- $\leq$ 2 consecutive hours of recordings are missing.

Participants who cannot complete the 25-hour ABPM assessment at randomisation within two attempts will be considered screen failures.

If a participant cannot complete the 25-hour ABPM assessment at EoT within two attempts, the data will be considered missing, and the participant will be excluded from the primary analysis on ABPM endpoints. Only completed and valid ABPM assessment will be included in the analysis and reporting.

Average values will be calculated for each clock hour, over the 24 hours (elapsed time) starting from the first reading after removing the first hour. The 24-hour average will be calculated by taking the averages of 24-hourly average values. The daytime average will be calculated by taking the averages of 16 hourly average values starting at 0600 in the morning and ending at 2159 in the evening while night-time average will be calculated by taking the averages of 8 hourly average values starting at 2200 in the evening and ending at 0559 in the morning.

The hourly SBP and DBP averages will be calculated by taking the average of the 1-3 readings taken during the corresponding clock hour (for example, the average of SBP/DBP from 0700 to 0759 is represented by the measurements taken during this hour). Due to the difference between elapsed hours and clock hours, there may be measurements in the 25th clock hour (after removing the first hour) in some cases. The measurements in the 25th clock hour will be merged with those in the 24th clock hour in calculating the hourly average for the 24th clock hour.

For the purpose of presenting graphical information on the BP (SBP and DBP) and pulse rate values, the hourly averages will be used.

Definition of Nocturnal Dip and Dipper

The NDR is defined as the difference between ambulatory daytime average SBP and ambulatory night-time average SBP, expressed as a percentage of the daytime average SBP. The formula for calculation is as follows:

$$Nocturnal\ dipping\ rate\ (\%) = 100 \times (average\ daytime\ SBP - average\ nighttime\ SBP)/(average\ \ daytime\ SBP).$$

Participants who have ≥ 10% reduction in night-time SBP compared to daytime SBP will be characterised as dippers. Participants who have < 10% reduction in night-time SBP compared to daytime SBP will be characterised as non-dippers. The formula for calculation is as follows:

$$baseline\ dipping\ status = \begin{cases} dipping, & NDR \geq 10\% \\ non-dipping, & NDR < 10\%. \end{cases}$$

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 subject disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical/surgical history, prior and CM, and study drug compliance.**Subject Disposition and Completion Status**

4.1.1.1 Definitions and Derivations

Disposition will be presented for all enrolled subjects which is defined as subjects with an ICF date. The following categories will be presented:

- Subjects screened – defined as enrolled subjects
- Subjects started placebo run-in period
- Subjects screened but not randomised
- Subjects randomised, regardless of receiving IMP
- Subjects randomised, not treated
- Subjects started treatment, completed treatment, discontinued treatment

- Subjects completed study and withdrew from study

4.1.1.2 Presentation

Subject disposition of the enrolled population will be summarised by frequency. For categories of study completion/discontinuation post-randomisation, number of participants and percentages by treatment group and overall will be presented based on FAS.

Subject disposition, randomisation code, and investigational product batch number will be listed.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The analysis sets are defined in Table 1.

4.1.2.2 Presentation

Analysis sets will be presented by number of participants in each analysis set for all randomised participants, by treatment group and overall. The reason for exclusion from an analysis set will be presented.

Subjects excluded from any analysis set will be listed.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

The protocol deviations will be captured during the study and will be reviewed on a regular basis and finalised prior to CDL. IPDs are described in Section 3.3.5.

4.1.3.2 Presentation

The number and percentage of patients with at least one IPD will be summarised by total and by IPD category, for each treatment group and overall, in the FAS population. All IPDs will be listed for all patients included in the FAS population.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographic variables include age, age category (< 65 years; ≥ 65 – < 75 years, ≥ 75 years), sex, race, ethnicity, geographical region, and country. Participants selecting more than one race will be categorized as “Multiple”.

4.1.4.2 Presentation

The demographic attributes as described above will be summarised descriptively. The data will be presented for the FAS, by treatment group and overall.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristics include height (cm), weight (kg), BMI (kg/m^2), and BMI category (<25 kg/m^2, ≥25 - <30 kg/m2, ≥30 kg/m2). BMI (kg/m^2) is calculated as: weight (kg) divided by the square of height (m).

4.1.5.2 Presentation

The baseline characteristics as described above will be summarised descriptively, using frequency distributions and summary statistics for the FAS, by treatment group and overall, at study baseline.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Disease characteristics include ambulatory SBP and ambulatory DBP 24-hour average, night-time average and daytime average, as well as seated SBP, seated DBP, dipping status, pulse rate, HbA1c, Type 2 diabetes status (Yes, No), eGFR (Inker et al 2021), serum sodium, serum potassium, serum aldosterone and plasma renin activity at baseline. Randomisation stratification information of mean ambulatory SBP category (> 140, ≤ 140) will also be presented. Hypertension characteristics include but are not limited to hypertension type (essential versus secondary).

Number of background antihypertensive medications and background antihypertensive medication class will also be presented. A medication will be presented as a background medication for hypertension only if the PI reports it as such.

4.1.6.2 Presentation

The disease characteristics as described above will be summarised descriptively, using frequency distributions and summary statistics for the FAS. The data will be presented by treatment group and overall.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history as well as surgical history will be coded according to MedDRA. In addition, pre-specified specific medical and surgical history of interest will also be collected.

4.1.7.2 Presentation

Medical history and concomitant disease will be presented for FAS, by treatment group and overall, classified by SOC and PT. Percentages will be calculated with number of participants in FAS as denominator. 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. Medical and surgical history will be sorted by international order of SOC and alphabetically by PT.

Specific medical and surgical history will be presented for the FAS, by treatment and overall. Details of medical history for hypertension (Hypertension, Hypertension type, Secondary hypertension subtype) together with time since diagnosis of hypertension will be presented for the FAS, by treatment and overall.

Time since diagnosis will be derived as years between diagnosis date and screening date rounded to the nearest integer. Missing or incomplete medical history start dates are handled as described in Section 3.3.7.1.

Medical and surgical history will be listed for the FAS.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Prior medication is defined as any medication taken by the participant before the randomisation visit, regardless of when the medication ended. If the end date is on the day of the randomisation visit, it will be defined as a prior medication. CM is defined as any medication taken during the double-blind treatment period regardless of the start date of the medication. If the end date of the medication is prior to or on the day of the randomisation visit, the medication will not be considered to be taken concomitantly. It is possible for a medication to be classified as both prior medication and CM.

Prohibited (disallowed) CMs and rescue medications are described in the CSP. For prohibited CM, if the end date of the medication is prior to or on the day of the randomisation or start date of the medication is on or after the day of the last dose of IMP, the medication will not be considered as prohibited CM.

Rescue medications will be defined based on eCRF data entry.

All medications will be coded using the WHODD and presented by ATC classification and generic drug name.

4.1.8.2 Presentation

Prior medications, CMs, disallowed CMs, and rescue medications will be presented separately. The data will be summarised descriptively. The data will be presented for the FAS, by treatment group and overall. Participants are only counted once per ATC classification and generic drug name regardless of the number of medications within each category. Generic drug name will be presented nested within the relevant ATC classification and sorted alphabetically by ATC classification and then generic drug name.

CMs will be listed for the FAS.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Study drug compliance (%) is defined as the number of received doses, divided by the number of expected doses, multiplied by 100, expressed as a percentage. The number of received doses is defined as the tablet count difference between tablets dispensed and tablets returned. The number of expected doses is defined as the number of expected doses between the first dose and the last dose of the study drug, ie, 1 * (date of last dose – date of first dose + 1). If the number of tablets dispensed or the number of tablets returned is missing for at least 1 blister pack, compliance is not calculated for that participant. Study drug compliance is defined for baxdrostat or placebo and will be presented for the double-blind treatment period.

Categories for compliance are defined as < 80%, ≥ 80% to < 120% and ≥ 120%.

4.1.9.2 Presentation

Compliance will be presented for the Safety analysis set by treatment group. Compliance will be presented as a continuous variable and categorically by compliance group summarised descriptively.

4.1.10 Stratification Factors

4.1.10.1 Definitions and Derivations

The stratification factors at randomisation are described in Section 3.3.1.6.

4.1.10.2 Presentation

Stratification factors at randomisation will be presented for the FAS.

4.1.11 Nicotine use

4.1.11.1 Definitions and Derivations

Nicotine use, specifically cigarette consumption, will be collected at baseline and recorded in the eCRF.

4.1.11.2 Presentation

Cigarette consumption will be summarised descriptively by treatment group and overall. The results will be presented for FAS.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses, summarised in Table 4. The multiple testing procedure for the testing of the primary and secondary endpoints is described in Section 3.3.4.

Table 4 Analysis of Primary and Secondary Endpoints

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To assess the effect of baxdrostat 2 mg versus placebo on ambulatory 24-hour average SBP at Week 12.					
Primary Endpoint – Primary Analysis	Change from baseline in ambulatory 24-hour average SBP at Week 12	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, Without imputation)	4.2.1.4
Primary Endpoint – Sensitivity Analysis 1	Change from baseline in ambulatory 24-hour average SBP at Week 12	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, With imputation)	4.2.1.5
Primary Endpoint – Sensitivity Analysis 2	Change from baseline in ambulatory 24-hour average SBP at Week 12	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, With imputation)	4.2.1.5

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary Endpoint – Supplementary Analysis	Change from baseline in ambulatory 24-hour average SBP at Week 12	FAS	Treatment policy for IMP discontinuation and hypothetical strategy for initiation of rescue therapy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, With imputation)	4.2.1.6
Primary Endpoint – Supplementary Analysis	Change from baseline in ambulatory 24-hour average SBP at Week 12	PPS	Not applicable.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, Without imputation)	4.2.1.7
Objective 2: To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory night-time average SBP at Week 12.					
Secondary endpoint – Primary analysis	Change from baseline in ambulatory night-time average SBP at Week 12	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, Without imputation)	4.2.2.1

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Secondary endpoint – Sensitivity analysis	Change from baseline in ambulatory night-time average SBP at Week 12	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, With imputation)	4.2.2.2
Secondary Endpoint – Supplementary Analysis	Change from baseline in ambulatory night-time average SBP at Week 12	PPS	Not applicable.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, Without imputation)	4.2.2.3
Objective 3: To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory daytime average SBP at Week 12.					
Secondary endpoint – Primary analysis	Change from baseline in ambulatory daytime average SBP at Week 12	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, Without imputation)	4.2.3.1

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Secondary endpoint – Sensitivity analysis	Change from baseline in ambulatory daytime average SBP at Week 12	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, With imputation)	4.2.3.2
Secondary Endpoint – Supplementary Analysis	Change from baseline in ambulatory daytime average SBP at Week 12	PPS	Not applicable.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, Without imputation)	4.2.3.3
Objective 4: To assess the effect of treatment with baxdrostat 2 mg versus placebo on seated SBP at Week 12.					
Secondary endpoint – Primary analysis	Change from baseline in seated SBP at Week 12.	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, With imputation)	4.2.4.1

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Secondary endpoint – Supplementary analysis	Change from baseline in seated SBP at Week 12.	FAS	Treatment policy for IMP discontinuation and hypothetical strategy for initiation of rescue therapy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, With imputation)	4.2.4.2
Objective 5: To assess the effect of treatment with baxdrostat 2 mg versus placebo on achieving ambulatory 24-hour average SBP < 130 mmHg at Week 12.					
Secondary endpoint – Primary analysis	Participants achieving ambulatory 24-hour average SBP of < 130 mmHg at Week 12.	FAS	Treatment policy.	Odds ratio, 2 mg baxdrostat versus Placebo (Logistic regression, Without imputation)	4.2.5.1
Secondary endpoint – Sensitivity analysis	Participants achieving ambulatory 24-hour average SBP of < 130 mmHg at Week 12.	FAS	Treatment policy.	Odds ratio, 2 mg baxdrostat versus Placebo (Logistic regression, With imputation)	4.2.5.2
Objective 6: To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory 24-hour average DBP at Week 12.					
Secondary endpoint – Primary analysis	Change from baseline in ambulatory 24-hour average DBP at Week 12.	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, Without imputation)	4.2.6.1

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Secondary endpoint – Sensitivity analysis	Change from baseline in ambulatory 24-hour average DBP at Week 12.	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, With imputation)	4.2.6.2
Objective 7: To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory night-time average DBP at Week 12.					
Secondary endpoint – Primary analysis	Change from baseline in ambulatory night-time average DBP at Week 12.	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, Without imputation)	4.2.7.1
Secondary endpoint – Sensitivity analysis	Change from baseline in ambulatory night-time average DBP at Week 12.	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, With imputation)	4.2.7.2
Objective 8: To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory daytime average DBP at Week 12.					

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Secondary endpoint – Primary analysis	Change from baseline in ambulatory daytime average DBP at Week 12.	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, Without imputation)	4.2.8.1
Secondary endpoint – Sensitivity analysis	Change from baseline in ambulatory daytime average DBP at Week 12.	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, With imputation)	4.2.8.2
Objective 9: To assess the effect of treatment with baxdrostat 2 mg versus placebo on seated DBP at Week 12.					
Secondary endpoint – Primary analysis	Change from baseline on seated DBP at Week 12.	FAS	Treatment policy.	Least Square Mean difference between baxdrostat 2 mg and placebo (ANCOVA, With imputation)	4.2.9.1
Objective 10: To assess the effect of treatment with baxdrostat 2 mg versus placebo in the nocturnal dipping pattern at Week 12.					

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Secondary endpoint – Primary analysis	Participants achieving a nocturnal SBP dipping of ≥10% at Week 12	FAS	Treatment policy.	Odds ratio, 2 mg baxdrostat versus Placebo (Logistic regression, Without imputation)	4.2.10

4.2.1 Primary Endpoint

4.2.1.1 Definition

The primary objective of this study is to compare baxdrostat 2 mg with placebo with respect to the change from baseline in ambulatory 24-hour average SBP at Week 12.

The primary estimand is described by the following attributes:

- **Population:** participants with rHTN, as defined by the inclusion and exclusion criteria.
- **Endpoint:** change from baseline in ambulatory 24-hour average SBP at Week 12.
- **Treatment condition:** 2 mg baxdrostat QD and stable regimen of background antihypertensive medication, alternative treatment condition is placebo QD and stable regimen of background medication.
- **ICEs:** the ICE of treatment discontinuation will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of treatment discontinuation. The ICE of rescue therapy will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of initiation of rescue therapy. The ICE of death, if any, will be handled via a hypothetical strategy, ie, as if the subject had not died.
- **Population level summary:** difference in mean change from baseline between baxdrostat 2 mg versus placebo.

The hypothesis for the primary objective is as follows:

H_0: no difference in mean change from baseline in ambulatory 24-hour average SBP at Week 12 between 2 mg baxdrostat versus placebo.

H_1: difference in mean change from baseline in ambulatory 24-hour average SBP at Week 12 between 2 mg baxdrostat versus placebo.

4.2.1.2 Derivations

Change from baseline in ambulatory 24-hour average SBP at Week 12 is defined as ambulatory 24-hour average SBP value at Week 12 minus ambulatory 24-hour average SBP value at baseline.

Derivation of ABPM endpoints are provided in Section 3.3.10.

Figure showing hourly average SBP with standard error over the whole 24-hour period will be presented by treatment and by Visit (Baseline/Week 12). Another figure showing change in

ambulatory daytime and nigh-time SBP by treatment will also be presented. No ambulatory BP data will be imputed in these figures.

Descriptive statistics including n, arithmetic mean and standard deviation (SD), minimum, Q1, median, Q3 and maximum, will be presented for the observed values, absolute change from baseline for each scheduled assessment in the full study period will be presented.

4.2.1.3 Handling of Dropouts and Missing Data

Efforts will be made to achieve complete FU of the participants according to the protocol and minimise missing data. Participants who permanently discontinue treatment will be asked to attend the rest of the study visits and perform the study assessments as indicated in the protocol, with the exception of study intervention.

Missing 24-hour average SBP will not be imputed for the primary analysis.

4.2.1.4 Primary Analysis of Primary Endpoint

As the primary analysis, the primary endpoint will be analysed using an ANCOVA model with treatment as factor, and baseline ambulatory 24-hour average SBP value as a covariate, based on the FAS, including participants with completed and valid ABPM assessments at both baseline and Week 12. The model will be fitted using PROC GLM in SAS.

The response variable will include change from baseline in ambulatory 24-hour average SBP at Week 12. In accordance with the primary estimand and strategies for ICEs, the primary analysis will include all available measurements regardless of treatment discontinuation or initiation of rescue therapy.

The LS mean and 2-sided 95% CI for each treatment group, together with the least square mean difference, 95% CI and p-value of the comparison versus the placebo group will be provided.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

Sensitivity analysis 1: ANCOVA with imputation for missing ABPM data at Week 12 (Treatment policy)

Treatment policy strategy for both treatment discontinuation and rescue therapy, same as the strategy in the primary analysis will be used, ie, the ANCOVA model will include all available measurements regardless of treatment discontinuation or initiation of rescue therapy. As a sensitivity analysis with respect to the primary analysis which includes the participants with completed and valid ABPM assessments from both baseline and Week 12, missing data handling including multiple imputation of 24-hour average SBP measured by ABPM at week 12 will be used. The analysis will be based on the FAS, including participants with completed and valid ABPM assessment at baseline. Details are as follows,

1 Missing data following treatment discontinuation will be multiple imputed using MI-WO assuming MNAR for the baxdrostat group and MAR for the placebo group.
2 Missing data following initiation of rescue medication will be multiple imputed using MI-WO, assuming MNAR for the baxdrostat group and MAR for the placebo group.
3 Missing data not following treatment discontinuation or initiation of rescue medication, including incomplete or non-valid ABPM, will be multiple imputed assuming MAR.
4 Missing data following death will be imputed using appropriate methods based on any preceding ICE (i.e. treatment discontinuation, initiation of rescue medications) or other reasons unrelated to ICE of treatment discontinuation or initiation of rescue therapy.

Multiple imputation is described in Section 3.3.8.

After missing ABPM data have been imputed, the primary endpoint will be analysed using an ANCOVA model with treatment as factor, and baseline ambulatory 24-hour average SBP value as a covariate, based on the FAS including all randomised patients with measured ABPM as well as imputed data. The model will be fitted using PROC GLM in SAS.

The LS mean and 2-sided 95% CI for each treatment group, together with the comparison versus the placebo group will be provided.

Sensitivity analysis 2: Two-way tipping point analysis.
In order to assess the robustness of the primary analysis to missing data assumptions, the following tipping point analysis will be conducted:

- Participants from the baxdrostat group with missing observations at week 12 is given a penalty, i.e., it is assumed that participants with missing observations who are randomised to baxdrostat will have a change from baseline that is less beneficial than participants with observed values who are randomised to placebo.
- Participants from the placebo group with missing observations at week 12 is given a benefit, i.e., it is assumed that participants with missing observations who are randomised to placebo will have a change from baseline that is more beneficial than participants with observed values who are randomised to baxdrostat.
- Penalty/benefit is implemented by adding/subtracting a constant value to/from the imputed week 12 values for all participants in the treatment groups with imputed values, as appropriate.
- The analysis is repeated with increasing penalty/benefit values until the corresponding superiority analysis is no longer significant.

This analysis is only performed if superiority is confirmed in the primary analysis.

For each increase in penalty/benefit, an analysis will be performed and the least square mean for change from baseline to week 12 in ambulatory 24-hour average SBP and 95% CI by treatment group alongside the differences compared to placebo will be presented in the same way as for the primary analysis for the week12, with the penalty and benefit displayed.

4.2.1.6 Supplementary Analyses of the Primary Endpoint – Alternative ICE Strategy

ANCOVA with imputation for missing ABPM data at Week 12 (Treatment Policy for IMP discontinuation and hypothetical strategy for initiation of rescue medication)

As a supplementary analysis with respect to the primary estimand, the ICE of treatment discontinuation will still be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of treatment discontinuation while the ICE of rescue therapy will be handled via a hypothetical strategy, ie, to ascertain the treatment effect if rescue therapy were not initiated. The analysis will be based on the FAS, including participants with completed and valid ABPM assessment at baseline. Missing data at week 12 will be handled as follows, including using multiple imputation,

1 Missing data following treatment discontinuation will be multiple imputed using MI-WO assuming MNAR for the baxdrostat group and MAR for the placebo group.
2 Post-rescue data will be considered as missing and replaced with multiple imputed data using the MI-WO method, assuming MNAR for the baxdrostat group and MAR for the placebo group.
3 Missing data not following treatment discontinuation or initiation of rescue medication, including incomplete or non-valid ABPM, will be multiple imputed assuming MAR.
4 Missing data following death will be imputed using appropriate methods based on any preceding ICE (e.g. treatment discontinuation, initiation of rescue medications) or other reasons unrelated to ICE of treatment discontinuation or initiation of rescue therapy.

Multiple imputation is described in Section 3.3.8.

After missing ABPM data have been imputed, the primary endpoint will be analysed using an ANCOVA model with treatment as factor, and baseline ambulatory 24-hour average SBP value as a covariate, based on the FAS including all randomised patients with imputed data. The model will be fitted using PROC GLM in SAS.

The LS mean and 2-sided 95% CI for each treatment group, together with the comparison versus the placebo group will be provided.

4.2.1.7 Supplementary Analyses of the Primary Endpoint - Based on Per Protocol Set (EU)

As outlined in Section 3.2, PPS is defined as all participants in FAS who met the following criteria:

- no permanent discontinuation of IMP
- no rescue therapy initiated
- pre-specified minimal exposure of IMP, defined as participants with compliance >= 80%
- completed and valid ABPM assessment at Week 12
- no IPDs

The precise reasons for excluding subjects from the PPS will be fully defined and documented before breaking the blind.

As a supplementary analysis with respect to the primary analysis using the FAS, the primary endpoint will be analysed using an ANCOVA model with treatment as factor, and baseline ambulatory 24-hour average SBP value as a covariate, based on the PPS. The model will be fitted using PROC GLM in SAS.

The LS mean and 2-sided 95% CI for each treatment group, together with the comparison versus the placebo group will be provided.

4.2.1.8 Subgroup Analyses

Exploratory subgroup analyses will be conducted for the primary endpoint to assess consistency of treatment effect across subgroups of clinical interest. Pre-specified subgroup variables are listed in Table 5.

Table 5 Subgroup Variables

Baseline Characteristics	Categories
Age (years)	< 65 years, ≥ 65 – < 75 years, ≥ 75 years
Sex	Female, Male
Race	White, Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian, Other, Multiple
Ethnicity	Hispanic/Latino, not Hispanic/Latino

Baseline Characteristics	Categories
Geographic region	AMEA, Europe, Americas
Baseline ambulatory 24-hour SBP (mmHg) [a]	< 140, ≥ 140
Baseline eGFR (mL/min/1.73 m^2)	< 60, ≥ 60
Baseline BMI (kg/m^2)	< 30, ≥ 30

[a] The subgroup variable will be calculated by the Sponsor based on final validated ABPM dataset provided by third party vendor (Clario), not the stratification factor collected in the IRT.

The treatment effect within each subgroup category will be estimated by fitting the same ANCOVA model as for the primary analysis described in Section 4.2.1.4 to each subgroup category. The same ANCOVA model, adding the subgroup variable as explanatory variable and a subgroup-by-treatment interaction term will be fitted to each subgroup, to derive the p-value for the test of interaction between treatment group and subgroup.

Missing values in the subgroup variables are expected to be minimal. Participants with missing values in a subgroup variable will be excluded from the corresponding subgroup analysis. Missing ABPM data will not be imputed, and all available data will be used regardless of IMP discontinuation or initiation of rescue therapy.

The estimates within each subgroup, including least square mean estimates for each treatment and the difference between treatment, and 95% CIs, will be obtained in a similar way as for the primary analysis.

In general, subgroups with fewer than 10 participants within treatment groups will only be presented descriptively and subgroups with 5 or fewer participants within treatment groups will not be analysed or presented at all.

Results of the subgroup analyses will be presented in a table and a forest plot.

4.2.2 Secondary Endpoint – Change from Baseline in Average Ambulatory Night-Time SBP at Week 12

For the definitions of night-time ABPM, daytime ABPM, and dipping, please refer to Section 3.3.10.

4.2.2.1 Primary Analysis of Secondary Endpoint

The primary analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the primary endpoint but using night-time SBP (from 2200 to 0559).

The ANCOVA model will use change from baseline in ambulatory night-time SBP at Week 12 as the response variable and will include treatment as a factor, and baseline night-time ambulatory average SBP value as a covariate, based on the FAS, including participants with completed and valid ABPM assessments at both baseline and Week 12, defined in Section 4.2.1.4. The model will be fitted using PROC GLM in SAS.

In accordance with the primary estimand for this secondary endpoint and strategies for ICEs, the primary analysis will include all available measurements regardless of treatment discontinuation or the initiation of rescue therapy.

The LS mean and 2-sided 95% CI for each treatment group, together with the comparison versus the placebo group will be provided.

4.2.2.2 Sensitivity Analysis of the Secondary Endpoint

ANCOVA with Imputation for Missing ABPM Data at Week 12 (Treatment Policy)

The sensitivity analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the sensitivity analysis of the primary endpoint as specified in Section 4.2.1.5 but using night-time SBP (from 2200 to 0559).

Treatment policy strategy for both treatment discontinuation and rescue therapy, same as the strategy in the primary analysis will be used, ie, the ANCOVA model will include all available measurements regardless of treatment discontinuation or initiation of rescue therapy. Missing data at week 12 will be handled with imputation, the same as the sensitivity analysis of the primary endpoint as specified in Section 4.2.1.5 but using night-time SBP.

4.2.2.3 Supplementary Analyses of the Secondary Endpoint - Based on PPS (EU)

As a supplementary analysis with respect to the secondary analysis using the FAS, the secondary endpoint will be analysed using an ANCOVA model with treatment as factor, and baseline night-time ambulatory average SBP value as a covariate, based on the PPS. The model will be fitted using PROC GLM in SAS.

The LS mean and 2-sided 95% CI for each treatment group, together with the comparison versus the placebo group will be provided.

4.2.3 Secondary Endpoint – Change from Baseline in Ambulatory Daytime Average SBP at Week 12

4.2.3.1 Primary Analysis of Secondary Endpoint

The primary analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the primary endpoint but using daytime SBP (from 0600 to 2159).

The ANCOVA model will use change from baseline in ambulatory daytime SBP at Week 12 as the response variable and will include treatment as a factor, and baseline daytime ambulatory average SBP value as a covariate, based on the FAS, including participants with completed and valid ABPM assessments at both baseline and Week 12, defined in Section 4.2.1.4. The model will be fitted using PROC GLM in SAS.

In accordance with the primary estimand for this secondary endpoint and strategies for ICEs, the primary analysis will include all available measurements regardless of treatment discontinuation or the initiation of rescue therapy.

The LS mean and 2-sided 95% CI for each treatment group, together with the comparison versus the placebo group will be provided.

4.2.3.2 Sensitivity Analysis of the Secondary Endpoint

ANCOVA with Imputation for Missing ABPM Data at Week 12 (Treatment Policy)

The sensitivity analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the sensitivity analysis of the primary endpoint as specified in Section 4.2.1.5 but using daytime SBP (from 0600 to 2159).

Treatment policy strategy for both treatment discontinuation and rescue therapy, same as the strategy in the primary analysis will be used, ie, the ANCOVA model will include all available measurements regardless of treatment discontinuation or initiation of rescue therapy. Missing data at week 12 will be handled the same as the sensitivity analysis of the primary endpoint as specified in Section 4.2.1.5 but using daytime SBP.

4.2.3.3 Supplementary Analyses of the Secondary Endpoint - Based on PPS (EU)

As a supplementary analysis with respect to the secondary analysis using the FAS, the secondary endpoint will be analysed using an ANCOVA model with treatment as factor, and baseline daytime ambulatory average SBP value as a covariate, based on the PPS. The model will be fitted using PROC GLM in SAS.

The LS mean and 2-sided 95% CI for each treatment group, together with the comparison versus the placebo group will be provided.

4.2.4 Secondary Endpoint – Change from Baseline in Seated SBP at Week 12

The secondary estimand is described by the following attributes:

- **Population:** participants with rHTN, as defined by the inclusion and exclusion criteria. Implemented through the use of the FAS.
- **Endpoint:** change from baseline in seated SBP at Week 12.

- **Treatment condition:** 2 mg baxdrostat QD and stable regimen of background antihypertensive medication, alternative treatment condition is placebo QD and stable regimen of background medication.
- **ICEs:** the ICE of treatment discontinuation will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of treatment discontinuation. The ICE of rescue therapy will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of initiation of rescue therapy. The ICE of death if any, will be handled via a hypothetical strategy, ie, as if the subject had not died.
- **Population level summary:** difference in mean change from baseline between baxdrostat 2 mg versus placebo.

Derivations

The seated SBP values used for analysis will be assessed by the following procedure:

- Three seated BP measurements (each approximately 1 minute apart) should be obtained using the same arm and the AOBPM device at each clinical site visit. Mean seated BP is defined as the average of the last 2 seated BP measurements of the total 3 measurements, at any single clinical site visit as per CSP. If multiple mean seated BP readings are obtained during the baseline visit, the last mean seated BP will be used (Section 3.3.1.1). For any post-baseline visit, the first mean seated BP will be used in the analysis, as long as the difference between the last two measurements is within 20 mmHg. If the difference is greater than 20 mmHg, the first mean seated BP with the difference within 20 mmHg will be used in the analysis.
- During any post-baseline visit, if all available mean seated SBP show a difference greater than 20 mmHg between the two last measurements, the last available mean seated SBP should be used in the analysis.
- Each mean seated BP is rounded up to nearest integer.

Change from baseline in seated SBP at Week 12 is defined as seated SBP value at Week 12 minus seated SBP value at baseline.

Handling of Dropouts and Missing Data

Multiple imputation of missing data is described in Section 3.3.8.

4.2.4.1 Primary Analysis of secondary Endpoint

ANCOVA with Imputation for Missing Seated SBP Data at Week 12 (Treatment Policy)

As the primary analysis, the secondary endpoint will be analysed using an ANCOVA model with change from Baseline in seated SBP at week 12 as response variable, treatment as factor,

and baseline seated SBP value as a covariate, based on the FAS. The model will be fitted using PROC GLM in SAS.

The response variable will include available seated SBP observations at Week 12 as well as multiple imputed data where applicable. In accordance with the estimand and strategies for ICEs, the primary analysis will include all available measurements regardless of treatment discontinuation or the initiation of rescue therapy.

Missing data at Week 12 following treatment discontinuation will be imputed using MI-WO assuming MNAR for the baxdrostat group and MAR for the placebo group. Missing data at Week 12 following initiation of rescue therapy will be imputed with MI-WO method. Missing data at Week 12 unrelated to ICEs of treatment discontinuation or initiation of rescue therapy will be imputed based on MAR assumption.

Intercurrent events of deaths will be handled using the hypothetical strategy (i.e., as if the subject had not died). Consequently, missing data following death will be imputed using appropriate methods based on any preceding ICE (e.g. treatment discontinuation, initiation of rescue medications) or other reasons unrelated to ICE of treatment discontinuation or initiation of rescue therapy.

Multiple imputation and combining analysis results are described in Section 3.3.8.

The LS mean and 2-sided 95% CI for each treatment group, together with the comparison versus the placebo group will be provided.

4.2.4.2 Supplementary Analysis of Secondary Endpoint

ANCOVA with Imputation for Missing Seated SBP Data at Week 12 (Treatment Policy Strategy for Treatment Discontinuation and Hypothetical Strategy for Rescue Therapy)

As a supplementary analysis with respect to the primary estimand, the treatment policy strategy will be used for treatment discontinuation and hypothetical strategy will be used for initiation of rescue therapy. Specifically, the ANCOVA model will include all available measurements regardless of treatment discontinuation, however, will exclude measurements made after the initiation of rescue therapy. In other words, in the supplementary analysis, post-rescue data will be considered as missing data. Missing data following treatment discontinuation will be imputed in the same way as in the primary analysis. Post-rescue data will be considered as missing and replaced with imputed data using the MI-WO method.

The secondary endpoint will be analysed using an ANCOVA model with treatment as factor, and baseline seated SBP value as a covariate, based on the FAS. The model will be fitted using PROC GLM in SAS.

The LS mean and 2-sided 95% CI for each treatment group, together with the comparison versus the placebo group will be provided.

4.2.5 Secondary Endpoint – Participants Achieving Ambulatory 24-hour Average SBP of < 130 mmHg at Week 12

4.2.5.1 Primary Analysis of Secondary Endpoint

The primary analysis of this endpoint will be conducted using a similar estimand as for the primary analysis of the primary endpoint but with odds ratio as the population level summary.

As the first step, the dichotomous response variable (yes, no) will be derived based on available ambulatory 24-hour average SBP measurements at Week 12.

The treatment policy estimand implies that the derivation will include all available measurements regardless of treatment discontinuation or the initiation of rescue therapy.

The response variable will be analysed via a logistic regression model which will include baseline ambulatory 24-hour average SBP value as a covariate and treatment as a factor, based on the FAS, including participants with completed and valid ABPM assessments at both baseline and Week 12. The logistic model will be fitted using PROC LOGISTIC in SAS. This analysis will only include participants with baseline ambulatory 24-hour average SBP of 130 mmHg or higher.

The proportion of participants achieving ambulatory 24-hour average SBP of <130 mmHg by treatment group, and estimated odds ratio with 95% CI and p-value from the logistic regression model will be provided.

4.2.5.2 Sensitivity Analysis of Secondary Endpoint

Treatment policy strategy for both treatment discontinuation and rescue therapy, same as the strategy in the primary analysis will be used, ie, the logistic regression model will include all available measurements regardless of treatment discontinuation or initiation of rescue therapy. As a sensitivity analysis with respect to the primary analysis which includes the participants with completed and valid ABPM assessments from both baseline and Week 12, missing data handling including multiple imputation of 24-hour average SBP measured by ABPM will be performed the same as specified in Section 4.2.1.5.

After missing ABPM data have been imputed, the dichotomous response variable (yes, no) will be derived based on the ambulatory 24-hour average SBP measurements at Week 12 including both measured data and imputed data.

The secondary endpoint will be analysed using a logistic regression model with treatment as factor, and baseline ambulatory 24-hour average SBP value as a covariate, based on the FAS

including all randomised patients with measured ABPM as well as imputed data. The model will be fitted using PROC LOGISTIC in SAS.

The logistic regression model will provide subjects achieving ambulatory 24-hour average SBP of < 130 mmHg by treatment group, estimated comparison of odds ratio as well as 95% CI and p-value.

4.2.6 Secondary Endpoint – Change from Baseline in Ambulatory 24-hour Average DBP at Week 12

4.2.6.1 Primary Analysis of Secondary Endpoint

The primary analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the primary endpoint, specified in Section 4.2.1.4 but with change from baseline in ambulatory 24-hour average DBP at Week 12 as the response variable. Participants with completed and valid ABPM at both Baseline and Week 12 will be included in the analysis.

4.2.6.2 Sensitivity Analysis of Secondary Endpoint

The sensitivity analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the sensitivity analysis of the primary endpoint, specified in Section 4.2.1.5 but with change from baseline in ambulatory 24-hour average DBP at Week 12 as the response variable. Missing data will be handled with imputation, the same as the sensitivity analysis of the primary endpoint as specified in Section 4.2.1.5 but using 24-hour average DBP. Both measured ABPM and imputed data will be included in the ANCOVA model.

4.2.7 Secondary Endpoint – Change from Baseline in Ambulatory Night-Time Average DBP at Week 12

4.2.7.1 Primary Analysis of Secondary Endpoint

The primary analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the secondary endpoint in Section 4.2.2.1, but with change from baseline in ambulatory night-time average DBP at Week 12 as the response variable. Participants with completed and valid ABPM at both Baseline and Week 12 will be included in the analysis.

4.2.7.2 Sensitivity Analysis of Secondary Endpoint

The sensitivity analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the sensitivity analysis of the secondary endpoint, specified in Section 4.2.2.2 but with ambulatory night-time average DBP at Week 12 as the response variable. Missing data will be handled with imputation, the same as the sensitivity analysis of the primary endpoint as specified in Section 4.2.1.5 but using night-time average DBP. Both measured ABPM and imputed data will be included in the ANCOVA model.

4.2.8 Secondary Endpoint – Change from Baseline in Ambulatory Daytime Average DBP at Week 12

4.2.8.1 Primary Analysis of Secondary Endpoint

The primary analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the secondary endpoint in Section 4.2.3.1, but with change from baseline in ambulatory daytime average DBP at Week 12 as the response variable. Participants with completed and valid ABPM at both Baseline and Week 12 will be included in the analysis.

4.2.8.2 Sensitivity Analysis of Secondary Endpoint

The sensitivity analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the sensitivity analysis of the secondary endpoint, specified in Section 4.2.3.2 but with ambulatory daytime average DBP at Week 12 as the response variable. Missing data will be handled with imputation, the same as the sensitivity analysis of the primary endpoint as specified in Section 4.2.1.5 but using daytime average DBP. Both measured ABPM and imputed data will be included in the ANCOVA model.

4.2.9 Secondary Endpoint – Change from Baseline in Seated DBP at Week 12

4.2.9.1 Primary Analysis of Secondary Endpoint

The primary analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the secondar endpoint of seated SBP in Section 4.2.4.1, but with change from baseline in seated DBP at Week 12 as the response variable. Missing data of seated DBP at Week 12 will be handled similarly.

The response variable will include available seated SBP observations at Week 12 as well as multiple imputed data where applicable. In accordance with the primary estimand and strategies for ICEs, the primary analysis will include all available measurements regardless of treatment discontinuation or the initiation of rescue therapy.

4.2.10 Secondary Endpoint – Participants Achieving a Nocturnal SBP Dipping of ≥ 10% at Week 12

The primary analysis of this endpoint will be conducted using a similar estimand as for the primary analysis of the primary endpoint but with odds ratio as the population level summary.

As the first step, the dichotomous response variable (yes, no) will be derived based on the participant's NDR ≥ 10% at Week 12 as defined in Section 3.3.10 using ABPM data.

The treatment policy estimand implies that the derivation will include all available measurements regardless of treatment discontinuation, or the initiation of rescue therapy.

The response variable will be analysed via a logistic regression model which will include baseline dipping status (≥ 10% versus < 10%) as a covariate and treatment as a factor, based on the FAS, including participants with completed and valid ABPM assessments at both baseline and Week 12. The logistic model will be fitted using PROC LOGISTIC in SAS.

The logistic regression model will provide subjects achieving nocturnal SBP dipping by treatment group, estimated comparison of odds ratio as well as 95% CI and p-value.

4.2.11 Exploratory Endpoint

Table 6 Exploratory Endpoints

Objectives	Endpoints
To assess the effect of treatment with baxdrostat 2 mg versus placebo on seated SBP.	Change from baseline in seated SBP at Week 4. Change from baseline in seated SBP at Week 8.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on seated DBP.	Change from baseline in seated DBP at Week 4. Change from baseline in seated DBP at Week 8.

Each of these exploratory endpoints will be analysed analogously to the primary analysis of the secondary endpoint of change from baseline in seated SBP at Week 12 in Section 4.2.4. Treatment policy strategy implies that all available seated BP data will be used in the model regardless of IMP discontinuation or initiation of rescue therapy.

4.3 Pharmacodynamic Endpoint(s)

4.3.1 Definitions and Derivations

PD exploratory variables analysed during the study may include, but are not limited to:

- Aldosterone and its precursors (11-deoxycorticosterone, 18-OH corticosterone, and corticosterone).
- Plasma renin activity.
- Calculation of aldosterone/plasma renin activity ratio.

Pre-dose blood samples for PD analysis will be collected at Visit 4, 6 and 9.

4.3.2 Analysis

For the distinct types of PD parameters, the following summaries over time per timepoint will be provided based on FAS; since PD parameters are continuous parameters, for observed values and change from baseline assessments as per analysis visit windows (see Section 3.3.2) will be used.

Number of subjects who provided a measurement: (n), Mean, SD, Min, Q1, Median, Q3, Max, by treatment group and timepoint. Geometric mean and CV will be calculated in addition to arithmetic mean and SD, if appropriate.

4.3.3 Presentation

The outputs for PD variables will be presented using box plots by treatment group and Visit. Analysis of the relationship between PD and baxdrostat concentration may be conducted in separate reports.

4.4 Pharmacokinetics

4.4.1 Definitions and Derivations

Table 7 Pharmacokinetic Endpoint

Exploratory objective	Endpoint
To evaluate the PK of baxdrostat.	Plasma concentrations of baxdrostat.

Evaluating the PK of baxdrostat is an exploratory objective. PK blood samples will be collected for measurement of plasma concentrations pre-dose at Visit 6 and 9. For participants who are discontinued from IMP due to hyperkalaemia, a PK sample should be collected at the EoT visit.

Any modelling related to PK will be presented in separate reports, as stated in CSP.

4.4.2 Presentation

Baxdrostat PK concentrations in plasma will be summarised using descriptive statistics by visit (Visit 6 and 9) and presented using box plot. They will also be listed on individual level based on the PK analysis set. For PK parameter the following statistics will be derived and presented in a table: number of subjects (n), number of subjects with concentration below LLOQ (n < LLOQ), mean, standard deviation, geometric mean, geometric CV%, min, median and max. In addition, a boxplot of the primary endpoint, as in the primary analysis of the primary endpoint, by quartiles of plasma concentrations of baxdrostat will be presented.

Concentrations in the box plot will be plotted on a natural logarithmic scale.

4.5 Immunogenicity

Not applicable.

4.6 Safety Analyses

Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory, and ECG, summarised in Table 8. In addition, extra evaluation will be done for the following AESIs: hyperkalaemia events that require medical intervention, hyponatraemia events that

require medical intervention and hypotension events that require medical intervention. Exposure to study treatment will be described.

Table 8 Safety Analyses

Type	Safety Endpoint	Details in section
General Safety Objective: To assess the safety and tolerability of baxdrostat 2 mg as compared to placebo in patients with rHTN		
AEs	Occurrence and time to first occurrence of AE, SAE, SAE with outcome death, AE leading to discontinuation of IMP, possibly related AE as assessed by investigator, possibly related SAE as assessed by investigator.	4.6.2
Clinical laboratory	Observed laboratory value, change from baseline and time to first treatment emergent abnormality.	4.6.3, 4.6.4
Vital signs	Observed vital sign value (including BP, pulse rate and BMI), change from baseline, and time to first treatment emergent abnormality.	4.6.6
ECG	Observed ECG parameter (overall assessment, QRS interval, pulse rate, RR interval, QT interval and QTc (QTcF)), change from baseline, time to first treatment emergent abnormality (QTcF).	4.6.7
Other	Occurrence and time to first event for AESIs (hyperkalaemia events that require medical intervention, hyponatraemia events that require medical intervention and hypotension events that require medical intervention).	4.6.8

Safety Estimand Definition

The aim with the analyses of safety data is to assess the general safety objective, evaluated in a scenario where study treatment is not prematurely discontinued. Two analysis approaches are considered complementary to assess this hypothetical scenario 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 (Hedman et al 2024):

Population: participants with rHTN, as defined by the inclusion and exclusion criteria. Implemented through the use of the Safety analysis set.

Treatment condition: 2 mg baxdrostat QD and stable regimen of background antihypertensive medication, alternative treatment condition is placebo QD and stable regimen of background medication.

ICEs:

- **Premature study treatment discontinuation:** All analyses will be provided using 2 complementary approaches, unless otherwise stated;
  - Hypothetical as if this ICE cannot happen, implemented by excluding/censoring data after premature study treatment discontinuation + 10 days, using the On-treatment analysis period (Section 3.3.1.4).
  - Treatment policy by ignoring this ICE, implemented by including all available data, using the On-study analysis period (Section 3.3.1.4).
- **Initiation or change of CM, including rescue therapy:** 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:

- Main estimators: Probability of the event (eg, AE, lab abnormality) occurring before a predefined time point. Difference in these between the treatment arms.
- Supplementary estimators: HR. 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 participants, included in the analysis set used for safety, are followed up regardless of study intervention compliance and adherence to the study protocol (for planned treatment period and safety FU).

Analysis

All safety analyses proposed below are descriptive in nature and are intended to facilitate signal detection. HR 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% CI will be obtained from the same model.

The CDF of time to event of interest in the respective treatment group will be estimated by a KM estimator. The probability of the event of interest occurring before predefined timepoint will be estimated by the KM estimator on study Day 85 for AEs and AESIs, and study day 89

for laboratory, vital signs and ECG parameters, by treatment group for the defined analysis periods (On-study and On-treatment respectively), and the treatment group difference will be estimated at the same timepoint. For the estimate of difference in probabilities, 95% CI will be obtained.

Time to event definition: For participants presenting the defined event in the defined analysis period, time to event is defined as time from start date in the defined analysis period to onset date for the first occurrence of the defined event. For participants who do not present the defined event in the defined analysis period, time to event is censored at the participant's last timepoint in the defined analysis period.

Presentation
AEs and safety parameters will be presented based on the Safety analysis set (Section 4.1.2) by treatment group. Unless otherwise stated all outputs will be presented for both the On-treatment analysis period and the On-study analysis period (Section 3.3.1.4).

For presentations using data cumulatively over a defined analysis period, comparisons between treatment groups will be presented with their associated 95% CI. Since all safety analyses are descriptive, no p-values will be presented, and the CIs are provided as an 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.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Exposure is calculated for all participants in the Safety analysis set.

Total exposure
Total exposure (days) is defined as the number of days from the date of first dose of IMP in the double-blind treatment period to the date of last IMP administration plus one day, ie,

$$Total\ exposure\ (days) = date\ of\ last\ dose\ of\ IMP - date\ of\ first\ dose\ of\ IMP + 1$$

Exposure is defined for baxdrostat or placebo treatment groups, respectively. Total exposure time across each treatment group will be expressed in days in data presentations.

Actual exposure (days) is defined as total exposure where days of temporary interruption of IMP are removed.

Presentation
Exposure will be presented by treatment group, summary statistics of total exposure will be presented, as well as actual exposure time.

Exposure will be summarised descriptively as a continuous variable.

Participants who received incorrect IMP at any point during the study will be presented in a listing.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

For definition of AE and SAE, see CSP Appendix B.

All AEs will be classified by SOC and PT according to a MedDRA version not more than one older than the latest version available at the time of CDL as applicable.

Subjects with any AE

Defined as subjects with at least one reported AE with an onset date within the defined analysis period.

Subjects with any SAE with outcome death

Defined as subjects with one reported AE with a 'Fatal' outcome and with an onset date within the defined analysis period. The onset date of the AE determines the analysis period, irrespective of date of death.

Subjects with any AE leading to discontinuation of IMP

Defined as subjects with at least one reported AE with action taken "Drug permanently discontinued" and with an onset date within the defined analysis period. The onset date of the AE determines the analysis period, irrespective of date of discontinuation of IMP.

Subjects with any AE leading to temporary interruption of IMP

Defined as subjects with at least one reported AE with action taken "Drug interrupted". The onset date of the AE determines the analysis period, irrespective of date of temporary interruption of IMP. The onset date of the AE leading to temporary interruption determined whether the AE belongs to the analysis period, irrespective of date of temporary interruption of IMP.

Subjects with any SAEs

Defined as subjects with at least one reported SAE, 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.

Subjects with any AEs possibly related to IMP

Defined as subjects 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.

Subjects with any SAEs possibly related to IMP

Defined as subjects with at least one reported SAE, irrespective of outcome, with "Reasonable possibility AE caused by IMP" marked as "Yes" and 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 in the following categories "Any intensity", "Any moderate or severe intensity", or "Any severe intensity". If a participant has multiple AEs within the same category of different intensities, the more severe intensity will be considered in the presentations.

4.6.2.2 Analysis

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

- Number and percentage of subjects who experienced an event, by treatment group
- KM estimate in percent (KM%) on Study day 85 from baseline, by treatment group.
- Difference between treatment groups in KM% on Study day 85 from baseline together with 95% CI.
- HR between treatment groups together with 95% CI.

Missing data

Missing AE data will generally not be imputed, except for the incomplete AE dates, specified in Section 3.3.7.1. For example, AEs that have missing causality or missing intensity, after data querying, will be left as missing.

4.6.2.3 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 as described in below table:

Table 9 Brief Output Description for AE

Overall summary of AE KM% table [A1] of categories: Any AE, Any SAE, Any SAE with outcome death, Any AE leading to discontinuation of IMP, Any intensity.

Any AE by SOC and PT KM% table[A1] for each respective category: Any AE, Any SAE, Any SAE with outcome death, Any AE leading to discontinuation of IMP, Any possibly related AE [a], Any possibly related SAE [a].
AEs with KM% > 1% KM% table [A1], including all PTs with a KM% higher than 1%, presented in descending KM% value of baxdrostat 2 mg treatment group.
AE maximum intensity by SOC and PT KM% table [A1] of categories: Any intensity, Moderate or Severe, Severe.
Key subject information Tables with key information for subjects, categories include: SAE, SAE with outcome death, AE leading to discontinuation of IMP.
Listings SAE and SAE with outcome death during the Screening period An AE listing will cover details for each individual AE
Narratives Will be produced for all deaths, SAEs, AEs leading to discontinuation of IMP and AESIs.

[A1] The KM% table presents number and percentage of subjects with at least one event per treatment group, KM% per treatment group, difference in KM% between treatment groups, HR.

[a] Possibly related, as assessed by investigator.
AE, adverse event; HR, hazard ratio; IMP, investigational medicinal product; KM, Kaplan-Meier; PT, preferred term; SAE, serious adverse event; SOC, System Organ Class.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

Blood samples for determination of clinical laboratory assessments are collected according to the CSP SoA and specific parameters are listed in CSP Section 8.3.4. Clinical laboratory assessments of blood samples will be categorised into Haematology or Clinical Chemistry.

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 are 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:

- Serum potassium (mmol/L); <3.5, >5.0, > 5.5, >6.0 and >6.5.
- Serum potassium (mmol/L): Subjects who have
  - 3.5 to < 4.0 at baseline and < 3.5 post-baseline
  - ≥4 to <4.5 at baseline or ≥4.5 to ≤5 at baseline and
    - <3.5 post-baseline
    - >5.0 post-baseline

  - >5.5 post-baseline
  - >6.0 post-baseline
  - >6.5 post-baseline
- Serum sodium (mmol/L); < 125, <130 and < 135.
- eGFR (mL/min/1.73m2):
  - ≥ 30 % decrease from baseline
  - ≥ 50% decrease from baseline
  - Subjects who have ≥ 60 at baseline and
    - < 45 post-baseline
    - < 30 post-baseline
  - Subjects who have
    - ≥ 45 to < 60 at baseline and < 45 post-baseline
    - ≥ 30 to < 60 at baseline and < 30 post-baseline

In addition, parameter serum potassium (mmol/L), categorised by <3.5, > 5.0, > 5.5, > 6, > 6.5 and serum sodium (mmol/L), categorised by < 135, < 130, <125, will be cross-tabulated by subgroups defined by the three following criteria: baseline eGFR (mL/min/1.73m^2) (<60, ≥ 60), Diabetes status at baseline (Yes, No), Age category (years) (< 65 years, ≥ 65 – < 75 years, ≥ 75 years), by treatment group. These serum potassium abnormalities by subgroup will also be presented in respective scatter plots. For the 12-week double blind treatment period, potassium measurements of > 5.5 mmol/L and > 6.0 mmol/L based on central lab will be further assessed as follows:

- For central lab potassium values of > 6.0 mmol/L, the confirmation status will be assessed based on local lab potassium from the same day. Specifically, if the local potassium value is >6 mmol/L, then central potassium value is classified as “Confirmed”; if the local potassium value is ≤ 6 mmol/L, then the central potassium value is classified “Not Confirmed”; if local potassium value is not available, then the central potassium value is classified as “Undetermined”.

The criteria above take into consideration the different clinical management of participants with local potassium values ≥5.5 to <6 and ≥6 mmol/L, as specified in the protocol.

Potential Hy’s law is defined for post baseline values as AST ≥ 3 x ULN and/or ALT ≥ 3 x ULN, together with total bilirubin ≥ 2 x ULN; and for any such elevation in AST and/or ALT this must precede or occur on the same day as the elevation in total bilirubin.

4.6.3.2 Analysis

For the distinct types of treatment emergent abnormalities, the corresponding summaries/analyses as specified for AEs (in Section 4.6.2) will be provided based on the Safety analysis set 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 at analysis visits from baseline based on the Safety analysis set for the on-treatment analysis period as well as for the on-study analysis period. Assessments as per analysis visit windows (in Section 3.3.2) will be used.

For continuous parameters, for observed values and change from baseline:

Number of participants who provided a measurement (n), Mean, SD, Min, Q1, Median, Q3, Max; by treatment group and timepoint.

For categorical parameters, for observed class:

Number of participants who provided any observed class value (n), percentage of participants who provided a specific class level value based on n, by treatment group and timepoint.

Potential Hy's law analyses and extreme value analyses (minimum and maximum value post-baseline on baseline value) will be provided based on the Safety analysis set only for the on-study analysis period and will include both planned and unplanned assessments.

Missing data

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

- In analyses of occurrence of treatment emergent abnormalities, for participants 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 LLOQ) 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.

4.6.3.3 Presentations

The following outputs will be presented:

Table 10 Brief Output Description for Clinical Laboratory, Blood Sample Analyses

Box plots of observed values by treatment group at each planned timepoint, as per the SoA.
Box plots of change from baseline by treatment group at each planned timepoint, as per the SoA. For sufficiently continuous parameters.
Treatment Emergent Abnormalities by predefined additional criteria; KM% table [A1]. Treatment Emergent Abnormalities by predefined additional criteria per subgroup levels defined in Section 4.6.3.1; KM% table [A1].
KM estimate plot of serum potassium >5.5 and >6.0 respectively, by treatment group.
Potential Hy's law: Cross-tabulation of maximum post-baseline ALT and AST versus maximum post-baseline total bilirubin by treatment group, on-study. Scatter plot of maximum post-baseline total bilirubin on maximum post-baseline value of ALT and AST, on-study
Shift plot of observed maximum post-baseline value on observed baseline by treatment group, on-study. Shift plot of observed minimum post-baseline value on observed baseline by treatment group, on-study.
Scatter plot of observed maximum post baseline serum potassium value on baseline eGFR by treatment group, on-study. Scatter plot of observed maximum post baseline serum potassium value on baseline hba1c by treatment group, on-study. Scatter plot of observed maximum post baseline serum potassium value on baseline age by treatment group, on-study.
Spaghetti plot of individual subject level data over time for serum potassium above predefined levels by treatment group.
Key subject information: Tables with key information for participants with treatment emergent abnormalities, potential Hy's law and ACTH stimulation test (including the spot ACTH assessment and the stimulated cortisol level).
Listings: Individual subject data including variables such as assessment date and value, change from baseline, LLN, ULN, reference range indicator. Central lab potassium values of > 6.0 mmol/L in the 12-week double blind treatment period any available local lab potassium values, to facilitate assessment of confirmation status. Of note, local potassium measurements are recorded on the CRF only when an AESI of hyperkalaemia is reported.

[A1] 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.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

Urine samples for determination of clinical laboratory assessments are collected according to the CSP SoA and specific parameters are listed in CSP Section 8.3.4. Clinical laboratory safety tests are summarised in Table 2 and Table 8 of the CSP. Only baseline values are collected.

4.6.4.2 Analysis

Not applicable.

4.6.4.3 Presentations

Not applicable.

4.6.5 Other Laboratory Evaluations

Not applicable.

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

Vital sign parameters include BMI, pulse rate and BP measurements. Orthostatic vitals will include standing pulse rate and BP. Vital sign parameters are collected according to the CSP SoA and specific parameters are listed in CSP Section 8.3.2.

The definitions and derivations will follow the Clinical Laboratory, Blood Sample, in Section 4.6.3.

In addition, the following definitions of abnormalities will be used for specific parameters:

- Mean seated SBP (< 90 mmHg)
- Mean seated DBP (< 50 mmHg)
- Pulse rate (< 50, > 100 beats/min)

4.6.6.2 Analysis

The analyses will follow the Clinical Laboratory, Blood Sample, analyses in Section 4.6.3.

4.6.6.3 Presentations

The following outputs will be presented:

Table 11 Brief Output Description for Vital signs

Box plots of observed values from baseline; by treatment group at each planned timepoint as per SoA.
Box plots of change from baseline; by treatment group at each planned timepoint as per SoA.

Box plots of observed values from baseline; by treatment group at each planned timepoint as per SoA.
Treatment Emergent Abnormalities by predefined criteria: KM% table [A1].

[A1] The KM% table presents number and percentage of subjects with at least one event per treatment group, KM% per treatment group, difference in KM% between treatment groups, HR.
HR, hazard ratio; KM, Kaplan-Meier.

4.6.7 Electrocardiogram

4.6.7.1 Definitions and Derivations

ECG parameters include: overall assessment, QRS interval, pulse rate, RR interval, QT interval and QTc (QTcF). ECG evaluations are collected according to the CSP SoA, and specific parameters are listed in CSP Section 8.3.3.

The definitions and derivations will follow the Clinical Laboratory, Blood Sample, in Section 4.6.3.

The (uncorrected) QT interval will be corrected according to the Fridericia's formula (QTcF). The following definitions of abnormalities will be used for specific parameter of QTcF:

- QTcF (ms); > 450, > 480 and > 500.
- QTcF (ms) increase from baseline: > 30 and > 60

Overall assessment of ECG is defined by categories: "Normal", "Borderline", "Abnormal, not clinically significant" and "Abnormal, clinically significant".

4.6.7.2 Analysis

The analyses will follow the Clinical Laboratory, Blood Sample, analyses in Section 4.6.3. In addition, for categorical parameters, for observed class and class change from baseline (Class decreased, Class no change, Class increased):

- Number of participants who provided any observed class value (n), percentage of participants who provided a specific class level value based on n, by treatment group and timepoint.

4.6.7.3 Presentations

The following outputs will be presented:

Table 12 Brief Output Description for ECG

Box plots of observed values; by treatment group at each planned timepoint as per SoA.

Box plots of change from baseline; by treatment group at each planned timepoint as per SoA.
Treatment Emergent Abnormalities for QTcF: KM% table A1.
Bar chart of observed class of overall assessment of ECG over time; by treatment group.
Shift plot of observed maximum post-baseline value on observed baseline by treatment group, on-study. Shift plot of observed minimum post-baseline value on observed baseline by treatment group, on-study.

[A1] The KM% table presents number and percentage of subjects with at least one event per treatment group, KM% per treatment group, difference in KM% between treatment groups, HR.
HR, hazard ratio; KM, Kaplan-Meier.

4.6.8 Other Safety Assessments

4.6.8.1 Definitions and Derivations

Other safety parameters include:

AESIs:

- Hyperkalaemia event that requires medical intervention
- Hyponatraemia event that requires medical intervention
- Hypotension event that requires medical intervention

Any safety parameters can be, or contribute to, an AE. For these data, the process stated for AE will be followed (Section 4.6.2). In addition, the following additional evaluations will be performed for the above list of other safety parameters.

AESIs
The PTs listed below will be reassessed to ensure alignment with the specified MedDRA version for the analyses. The final list of PTs will be documented in the AESI mapping table.

Hyperkalaemia event that requires medical intervention
Definition: Hyperkalaemia event that requires medical intervention as assessed by the investigator and has as PT one of the following: Hyperkalaemia, Blood Potassium increase.

Hyponatraemia event that requires medical intervention
Definition: Hyponatraemia event that requires medical intervention as assessed by the investigator and has as PT one of the following: Hyponatraemia, Blood Sodium decrease.

Hypotension event that requires medical intervention
Definition: Hypotension event that requires medical intervention as assessed by the investigator and has as PT one of the following: Hypotension, BP decreased, BP systolic decreased.

Additional definitions

Participants with any AESI is defined as participants with at least one reported defined PT with an onset date within the defined analysis period.

For each participant with an AESI of hyperkalaemia event that requires medical intervention, hyponatraemia event that requires medical intervention, and hypotension event that requires medical intervention, respectively, the following AE and SAE categories will be defined based on the PT included in the definition of the AESI (derivations will follow those of AEs in Section 4.6.2.1):

- Any SAE
- Any SAE with outcome death
- Any possibly related SAE (as assessed by the investigator)
- Any AE leading to discontinuation of IMP
- Any AE leading to temporary interruption of IMP
- Any possibly related AE (as assessed by the investigator)
- Maximum intensity

4.6.8.2 Analysis

The analyses will follow the AE analyses in Section 4.6.2.2.

4.6.8.3 Presentations

Outputs presenting SOC or PT will be sorted by international order for SOC and alphabetical order for PT.

The following outputs will be presented:

Table 13 Brief Output Description for AESI

Mapping table for AESIs.
KM% table [A1] per AESI event including, SAE, deaths, AE leading to discontinuation of IMP, possible relation to IMP (as assessed by investigator), maximum intensity and contributing factors.
Medications table for AESI Hyperkalaemia event that requires medical intervention.

[A1] The KM% table presents number and proportion of participants with at least one event per treatment group, KM% per treatment group with 95% CI, difference in KM% between treatment groups with 95% CI, and between treatment HR with 95% CI.

5 INTERIM ANALYSIS

Interim analysis is not planned for this study.

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