STATISTICAL ANALYSIS PLAN

Study Code	D6970C00002
Edition Number	3.0
Date	4-Jun-2025

A Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Efficacy and Safety of Baxdrostat in Participants with Uncontrolled Hypertension on Two or More Medications including Participants with Resistant Hypertension

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LIST OF ABBREVIATIONS

Abbreviation or Specialised Term	Definition
ABPM	Ambulatory blood pressure monitoring
ACEi	Angiotensin-Converting-Enzyme Inhibitors
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AOBPM	Automated office blood pressure measurement
ARB	Angiotensin II Receptor Blockers
ATC	Anatomic Therapeutic Chemical
BMI	Body mass index
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
DB	Double-blind
DBP	Diastolic blood pressure
EAC	Event Adjudication Committee
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
GCP	Good Clinical Practice
HTN	Hypertension
HR	Hazard ratio
ICF	Informed consent form
IMP	Investigational medicinal product
IPD	Important protocol deviation
IRT	Interactive response technology

Abbreviation or Specialised Term	Definition
LS	Least squares
MACE	Major adverse cardiovascular events
MAR	Missing at random
MCAR	Missing completely at random
MCMC	Markov Chain Monte Carlo
MH	Medical history
MNAR	Missing not at random
MRA	Mineralocorticoid receptor antagonists
MI	Multiple imputations
MI-RD	Multiple imputations – Retrieved dropouts
MI-WO	Multiple imputations – Washout
OR	Odds ratio
PD	Pharmacodynamic
PK	Pharmacokinetics
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)
rHTN	Resistant hypertension
RWD	Randomised withdrawal
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SFU	Safety follow-up
SMQ	Standardized MedDRA query
SoA	Schedule of assessments
SOC	System organ class
SoC	Standard-of-care
uHTN	Uncontrolled hypertension
WHODD	WHO drug dictionary

AMENDMENT HISTORY FOR VERSION 3.0

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Section 2 Changes to Protocol Planned Analyses	04-Jun-2025	Added the intercurrent event of death and its handling strategy in the estimand definitions for the primary and secondary efficacy endpoints	No	Revision in response to scientific advice received from FDA
Section 3.3.1.1 Baseline	04-Jun-2025	Baseline definition clarified	Yes	Clarification
Section 3.3.1.4 Analysis Periods	04-Jun-2025	Definition of analysis periods clarified	Yes	Clarification
Section 3.3.2 Analysis Visit Windows	04-Jun-2025	Footnotes under Table 4 and Table 5 updated for visit window adaptations to be made for visits that belong to multiple analysis periods Analysis measurement selection rules added for mean seated SBP, mean seated DBP and seated pulse rate	Yes	Clarification
Section 3.3.10 ABPM Definition and General Considerations	04-Jun-2025	Updated the analysis approach for ABPM regarding the calculation of 24-hour averages	Yes	To align analysis approach used for ABPM within program
Section 4.1.4 Demographics	04-Jun-2025	Added presentations for uHTN and rHTN subpopulations	Yes	Clarification
Section 4.1.6 Disease Characteristics	04-Jun-2025	Added details for derivations and analysis approach of background antihypertensive medications Added details for the derivation of baseline HTN categories based on data collected in clinical database	Yes	New details provided
Section 4.1.8	04-Jun-2025	Added details for derivations of prohibited CM and rescue medications	Yes	New details provided

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Prior and Concomitant Medications		Added details for the summaries for background antihypertensive medications over time		
		Updated the definition of the concomitant medications and the prohibited concomitant medications		
Section 4.2.1 Primary Endpoint	04-Jun-2025	Clarified the definition of subgroup variables will be based on data collected at first randomisation	Yes	Clarification
		Added the intercurrent event of death and its handling strategy in the estimand definitions for the primary efficacy endpoint	No	Revision in response to scientific advice received from FDA
		Added the imputation approach for missing data following the intercurrent event of death		
Section 4.2.2 Secondary Endpoint – Change from RWD Baseline (Week 24) in Seated SBP at Week 32	04-Jun-2025	Changed multiple imputation method to MI-WO in primary analysis; Consequently, sensitivity analysis will be MMRM analysis only	Yes	Due to insufficient retrieved dropouts in RWD period, MI-RD method won't converge for missing data following treatment discontinuations
		Added the intercurrent event of death and its handling strategy in the estimand definitions for the secondary efficacy endpoint	No	Revision in response to scientific advice received from FDA
		Added the imputation approach for missing data following the intercurrent event of death		
Section 4.2.5 Secondary Endpoint – Achieving Seated SBP < 130 mmHg at Week 12	04-Jun-2025	Added the intercurrent event of death and its handling strategy in the estimand definitions for the secondary efficacy endpoint	No	Revision in response to scientific advice received from FDA

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Section 4.3 Pharmacodynamic Endpoints	04-Jun-2025	Clarified that proteomic panel data will not be available at PDL	Yes	Clarification
Section 4.6 Safety Analyses	04-Jun-2025	Updated the timepoints (in study days) used for the KM estimates for AE, AESI and laboratory, vital signs and ECG parameters	Yes	Clarification and new details provided
		Added rationale for the different timepoints used for KM estimates		
		Added censoring rules for subjects who did not have the defined event		
		Clarified the definition of subgroup variables will be based on data collected at first randomisation		
		Updated race subgroup to include only White, black or African American and Asian categories		
		Provided definitions and clarifications for preliminary long-term safety and 42-week period safety data analysis at PDL		
Section 4.6.2 Adverse Events	04-Jun-2025	Updated brief output description for AE table	Yes	For consistency in the program
Section 4.6.3 Clinical Laboratory, Blood Sample	04-Jun-2025	Updated definitions of abnormalities for serum potassium and eGFR	Yes	For consistency in the program and new details provided
		Updated text for potential Hy's law		

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
		Added details and presentation method for confirmation analyses of central lab serum potassium > 5.5 mmol/L and > 6.0 mmol/L		
		Clarified the definition of subgroup variables will be based on data collected at first randomisation		
		Updated brief output description table for clinical chemistry and blood sample table		
Section 4.6.4 Vital Signs	04-Jun-2025	Clarified vital sign parameters to be analysed and presented	Yes	Clarification
Section 4.6.6 Electrocardiogram	04-Jun-2025	Clarified ECG parameters to be analysed and presented	Yes	Clarification and new details provided
		Updated brief output description for ECG table		
Section 4.6.7 Other Safety Assessments	04-Jun-2025	Updated definitions for hyperkalaemia, hyponatraemia and hypotension event that requires medical intervention	Yes	For consistency in the program
		Updated brief output description for AESI table and brief output description for pre-specified safety categories table		
Section 5 Interim Analysis	04-Jun-2025	Added preliminary 42-week period safety analysis at PDL	Yes	New details provided

AMENDMENT HISTORY FOR VERSION 2.0

AMENDMENT HISTORY FOR VERSION 2.0

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	2-Feb-2024	Initial approved SAP version 1.0	N/A	N/A
Section 3.1 Timing of analyses	18-Dec-2024	Added details on analyses for PDL and CDL.	Yes	Clarification
Section 3.3.1.1 Baseline	18-Dec-2024	Baseline definition aligned with study design.	Yes	Clarification
Section 3.3.1.4 Analysis Periods	18-Dec-2024	On-treatment analysis periods for RWD, 24-week, 42-week and 52-week periods removed	Yes	For consistency in the program
Section 3.3.2 Analysis Visit Windows	18-Dec-2024	Analysis visit window for baseline aligned with update to Section 3.3.1.1. Visit 7 and Visit 11 analysis windows widened. Details for assigning measurements outside analysis visit windows updated.	Yes	Clarification and correction
Section 3.3.4 Multiplicity/Multiple Comparisons	18-Dec-2024	Text aligned with CSP version 4.0 EU	Yes	To align with CSP
Section 3.3.5 Handling of Protocol Deviations in Study Analysis	18-Dec-2024	Corrected definitions of IPDs to align with study design	Yes	Clarification
Section 3.3.7.1 Handling of incomplete dates	18-Dec-2024	Included definition of CM dates and MH start dates.	Yes	Clarification
Section 3.3.8 Multiple Imputation	18-Dec-2024	Further clarification regarding the implementation of the multiple imputation methods	Yes	Clarification
Section 4.1.6 Disease Characteristics	18-Dec-2024	Correction of which disease characteristics that will be presented	Yes	Correction
Section 4.1.7 Medical and surgical history	18-Dec-2024	Analysis “Time since diagnosis” included.	Yes	New details provided

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Section 4.1.8 Prior and Concomitant Medications	18-Dec-2024	Updated the definition of prior medication to better align with study design	Yes	Clarification
		Updated to present for FAS instead of Safety analysis set.		
Section 4.2 Endpoint Analyses	18-Dec-2024	The intercurrent event of rescue therapy will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of initiation of rescue therapy.	Yes	For consistency in the program.
		The two secondary objectives for ABPM moved to exploratory objectives.		
		Definition of mean seated BP updated to better align with study design.		
		Analyses and presentation of subgroup variables clarified.		
		Additional exploratory endpoints for SBP and DBP at Week 4 and 8 included.		
Section 4.3 Pharmacodynamic Endpoints	18-Dec-2024	Added sentence that analysis of PD that may be presented outside of CSR.	Yes	Clarification
Section 4.4 Pharmacokinetic Endpoints	18-Dec-2024	Description of PK reports outside of CSR has been limited	Yes	Lean writing approach
Section 4.6 Safety Analyses	18-Dec-2024	Specific study day for calculating KM% added.	Yes	New details provided
Section 4.6.2 Adverse Events	18-Dec-2024	Details for analyses and presentation corrected. Brief description of tables included in presentation of safety analyses updated.	Yes	For consistency in the program

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Section 4.6.3 Clinical Laboratory, Blood Sample	18-Dec-2024	Criteria for treatment abnormalities related to serum potassium and eGFR updated	Yes	New details provided
		Text for potential Hy's law added.		
		Text for ACTH simulation test added.		
		Categories that will be used for subgroup analyses of treatment emergent abnormalities included.		
		Brief description of tables included in presentation of safety analyses updated.		
Section 4.6.6 Electrocardiogram	18-Dec-2024	Definition of abnormalities included.	Yes	New details provided
		Brief description of tables included in presentation of safety analyses updated.		
Section 4.6.7 Other Safety Assessments	18-Dec-2024	Details regarding AESI added for contributing factors.	Yes	For consistency in the program
		Brief description of tables included in presentation of safety analyses updated.		
		Pregnancy and Overdose will not be presented and sections removed.		
Section 5 Interim Analysis	18-Dec-2024	Details regarding PDL and CDL included	Yes	New details provided
Section 6 References	18-Dec-2024	Hedman et al 2024 added as reference for details for safety analyses.	Yes	New details provided

1 INTRODUCTION

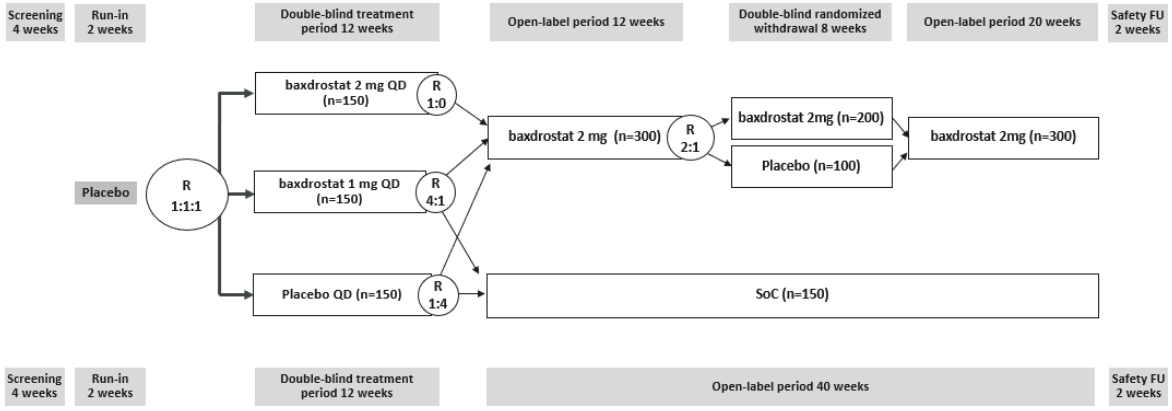
The purpose of this document is to provide details for the statistical analysis of study D6970C00002 supporting the CSR. The SAP is based on the CSP version 3.0 dated 10 April 2024 and CSP version 6.0 EU dated 28 May 2025.

1.1 Study Design

This is a Phase III, multicentre, randomised, double-blinded, placebo-controlled, parallel group study to evaluate the safety, tolerability, and effect of 1 or 2 mg baxdrostat versus placebo, administered QD orally, on the reduction of SBP in approximately 720 participants aged ≥ 18 years with HTN, despite a stable regimen of 2 antihypertensive agents at baseline, one of which is a diuretic (uHTN); or ≥ 3 antihypertensive agents at baseline, one of which is a diuretic (rHTN).

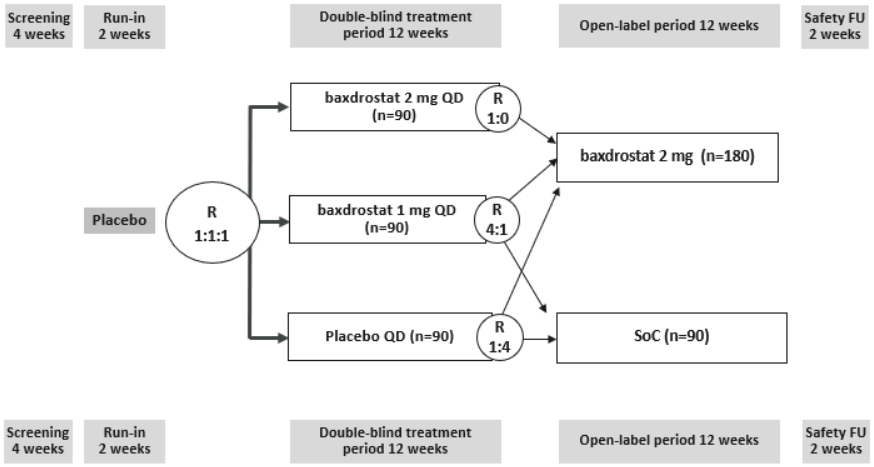
A schema of the study design for Cohort 1 and Cohort 2 is presented in Figure 1 and Figure 2, respectively.

Figure 1 Study Design Cohort 1



FU, follow-up; n, number of participants in that category; QD, once daily; R, randomisation; SoC, standard-of-care.

Figure 2 Study Design Cohort 2



FU, follow-up; n, number of participants in that category; QD, once daily; R, randomisation; SoC, standard-of-care

1.2 Sample Size

This study is planning to randomise 720 participants using a 1:1:1 ratio to either receive 2 mg baxdrostat QD, 1 mg baxdrostat QD or placebo QD, in addition to a stable regimen of background antihypertensive medication in the DB treatment period of 12 weeks (Week 0 to Week 12). The sample size takes into account the statistical power for the primary endpoints and important secondary endpoints. Furthermore, sample size determination is also based on providing adequately sized and controlled safety data according to ICH E1 (CPMP/ICH/375/95) for baxdrostat.

Assuming an effect size of 6 mmHg for the difference in mean change from baseline in seated SBP at Week 12 between baxdrostat (2 mg or 1 mg separately) versus placebo with a SD of 15 mmHg in change from baseline in seated SBP at Week 12, a sample size of 720 will provide a power of approximately 98% using a two-sample t-test with a two-sided significance level of 0.025. For the secondary endpoint in the rHTN subpopulation, using the previous assumptions and significance level, and assuming 50% of the randomised participants to be rHTN, we expect a power of approximately 80%.

The assumptions for the effect size and SD for change in SBP from baseline to Week 12 consider data from the Phase II studies BrigHTN (CIN-107-121) (Freeman et al 2023) and HALO (CIN-107-124, NCT06034743). With respect to the change in SBP from Week 24 to Week 32 (RWD), the same effect size is assumed due to lack of previous data, and the assumed SD considers data from the PRECISION trial (Schlaich et al 2023).

Assuming an attrition rate of no more than 20% during previous study periods, at least 240 participants will be eligible to enter the DB RWD period and randomised in a 2:1 ratio to

either 2 mg baxdrostat or placebo. Assuming an effect size of 6 mmHg for the difference in mean change from RWD baseline (Week 24) in seated SBP at Week 32 between participants receiving 2 mg baxdrostat and participants receiving placebo, with a SD of 13 mmHg in change from RWD baseline (Week 24) in seated SBP at Week 32, the sample size will provide a power of approximately 86% using a two-sample t-test with a two-sided significance level of 0.025.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

New exploratory objectives have been included to assess SBP and DBP at weeks 4 and 8 (Section 4.2.6).

The intercurrent event 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

Two CDLs will be performed for this study. The first CDL, Primary Data Lock (PDL), and unblinding will occur after participants in both cohorts have completed the 12-week DB period and participants in Cohort 1 have completed the DB RWD period. Data from PDL will be used for final analysis for efficacy and short-term safety (12 Week) and preliminary analysis of long-term safety. The final CDL will occur when all participants in Cohort 1 and Cohort 2 have completed the study, including the SFU Visit. The final analysis of long-term safety (24- and 52 Week) will be based on the data from the final CDL. The data from the final CDL will include all safety data and be reported separately.

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. Unless otherwise stated, 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, except those defined in the RWD period.
Safety Analysis Set	All randomised participants who received at least one administration of IMP. Treatment classification will be based on IMP that participants actually received (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.
RWD Set	All participants who are randomised into the RWD period and have received at least one dose of IMP in the RWD period. Data from participants will be analysed according to the treatment group to which they were randomly assigned in the RWD period. This analysis set will be used for efficacy endpoints in the RWD period.
ABPM Analysis Set	All participants in the FAS with completed ABPM session at both run-in and Week 12. This analysis set will be used for the efficacy analyses regarding ABPM.
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. Group assignment based on actual treatment at PK measurement. PK analysis set not bound to any period.

ABPM, automated blood pressure measurement; FAS, full analysis set; IMP, investigational medical product; PK, pharmacokinetic; RWD, randomised withdrawal.

3.3 General Considerations

Statistical analyses will be based on data from the two sequential cohorts (Cohort 1 and Cohort 2) combined.

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

Unless otherwise specified, the baseline value for statistical analysis in the 12-week DB period, 24-week period and 52-week period is the last non-missing value prior to or on the date of randomisation to DB period. The baseline value for statistical analysis in the 42-week period is the last non-missing value prior to or on the date of randomisation to open-label period 12 weeks. The baseline value for statistical analysis in the DB RWD period is the last non-missing value prior to or on the date of randomisation to DB RWD period.

The Placebo run-in period will be considered for derivation of baseline value for ABPM endpoints. The baseline value for statistical analysis of ABPM endpoints is the last non-missing value prior to the randomisation at Visit 3.

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 first randomisation. Day 1 is the day of the first randomisation and Day -1 is the day prior to the first randomisation. There is no Day 0.

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

3.3.1.4 Analysis Periods

Analysis periods will be used in reporting statistical analyses.

<u>Screening period</u>

The Screening period starts on the date of first ICF and ends on the date of the run-in visit.

Run-in period

The Run-in period starts on the date of the run-in visit and ends on the date of randomisation (Visit 3).

12-week double-blind period (Week 0 to Week 12)

- On-study approach: The analysis period starts on the date of randomisation (Visit 3) and ends on the date of randomisation to open-label period 12 weeks. If the subject was not randomised to open-label period 12 weeks, then the earliest of last visit within the analysis period, date of death and date of withdrawal of consent will be used as the end of the period.
- On-treatment approach: The analysis period starts on the date of randomisation (Visit 3) and ends on the earliest of 10 days following the date of last dose of IMP or the end of the analysis period when using the on-study approach.

24-week period (Week 0 to Week 24 (including Safety follow-up for Cohort 2))

- On-study approach: The analysis period starts on the date of randomisation visit (Visit 3) and ends on the date of randomisation to DB RWD period. If the subject was not randomised to DB RWD period, then the earliest of last visit within the analysis period, date of death and date of withdrawal of consent will be used as the end of the period.

52-week period (Week 0 to Week 54 (including Safety follow-up))

- On-study approach: The analysis period starts on the date of randomisation visit (Visit 3) and ends on the date of last visit within the analysis period, unless the subject dies or withdraws consent, in which case the date of death or date of consent withdrawal will be used as the end of the analysis period.

Double-Blind Randomised Withdrawal period (Week 24 to Week 32)

- On-study approach: The analysis period starts on the date of RWD randomisation visit (Visit 9) and ends on the date of last visit within the analysis period, unless the subject dies or withdraws consent, in which case the date of death or date of consent withdrawal will be used as the end of the analysis period.

42-week period (Week 12 to Week 54 (including Safety follow-up))

- On-study approach: The analysis period starts on the date of randomisation visit (Visit 7) and ends on the date of last visit within the analysis period, unless the subject dies or withdraws consent, in which case the date of death or date of consent withdrawal will be used as the end of the analysis period.

The rationale of adding 10 days post last dose of IMP for the on-treatment approach 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.

A visit that belongs to two adjacent periods will be assessed as the last visit in the preceding period and as the first visit in the next period.

The analysis periods spanning over multiple study periods will report safety, and efficacy where applicable.

3.3.1.5 Treatment Groups

The study includes 4 study periods for the participants in Cohort 1, and 2 study periods for the participants in Cohort 2, excluding the screening, placebo run-in and SFU periods. A participant may be assigned to different treatment groups in the different study periods (Table 2). Specifically, in a summary or analysis defined for a specific analysis period, a participant will be presented under the treatment in the specific period while in a summary or analysis spanning multiple study periods, continuity regarding treatment group will be considered, in particular for the safety analysis. For example, in the 24-week period, the participants who receive placebo in the DB period of 12 weeks and receive SoC in the open-label period of 12 weeks will be presented under the treatment placebo/SoC while the participants receiving baxdrostat 1 mg or 2 mg in these two periods will be presented under the treatment baxdrostat. Additional details for the safety analyses are provided in Section 4.6. Table 3 summarises which study periods that are considered for each analysis periods as well as treatments within analysis periods.

Table 2 Treatment Groups Within Study Periods

<table>
<tr><th>Double-blind period</th><th>RR</th><th>Open-label period 12 weeks</th><th>RR[a]</th><th>Double-blind RWD period[a]</th><th>Open-label period 20 weeks[a]</th></tr>
<tr><td rowspan="2">Baxdrostat 2 mg</td><td rowspan="2">1:0</td><td rowspan="2">Baxdrostat 2 mg</td><td rowspan="2">2:1</td><td>Baxdrostat 2 mg</td><td rowspan="2">Baxdrostat 2 mg</td></tr>
<tr><td>Placebo</td></tr>
<tr><td rowspan="3">Baxdrostat 1 mg</td><td rowspan="3">4:1</td><td rowspan="2">Baxdrostat 2 mg</td><td rowspan="2">2:1</td><td>Baxdrostat 2 mg</td><td rowspan="2">Baxdrostat 2 mg</td></tr>
<tr><td>Placebo</td></tr>
<tr><td>SoC</td><td>N/A[b]</td><td colspan="2">SoC</td></tr>
<tr><td rowspan="3">Placebo</td><td rowspan="3">1:4</td><td rowspan="2">Baxdrostat 2 mg</td><td rowspan="2">2:1</td><td>Baxdrostat 2 mg</td><td rowspan="2">Baxdrostat 2 mg</td></tr>
<tr><td>Placebo</td></tr>
<tr><td>SoC</td><td>N/A[b]</td><td colspan="2">SoC</td></tr>
</table>

[a] Cohort 1.
[b] No randomisation for participants in SoC.
N/A Not applicable. RR Randomisation ratio. SoC Standard of care.

Table 3 Treatment Within Analysis Periods

	Study period			
Analysis period	**Double-blind period**	**Open-label period 12 weeks**	**Double-blind RWD period**	**Open-label period 20 weeks**
DB period	Baxdrostat 2 mg Baxdrostat 1 mg Placebo			
DB RWD period			Baxdrostat 2 mg Placebo	
24-week period	Baxdrostat[a] Placebo/SoC			
52-week period[c]	Baxdrostat[a] Placebo/SoC			
42-week period[c]		Baxdrostat 2 mg[b] SoC		

Greyed out area not included in analysis period.
[a] Includes baxdrostat 2 mg and baxdrostat 1 mg.
[b] Includes placebo in DB RWD period.
[c] Includes SFU 2 weeks.

3.3.1.6 Stratification Factors

The two stratification factors for randomisation in the 12-week DB period are HTN at baseline (uHTN, rHTN) and seated SBP at baseline (< 145 mmHg, ≥ 145 mmHg). The stratification factors for the randomisation in the DB RWD period are HTN at baseline (uHTN, rHTN) and seated SBP at RWD baseline (< 130 mmHg, ≥ 130 mmHg). The information on these stratification factors is provided by the site staff for the purpose of randomisation and is captured in the IRT system. The primary analyses will use the stratification variable HTN at baseline (uHTN, rHTN) based on the IRT data. There may be occasional discrepancies between the information captured in the IRT and the information captured in the clinical database. The impact of any such discrepancies will be explored and any notable differences will be noted in the CSR.

3.3.2 Analysis Visit Windows

For the purpose of by-visit analyses, the following analysis visits will be derived to map all assessments from scheduled and unscheduled visits to a specific analysis visit. Analysis visit windows will be defined in accordance with the SoA in CSP and are given in Table 4 and Table 5. 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) and Visit 2 (Placebo run-in). These assessments will be summarised or analysed based on the recorded visit.

Table 4 Analysis Visit Windows for Cohort 1

Visit number in CSP	Analysis Visit	Target Study Day	Study Day Range – All assessments except safety labs	Study Day Range – Safety labs only
3	Baseline	1	[-Inf, 1]	[-Inf, 1]
4.1	Week 1	8	N/A	[2, 12]
4.2	Week 2	16	N/A	[13, 21]
5	Week 4	29	[2, 42]	[22, 42]
6	Week 8	57	[43, 70]	[43, 70]
7	Week 12[a]	85	[71, 99[b]]	[71, 89[b]]
7.1	Week 13	93	N/A	[90[c], 96]
7.2	Week 14	100	N/A	[97, 106]
8	Week 16	113	[100[c], 140]	[107, 140]
9	Week 24[d]	169	[141, 182[e]]	[141, 182[e]]
10	Week 28	197	[183[f], 210]	[183[f], 210]
11	Week 32	225	[211, 239[g]]	[211, 231[g]]
11.1	Week 34	239	N/A	[232, 259]
12	Week 40	281	[240, 322]	[260, 322]
13	Week 52	365	[323, 371]	[323, 371]
SFU	Week 54	379	[372, Inf]	[372, Inf]

Footnotes c, f may apply to the next analysis visit within the analysis period in cases where the study day of the start of the analysis period was on the same day or later than the upper limit/boundary of the nominal second visit, i.e. the next visit will become the second visit within the analysis period and its corresponding lower limit/boundary will be updated to the study day of the start of the analysis window + 1 day.

[a] For the 42-week period, Week 12 is the baseline visit where baseline value is defined as the last non-missing value prior to or on the date of randomisation to Open-label period 12 weeks.

[b] For DB period, the upper limit/boundary is defined as the latest of the current upper limit/boundary or the end of the DB analysis period.

[c] For 42-week period, the lower limit/boundary is defined as the study day of randomisation to Open-label period 12 weeks + 1 day.

[d] For the DB RWD period, Week 24 is the baseline visit where baseline value is defined as the last non-missing value prior to or on the date of randomisation to DB RWD period.

[e] For 24-week period, the upper limit/boundary is defined as the latest of the current upper limit/boundary or the end of the 24-week analysis period.

[f] For DB RWD period, the lower limit/boundary is defined as the study day of randomisation to DB RWD period + 1 day.

[g] For DB RWD period, the upper limit/boundary is defined as the latest of the current upper limit/boundary or the end of DB RWD analysis period.

Table 5 Analysis Visit Windows for Cohort 2

Visit number in CSP	Analysis Visit	Target Study Day	Study Day Range – All assessments except safety labs	Study Day Range – Safety labs only
3	Baseline	1	[-Inf, 1]	[-Inf, 1]
4.1	Week 1	8	N/A	[2, 12]
4.2	Week 2	16	N/A	[13, 21]
5	Week 4	29	[2, 42]	[22, 42]
6	Week 8	57	[43, 70]	[43, 70]
7	Week 12[a]	85	[71, 99[b]]	[71, 89[b]]
7.1	Week 13	93	N/A	[90[c], 96]
7.2	Week 14a	100	N/A	[97, 106]
8	Week 16	113	[100[c], 140]	[107, 140]
9	Week 24	169	[141, 178]	[141, 178]
SFU	Week 26	183	[179, Inf]	[179, Inf]

Footnote c may apply to the next analysis visit within the analysis period in cases where the study day of the start of the analysis period was on the same day or later than the upper limit/boundary of the nominal second visit, i.e. the next visit will become the second visit within the analysis period and its corresponding lower limit/boundary will be updated to the study day of the start of the analysis window + 1 day.
[a] For the 42-week period, Week 12 is the baseline visit where baseline value is defined as the last non-missing value prior to or on the date of randomisation to Open-label period 12 weeks.
[b] For DB period, the upper limit/boundary is defined as the latest of the current upper limit/boundary or the end of the DB analysis period.
[c] For 42-week period, the lower limit/boundary is defined as the study day of randomisation to Open-label period 12 weeks + 1 day.

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

For multiple mean seated SBP assessments within the same analysis visit window for both efficacy and safety analyses, special analysis measurement selection criteria are specified in Section 4.2.1.2. Analysis measurement for mean seated DBP and seated pulse rate for both efficacy and safety analyses are selected from the same analysis measurement session as the mean seated SBP.

For the by-visit analyses, the assessments at visits that belong to two periods will be used as the last assessment in one period and as the first assessment in the next period. Visit 7 assessments will be used in both 12-week DB period and open-label period 12 weeks. Visit 9 assessments will be used in both open-label period 12 weeks and DB RWD period. Visit 11 assessments will be used in both DB RWD period and open-label period 20 weeks.

The analysis visit windows should be aligned with the relevant analysis periods. Therefore, assessments should first be assigned to a specific analysis period. After that, they can be allocated to an analysis visit window within that period, as detailed in Section 3.3.1.4. If participants miss the designated analysis window but are still in the analysis period, they should be slotted into the period they still belong to whenever possible.

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 dual primary endpoints will be tested simultaneously at two-sided alpha of 0.025. If both are rejected at their respective significance level, the first secondary endpoint will be tested at two-sided alpha of 0.05. If only one of them is rejected, the first secondary endpoint will be tested using 0.025. For testing the following secondary endpoints in the pre-defined sequence, alpha will be retained for the next hypothesis until a test fails to reject the null hypothesis or until all listed null hypotheses for secondary endpoints are rejected. The p-values from all endpoints in the multiple testing procedure below the first non-rejected null hypothesis for a secondary endpoint will not be adjusted, thus will be nominal and considered explorative.

Following successful rejection of at least one of the primary hypotheses in the multiple testing procedure, the secondary hypotheses will be tested in the following order:

- Difference in mean change from RWD baseline (Week 24) in seated SBP at Week 32 between participants receiving 2 mg baxdrostat versus participants receiving placebo.
- Difference in mean change from baseline in seated SBP at Week 12 between participants receiving 2 mg baxdrostat versus participants receiving placebo in the rHTN subpopulation.
- Difference in mean change from baseline in seated DBP at Week 12 between participants receiving 2 mg baxdrostat versus participants receiving placebo.
- Difference in the proportion of participants achieving seated SBP < 130 mmHg at Week 12 between participants receiving 2 mg baxdrostat versus participants receiving placebo.

- Difference in mean change from baseline in seated SBP at Week 12 between participants receiving 1 mg baxdrostat versus participants receiving placebo in the rHTN subpopulation.
- Difference in mean change from baseline in seated DBP at Week 12 between participants receiving 1 mg baxdrostat versus participants receiving placebo.
- Difference in the proportion of participants achieving seated SBP < 130 mmHg at Week 12 between participants receiving 1 mg baxdrostat versus participants receiving placebo.

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

Important protocol deviations 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):

- Inclusion criteria
- Exclusion criteria
- Discontinuation criteria for study product met but subject not withdrawn from study treatment
- Discontinuation criteria for overall study withdrawal met but subject not withdrawn from study
- Investigational product deviation
- Excluded medication taken
- Deviations related to study procedure
- Other IPDs

IPDs will not be used to exclude any subject or subject data from the FAS.

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

3.3.6 Descriptive Statistics

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, 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 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.

A general rule is to present descriptive statistics (mean, SD, median, Q1, Q3) to 1 more decimal place than the values collected. The minimum and maximum values should be reported to the same number of decimal places as the individual values reported.

The CI for data presentations is 95% unless otherwise specified.

3.3.7 Handling of Missing Data

For the primary and secondary endpoints concerning office blood pressure measurements, 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.

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

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 3) and date of first dose of IMP, then the latest of randomisation (Visit 3) 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 3) and the date of first dose of IMP, then the latest of randomisation (Visit 3) and the date of first dose of IMP will be used.
- If the AE onset date is completely missing, the latest of randomisation (Visit 3) 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. Partially or completely missing CM start dates (where applicable) will be imputed as follows:

- If only the day value of the CM 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 randomisation, then the date of randomisation will be used.
- If the day and month values of the CM start date are missing, January 1 will be used; unless this occurs in the same year as the date of randomisation, then the date of randomisation will be used.
- If the CM start date is completely missing, the date of randomisation will be used.

If CM is marked as "Ongoing" the end date will not be imputed. Partially or completely missing CM end dates (where applicable) will be imputed as follows:

- If only the day value of the CM end date is missing, the last day of the month will be used; unless this occurs in the same month and year as the last visit, then the date of the last visit will be used.
- If the day and month values of the CM end date are missing, December 31 will be used; unless this occurs in the same year as the last visit, then the date of the last visit will be used.
- If the CM end date is completely missing, the date of last visit will be used.

Incomplete medical history dates

Missing medial history start dates (where applicable) will be imputed as follows:

- If only the day value of the MH 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 first ICF, then the date before first ICF will be used.

- If the day and month values of the MH start date are missing, January 1 will be used; unless this occurs in the same year as the date of first ICF, then the date before first ICF will be used.
- If the MH start date is completely missing, the date of before first ICF date will be used.

Missing MH end dates will not be imputed.

3.3.8 Multiple Imputation

3.3.8.1 Monotone and Non-monotone Missing Data Patterns

Monotone missing data are defined as missing data after the last observation at time point *t* to the end of FU, while non-monotone missing data means that there are observations made after the missing time point *t*. As the first step for any of the imputation methods described below, 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 a monotone missing data pattern will be generated, using a seed of 1580. The datasets with monotone missing data pattern will be the starting point for implementing the imputation methods below, using a seed of 158010.

The SAS procedure PROC MI will be used to perform the imputation of non-monotone missing data, 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, as well as HTN category at baseline (uHTN, rHTN) where applicable. The imputations will be conducted separately for each treatment group.

Multiple imputation methods for monotone missing data associated with the intercurrent events of treatment discontinuation or initiation of rescue therapy are specified in Sections 3.3.8.2 and 3.3.8.3.

Monotone missing data due to other reasons not associated with intercurrent events of treatment discontinuation or initiation of rescue therapy are assumed MAR and will be 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.

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.

3.3.8.2 Multiple Imputation Retrieved Dropouts

In the primary analysis missing data following treatment discontinuation will be imputed with a retrieved dropouts method based on MNAR assumption. The MI-RD method assumes that the pattern of endpoint measurement in participants who discontinue treatment and subsequently do not have endpoint measurement at Week *t* is similar to the pattern in participants in the same treatment group who discontinue treatment but continue in the study and have endpoint measurement at Week *t* (ie, retrieved dropouts). As such, for these participants the imputation of the missing endpoint measurement at Week *t* can be informed by the retrieved dropouts in the same treatment group.

The SAS procedure PROC MI will be used to perform MI-RD, with the MONOTONE statement together with the REGRESSION option. The imputation model will include baseline and post-baseline endpoint values at scheduled visits up to Week *t* in chronological order, as well as HTN category at baseline (uHTN, rHTN) where applicable. 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 intercurrent event (i.e. treatment discontinuation or initiation of rescue medication) and subsequently do not have endpoint measurement at Week *t* is similar to the pattern in participants in the placebo group (reference group).

For participants in the baxdrostat treatment group, imputation of missing endpoint measurements at Week *t* will be based on observed endpoint measurements at Week *t* in participants in the placebo group assuming data pattern follows MNAR. The imputation model will include; HTN category at baseline (uHTN, rHTN), baseline endpoint value, and endpoint value at Week *t*.

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; HTN category at baseline (uHTN, rHTN) where applicable, baseline endpoint value, and endpoint value at each post-baseline visit up to Week *t*. The SAS procedure PROC MI will be used to perform MI-WO, with the MONOTONE statement together with the REGRESSION option.

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 SEs. The LS mean coefficients will be computed using the observed proportions of the categorical variable (HTN category at baseline). 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 SE in each of the *m* imputed data sets. Rubin's rules assumes that multiple imputation estimates are asymptotically normally distributed. The following steps will be performed to estimate the OR:

- Combine the log-transformed estimate 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 OR and 95% CIs for the OR.

3.3.9 Geographic Regions

Geographic regions as defined in Table 6 will be used in the statistical analysis and reporting as applicable, such as recruitment summary by region and subgroup analysis by region.

Table 6 Geographic Regions

Region	Country
Asia Pacific, Middle East, and Africa (AMEA)	Australia
	India
	Japan
	Malaysia
	South Africa
	South Korea
	Taiwan
	Thailand
	Vietnam

Region	Country
Americas	Argentina
	Canada
	United States
Europe	Austria
	Belgium
	Bulgaria
	Czech Republic
	Denmark
	France
	Germany
	Hungary
	Israel
	Italy
	Netherlands
	Poland
	Slovakia
	Spain
	Sweden
	Turkey
	United Kingdom

3.3.10 ABPM Definition and General Considerations

Ambulatory blood pressure measurements will be performed for at least 25 hours; this will allow a minimum of 24-hour readings because 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 the ABPM device vendor.

The ABPM device will record blood pressure measurements every 20 minutes during a 16-hour daytime period (from 0600 to 2159), more specifically, at the timepoints corresponding to the 00 minute, 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 minute and 30 minutes of every hour.

Data validity

The ABPM assessment will be considered complete when all the following three criteria are fulfilled:

- ≥ 20 hours are recorded by the ABPM device.
- ≥ 70% of the ABPM readings are recorded.
- ≤ 2 consecutive hours of recordings are missing.

Participants who cannot complete the 25-hour ABPM assessment 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 report.

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 and ending at 2159. The night-time average will be calculated by taking the averages of 8 hourly average values starting at 2200 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.

4 STATISTICAL ANALYSIS

4.1 Study Population

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

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

- Subjects screened – defined as enrolled subjects

- Screen failures
- Subjects randomised
- Subjects randomised but not treated
- Subjects started treatment
- Subjects completed treatment
- Subjects discontinued treatment
- Subjects completed study
- Subjects withdraw from study

4.1.1.2 Presentation

Participant disposition of the enrolled population will be summarised by number of subjects and percent of subjects by treatment group and overall.

Disposition will be presented for screening, run-in and each study period. Disposition terms, randomisation codes, and assigned kit IDs will be listed.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The analysis sets are defined in Table 1.

For the safety analysis set erroneously treated participants will be classified according to the treatment they actually received as follows; participants randomised to active treatment (baxdrostat 2 mg or 1 mg) but only received placebo will be classified as having received placebo and participants randomised to placebo but who received active treatment (baxdrostat 2 mg or 1 mg) will be classified according to highest active treatment received at any occasion.

Subjects will be included in an analysis set within an analysis period if fulfilling definition in Table 1 within the specific analysis period.

4.1.2.2 Presentation

Analysis sets will be presented by number of subjects in each analysis set for all randomised subjects, by treatment group and overall. Number of subjects excluded from an analysis set will be presented.

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 and finalised prior to PDL and final 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 protocol deviations 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 group, sex, race, ethnicity and geographical region.

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. The tables will be repeated for uHTN and rHTN (baseline HTN derived from data as collected in clinical database) subpopulations separately.

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. BMI (kg/m^2) is calculated as: weight (kg) divided by the square of height (cm)/100. Baseline characteristics, where applicable, will also be derived with reference to the RWD baseline (Week 24) in the RWD Set and presented.

4.1.5.2 Presentation

The baseline characteristics as described above will be summarised descriptively. The data will be presented for the FAS, by treatment group and overall, at baseline and at RWD baseline (Week 24). The tables will be repeated for uHTN and rHTN (baseline HTN derived from data as collected in clinical database) subpopulations separately.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Disease characteristics include seated SBP, seated DBP, baseline HTN (uHTN, rHTN), eGFR (Inker et al 2021), diabetes mellitus status (Yes, No), sodium, potassium, heart rate, creatinine, aldosterone, renin, HbA1c, number of background antihypertensive medications, background antihypertensive medication class.

Background antihypertensive medications will be defined based on eCRF data entry. Background antihypertensive medication classes are based on the Anatomical Therapeutic Chemical (ATC) codes.

Disease characteristics, where applicable, will also be defined with reference to the RWD baseline in the RWD Set.

Baseline HTN categories will be derived from data as collected in clinical database. uHTN is defined as subjects with 2 antihypertensive drugs of different classes at baseline, one of which is a diuretic. rHTN is defined as subjects with at least 3 antihypertensive drugs of different classes at baseline, one of which is a diuretic. Background antihypertensive medications classes listed in Section 4.1.6.2 are used for deriving the baseline HTN categories from data as collected in clinical database. For other antihypertensive medications, each unique ATC classification code will be considered as a different class.

4.1.6.2 Presentation

The disease characteristics described above will be summarised descriptively. The data will be presented by treatment group and overall, at baseline as well as RWD baseline (Week 24). The tables will be repeated for the uHTN and rHTN subpopulations separately.

The number of background antihypertensive medications per subject will be summarized based on unique ATC classification codes. The background antihypertensive medication class include:

- ACEi or ARB
- Beta Blockers
- Calcium Channel Blockers
- Diuretics
- Other Antihypertensive Medications

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical and surgical history will be coded according to MedDRA. Specific medical and surgical history based on inclusion and exclusion criteria will also be collected.

4.1.7.2 Presentation

Medical and surgical history will be presented for the FAS, by treatment and overall, classified by SOC and PT. Percentages will be calculated with number of subjects in FAS as denominator. Subjects with multiple events in the same SOC/PT will be counted only

once in that SOC/PT. Subjects with events in more than one SOC/PT will be counted once in each of those SOC/PT. Relevant 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. Specific medical and surgical history for HTN (Hypertension, Hypertension type, Secondary hypertension subtype) together with time since diagnosis of HTN 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 MH 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 subject before the randomisation visit. If the end date is on the day of the randomisation visit, a medication will be defined as a prior medication. Concomitant medication is defined as any medication taken during study on or after the date of randomisation 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, the medication will not be considered concomitant. It is possible for a medication to be classified as both a prior medication and a CM.

Prohibited CM will be defined based on the Section 6.9.1 in the CSP version 3.0 (or version 6.0 EU). 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.

The definition and derivation for background antihypertensive medications is defined in Section 4.1.6.1.

All medications will be coded to ATC classification and generic drug name and are coded using the WHODD.

4.1.8.2 Presentation

Prior medications, CM, prohibited CM, and rescue medications will be presented separately. The data will be summarised descriptively. The data will be presented by treatment groups and overall. Subjects 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.

Concomitant medications, prohibited CM, and rescue medications will be summarised separately for each analysis period. The same definitions and derivations for CM as above will be applied within an analysis period.

All medications collected in clinical database will be listed for the FAS.

Background antihypertensive medications will be summarized over time for the following analysis periods: 12-week DB period, 24-week period and 52-week period. Summaries will be presented by treatment group for each analysis period separately.

The number of background antihypertensive medications and the background antihypertensive medication class will be similarly summarized as specified in Section 4.1.6.2. In addition to the background antihypertensive medication classes specified in Section 4.1.6.2, the summaries will also include MRA and potassium-sparing diuretics as separate classes.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Study drug compliance (%) within an analysis period 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 within a treatment period, 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 observation, compliance is not calculated for that participant. Study drug compliance is only defined for baxdrostat or placebo and is not applicable for participants receiving SoC.

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

4.1.9.2 Presentation

Compliance will be presented by treatment groups separately for different analysis period. Compliance will be presented as a continuous variable as well as a categorical variable by compliance group summarised descriptively.

4.1.10 Stratification Factors

4.1.10.1 Definitions and Derivations

The stratification factors at first randomisation and at RWD randomisation are described in Section 3.3.1.6.

4.1.10.2 Presentation

Stratification factors at first randomisation will be presented for the FAS and stratification factors at RWD randomisation will be presented for the RWD set.

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 the FAS.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, exploratory endpoints including sensitivity and supplementary analyses. The multiplicity procedure for the testing of the primary and secondary endpoints is described in Section 3.3.4.

Table 7 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 2 mg baxdrostat versus placebo on seated SBP at week 12					
Primary Endpoint - Primary Analysis	Change from baseline in seated SBP at Week 12	FAS	Treatment policy	LS Mean difference between 2 mg baxdrostat and placebo (ANCOVA with MI-RD and MI-WO)	4.2.1
Primary Endpoint – Sensitivity Analysis	Change from baseline in seated SBP at Week 12	FAS	Treatment policy	LS Mean difference between 2 mg baxdrostat and placebo	4.2.1

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
				(ANCOVA with MI-WO)	
Primary Endpoint – Sensitivity Analysis	Change from baseline in seated SBP at Week 12	FAS	Treatment policy	LS Mean difference between 2 mg baxdrostat and placebo (MMRM)	4.2.1
Primary Endpoint – Supplementary Analysis	Change from baseline in seated SBP at Week 12	FAS	Treatment policy and hypothetical	LS Mean difference between 2 mg baxdrostat and placebo (ANCOVA with MI-RD and MI-WO)	4.2.1
Objective 2: To assess the effect of 1 mg baxdrostat versus placebo on seated SBP at week 12					
Primary Endpoint - Primary Analysis	Change from baseline in seated SBP at Week 12	FAS	Treatment policy	LS Mean difference between 1 mg baxdrostat and placebo (ANCOVA with MI-RD and MI-WO)	4.2.1
Primary Endpoint – Sensitivity Analysis	Change from baseline in seated SBP at Week 12	FAS	Treatment policy	LS Mean difference between 1 mg baxdrostat and placebo (ANCOVA with MI-WO)	4.2.1
Primary Endpoint – Sensitivity Analysis	Change from baseline in seated SBP at Week 12	FAS	Treatment policy	LS Mean difference between 1 mg baxdrostat and placebo (MMRM)	4.2.1
Primary Endpoint – Supplementary Analysis	Change from baseline in seated SBP at Week 12	FAS	Treatment policy and hypothetical	LS Mean difference between 1 mg baxdrostat and placebo	4.2.1

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
				(ANCOVA with MI-RD and MI-WO)	
Objective 3: To assess the effect of 2 mg baxdrostat versus placebo on seated SBP at 8 weeks after RWD					
Secondary Endpoint – Primary Analysis	Change from RWD baseline (Week 24) in seated SBP at Week 32	RWD set	Treatment policy	LS Mean difference between 2 mg baxdrostat and placebo (ANCOVA with MI-WO)	4.2.2
Secondary Endpoint – Sensitivity Analysis	Change from RWD baseline (Week 24) in seated SBP at Week 32	RWD set	Treatment policy	LS Mean difference between 2 mg baxdrostat and placebo (MMRM)	4.2.2
Secondary Endpoint – Supplementary Analysis	Change from RWD baseline (Week 24) in seated SBP at Week 32	RWD set	Treatment policy and hypothetical	LS Mean difference between 2 mg baxdrostat and placebo (ANCOVA with MI-WO)	4.2.2
Objective 4: To assess the effect of 2 mg baxdrostat versus placebo on seated SBP at Week 12 in the rHTN subpopulation					
Secondary Endpoint – Primary Analysis	Change from baseline in seated SBP at Week 12	FAS with rHTN	Treatment policy	LS Mean difference between 2 mg baxdrostat and placebo (ANCOVA with MI-RD and MI-WO)	4.2.3
Objective 5: To assess the effect of 2 mg baxdrostat versus placebo on seated DBP at Week 12					
Secondary Endpoint – Primary Analysis	Change from baseline in seated DBP at Week 12	FAS	Treatment policy	LS Mean difference between 2 mg baxdrostat and placebo (ANCOVA with MI-RD and MI-WO)	4.2.4

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 6: To assess the effect of 2 mg baxdrostat versus placebo on achieving seated SBP < 130 mmHg at Week 12					
Secondary Endpoint – Primary Analysis	Achieving seated SBP < 130 mmHg at Week 12	FAS	Treatment policy	OR, 2 mg baxdrostat versus placebo (ANCOVA with MI-RD and MI-WO)	4.2.5
Objective 7: To assess the effect of 1 mg baxdrostat versus placebo on seated SBP at Week 12 in the rHTN subpopulation					
Secondary Endpoint – Primary Analysis	Change from baseline in seated SBP at Week 12	FAS with rHTN	Treatment policy	LS Mean difference between 1 mg baxdrostat and placebo (ANCOVA with MI-RD and MI-WO)	4.2.3
Objective 8: To assess the effect of 1 mg baxdrostat versus placebo on seated DBP at Week 12					
Secondary Endpoint – Primary Analysis	Change from baseline in seated DBP at Week 12	FAS	Treatment policy	LS Mean difference between 1 mg baxdrostat and placebo (ANCOVA with MI-RD and MI-WO)	4.2.4
Objective 9: To assess the effect of 1 mg baxdrostat versus placebo on achieving SBP < 130 mmHg at Week 12					
Secondary Endpoint – Primary Analysis	Achieving seated SBP < 130 mmHg at Week 12	FAS	Treatment policy	OR, 1 mg baxdrostat versus placebo (ANCOVA with MI-RD and MI-WO)	4.2.5

4.2.1 Primary Endpoints

There are two primary objectives in this study,

- To assess the effect of 2 mg baxdrostat versus placebo in mean change from baseline in seated SBP at Week 12,

- To assess the effect of 1 mg baxdrostat versus placebo in mean change from baseline in seated SBP at Week 12.

The same primary analysis will be conducted for these two primary endpoints of mean change from baseline in seated SBP at Week 12. The descriptions in this section refer to 'baxdrostat' for simplicity, without distinguishing between 2 mg baxdrostat and 1 mg baxdrostat.

4.2.1.1 Definition

The primary estimand is described by the following attributes:

- Population: participants with uHTN or 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 or 1 mg baxdrostat QD and stable regimen of background antihypertensive medication, alternative treatment condition is placebo QD and stable regimen of background medication.
- Intercurrent events: the intercurrent event of treatment discontinuation will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of treatment discontinuation. The intercurrent event of rescue therapy will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of initiation of rescue therapy. The intercurrent event 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 or 1 mg separately) versus placebo.

4.2.1.2 Derivations

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

- Three seated SBP measurements (each approximately 1 minute apart) should be obtained using the same arm and the AOBPM device at each clinical site visit. Mean seated SBP is defined as the average of the last 2 seated SBP measurements of the total 3 measurements, at any single clinical site visit. If multiple mean seated SBP readings are obtained during the baseline visit, the last mean seated SBP will be used (Section 3.3.1.1). For any post-baseline visit, the first mean seated SBP 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 SBP 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 SBP is rounded up to the nearest integer.

The wording "seated SBP" will hereafter be used throughout the document instead of "mean seated SBP".

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

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 interventions.

Multiple imputation of missing data is described in Section 3.3.8.

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 and HTN at baseline (uHTN, rHTN) as factors, 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 imputed data where applicable. In accordance with the primary estimand and strategies for intercurrent events, the primary analysis will include all available measurements regardless of treatment discontinuation or initiation of rescue therapy.

Missing data at Week 12 following treatment discontinuation will be imputed based on MNAR assumptions, with MI-RD being the preferred method if there is sufficient data on retrieved dropouts. If MI-RD cannot be conducted because of an insufficient number of retrieved dropouts (ie the model fails to converge), MI-WO will be used instead 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 due to other reasons unrelated to intercurrent events 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 intercurrent events (e.g. treatment discontinuation, initiation of rescue medications) or other reasons unrelated to intercurrent events of treatment discontinuation or initiation of rescue therapy.

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

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

MI-WO for Treatment Discontinuation

As a sensitivity analysis with respect to the missing data assumptions, MI-WO, instead of MI-RD, will be used to impute the missing data at Week 12 following treatment discontinuation. MI-WO will continue to be used for the missing data at Week 12 following initiation of rescue medication. This analysis will be upgraded to the primary analysis if the planned primary analysis (Section 4.2.1.4) cannot be conducted due to insufficient number of retrieved dropouts (ie, the model fails to converge).

Mixed Model Repeated Measures (MMRM)

As a sensitivity analysis with respect to the missing data assumptions, the primary endpoint will be analysed in a MMRM model. In the MMRM model, missing post-baseline SBP assessments are implicitly handled in the likelihood-based parameter estimation assuming values in subjects with missing data are similar to those in subjects with observed data with the same treatment assignment and covariate values (ie, MAR).

The model will use change from baseline in SBP at each visit as the response variable and will include baseline SBP as a continuous fixed effect covariate and HTN at baseline (uHTN, rHTN), treatment, visit and treatment-by-visit interaction as fixed effect factors. The model will be fitted using PROC MIXED in SAS assuming an unstructured covariance structure with the Kenward-Roger correction applied to obtain the degrees of freedom. All available SBP measurements, regardless of treatment discontinuation or initiation of rescue medication, will be included in the analysis model.

Least square mean estimates for each treatment and the difference between treatments and 95% CIs for each estimate will be presented as well as the p-value for the difference between treatments at Week 12 and other visits. The LS mean coefficients will be computed using the observed proportions of the categorical variable (HTN category at baseline).

4.2.1.6 Supplementary Analyses of the Primary Endpoint

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 the hypothetical strategy for rescue therapy. Specifically, the ANCOVA model will include all available measurements regardless of treatment discontinuation and available measurement up to initiation of rescue therapy. 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.

4.2.1.7 Subgroup Analyses

Exploratory subgroup analyses will be conducted for the primary endpoints to assess consistency of treatment effect across subgroups of clinical interest. Pre-specified subgroup variables are listed in Table 8.

Table 8 Subgroup Variables

Baseline Characteristics	Categories
Age (years)	< 65, ≥ 65 - < 75, ≥75,
Sex	Female, Male
Race	Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian, White, Other, Multiple
Ethnicity	Hispanic or Latino, Not Hispanic or Latino
Geographic region	AMEA, Europe, Americas
HTN at baseline [a]	uHTN, rHTN
Baseline SBP (mmHg) [a]	< 145, ≥ 145
Baseline eGFR (mL/min/1.73 m^2)	< 60, ≥ 60
Baseline BMI (kg/m^2)	< 30, ≥ 30

[a] The subgroup variables are derived based on the data collected in the clinical database. See Section 4.1.6.1 for details.

Unless otherwise specified, all subgroup variables will be defined based on data collected at the time of the first randomisation (i.e., the DB period randomisation).

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. Multiple imputation with respect to the response variable will be handled in the same way as in the primary analysis.

The estimates within each subgroup, including LS 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. The subgroup-by-treatment interaction p-value will be calculated as the median p-value from the set of all imputations.

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 tables and a forest plot.

4.2.2 Secondary Endpoint – Change from RWD Baseline (Week 24) in Seated SBP at Week 32

4.2.2.1 Definition

The estimand is described by the following attributes:

- Population: participants with uHTN or rHTN, as defined by the inclusion and exclusion criteria. Implemented through the use of the RWD set.
- Endpoint: change from RWD baseline (Week 24) in seated SBP at Week 32.
- 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.
- Intercurrent events: the intercurrent event of treatment discontinuation will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of treatment discontinuation. The intercurrent event of rescue therapy will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of initiation of rescue therapy. The intercurrent event 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 RWD baseline (Week 24) between 2 mg baxdrostat versus placebo.

4.2.2.2 Derivations

See Section 4.2.1.2

Change from RWD baseline (Week 24) in seated SBP at Week 32 is defined as seated SBP value at Week 32 minus seated SBP value at RWD baseline (Week 24).

4.2.2.3 Handling of Dropouts and Missing Data

See Section 4.2.1.3.

4.2.2.4 Primary Analysis of Secondary Endpoint

The primary analysis of the secondary endpoint will be analysed using an ANCOVA model with treatment and HTN (uHTN, rHTN) as factors, and RWD baseline (Week 24) seated SBP value as a covariate, based on the RWD set. The model will be fitted using PROC GLM in SAS.

The response variable will include available seated SBP observations at Week 32 as well as imputed data where applicable. In accordance with the estimand and strategies for intercurrent events, the primary analysis will include all available measurements regardless of treatment discontinuation or initiation of rescue therapy.

As stated in the protocol, if the MI-RD method cannot be conducted due to insufficient number of retrieved dropouts (ie, the model fails to converge) then it will be replaced by the MI-WO method for imputation of missing data following treatment discontinuation. Therefore, due an insufficient number of retrieved dropouts in the RWD period, for the secondary endpoint for change from RWD baseline (Week 24) in seated SBP at Week 32, the MI-WO method will be used to impute missing data due to treatment discontinuation in the RWD period.

Missing data at Week 32 following treatment discontinuation will be imputed based on MNAR assumptions, with MI-WO being used assuming MNAR for the baxdrostat group and MAR for the placebo group. Missing data at Week 32 following initiation of rescue therapy will be imputed with MI-WO method as well. Missing data at Week 32 due to other reasons unrelated to intercurrent events 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 intercurrent events (e.g. treatment

discontinuation, initiation of rescue medications) or other reasons unrelated to intercurrent events of treatment discontinuation or initiation of rescue therapy.

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

No subgroup analysis will be performed for this secondary endpoint.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

See the MMRM sensitivity analysis in Section 4.2.1.5.

4.2.2.6 Supplementary Analyses of the Secondary Endpoint

See Section 4.2.1.6.

4.2.3 Secondary Endpoint – Change from Baseline in Seated SBP at Week 12 in the rHTN Subpopulation

This secondary endpoint is defined for 2 mg baxdrostat and 1 mg baxdrostat separately. The analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the primary endpoint (Section 4.2.1) but will only include participants with resistant HTN at baseline.

No sensitivity, supplementary or subgroup analyses will be performed for this secondary endpoint.

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

This secondary endpoint is defined for 2 mg baxdrostat and 1 mg baxdrostat separately. The analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the primary endpoint (Section 4.2.1), but replacing seated SBP measurements with seated DBP measurements and with change from baseline in seated DBP at Week 12 as the response variable.

No sensitivity, supplementary or subgroup analyses will be performed for these secondary endpoints.

4.2.5 Secondary Endpoint – Achieving Seated SBP < 130 mmHg at Week 12

This secondary endpoint is defined for 2 mg baxdrostat and 1 mg baxdrostat separately. The same primary analysis will be conducted for these two secondary endpoints. The descriptions in this section refer to ‘baxdrostat’ for simplicity, without distinguishing between 2 mg baxdrostat and 1 mg baxdrostat.

4.2.5.1 Definition

The estimand is described by the following attributes:

- Population: participants with uHTN or rHTN, as defined by the inclusion and exclusion criteria. Implemented through the use of the FAS.
- Endpoint: achieving seated SBP < 130 mmHg at Week 12.
- Treatment condition: 2 mg baxdrostat QD and stable regimen of background antihypertensive medication or 1 mg baxdrostat QD and stable regimen of background antihypertensive medication, alternative treatment condition is placebo QD and stable regimen of background medication.
- Intercurrent events: the intercurrent event of treatment discontinuation will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of treatment discontinuation. The intercurrent event of rescue therapy will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of initiation of rescue therapy. The intercurrent event of death, if any, will be handled via a hypothetical strategy, ie, as if the subject had not died.
- Population level summary: OR of baxdrostat (2 mg or 1 mg separately) versus placebo.

4.2.5.2 Derivations

Definition of a treatment responder in seated SBP will be based on the continuous measurement of seated SBP (Section 4.2.1.2). Achieving seated SBP < 130 mmHg at Week 12 will be derived as a categorical variable according to the following:

- If seated SBP value at Week 12 < 130 mmHg (responder) then equal to 1
- If seated SBP value at Week 12 ≥ 130 mmHg (non-responder) then equal to 0
- If seated SBP value at Week 12 is missing then set to missing.

4.2.5.3 Handling of Dropouts and Missing Data

See Section 4.2.1.3.

4.2.5.4 Primary Analysis of Secondary Endpoint

The primary analysis of the secondary endpoint will be analysed using a logistic regression model which will include baseline SBP value as a covariate and treatment and HTN category at baseline (uHTN, rHTN) as factors, based on the FAS. The logistic model will be fitted using PROC LOGISTIC in SAS. This analysis will only include participants with baseline SBP of 130 mmHg or higher.

Missing data for seated SBP at Week 12 will be imputed based on continuous seated SBP values in the same way as for the primary analysis of the primary endpoints (Section 4.2.1.4). The dichotomous response variable will then be derived based on the imputed values (Section 4.2.5.3).

No sensitivity, supplementary or subgroup analyses will be performed for these secondary endpoints.

4.2.6 Exploratory Endpoints

4.2.6.1 Change from Baseline in Seated SBP at Week 4

This exploratory endpoint is defined for 2 mg baxdrostat and 1 mg baxdrostat separately. The analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the primary endpoint (Section 4.2.1), but with change from baseline in seated SBP at Week 4 as the response variable.

No sensitivity, supplementary or subgroup analyses will be performed for the exploratory endpoint.

4.2.6.2 Change from Baseline in Seated SBP at Week 8

This exploratory endpoint is defined for 2 mg baxdrostat and 1 mg baxdrostat separately. The analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the primary endpoint (Section 4.2.1), but with change from baseline in seated SBP at Week 8 as the response variable.

No sensitivity, supplementary or subgroup analyses will be performed for the exploratory endpoint.

4.2.6.3 Change from Baseline in Seated DBP at Week 4

This exploratory endpoint is defined for 2 mg baxdrostat and 1 mg baxdrostat separately. The analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the primary endpoint (Section 4.2.1), but replacing seated SBP measurements with seated DBP measurements and with change from baseline in seated DBP at Week 4 as the response variable.

No sensitivity, supplementary or subgroup analyses will be performed for the exploratory endpoint.

4.2.6.4 Change from Baseline in Seated DBP at Week 8

This exploratory endpoint is defined for 2 mg baxdrostat and 1 mg baxdrostat separately. The analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the primary endpoint (Section 4.2.1), but

replacing seated SBP measurements with seated DBP measurements and with change from baseline in seated DBP at Week 8 as the response variable.

No sensitivity, supplementary or subgroup analyses will be performed for the exploratory endpoint.

4.2.6.5 Change from RWD Baseline (Week 24) in Seated SBP at Week 28

This exploratory endpoint is only defined for 2 mg baxdrostat. The analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the secondary endpoint, change from RWD baseline (Week 24) in seated SBP at Week 32 (Section 4.2.2).

4.2.6.6 Change from Baseline in Mean Ambulatory 24-Hour SBP at Week 12 as Measured by ABPM

This exploratory endpoint defined for 2 mg baxdrostat and 1 mg baxdrostat separately. The same analysis will be conducted for these two secondary endpoints. The descriptions in this section refer to 'baxdrostat' for simplicity, without distinguishing between 2 mg baxdrostat and 1 mg baxdrostat.

Derivation

Derivation of ABPM measurements is given in Section 3.3.10.

The 24-hour ABPM assessment performed at the Run-in Visit will start during that visit and participants will return the ABPM device after assessment completion (after completing a minimum of 25-hour ABPM readings). This assessment will be considered as the baseline measurement and will be performed pre-randomisation (Visit 3).

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.

Analysis

The analysis of the exploratory endpoint will be analysed using an ANCOVA model with treatment and HTN category at baseline (uHTN, rHTN) as factor, and baseline ambulatory 24-hour average SBP value as a covariate, based on the ABPM Analysis Set. The analysis will include participants with valid ABPM sessions at both start of run-in and Week 12. The response variable is ambulatory 24-hour average SBP at Week 12. In accordance with the primary estimand and strategies for intercurrent events, the primary analysis will include all available measurements regardless of treatment discontinuation and initiation of rescue therapy. There will be no imputation of missing data. The model will be fitted using PROC GLM in SAS.

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

No sensitivity, supplementary or subgroup analyses will be performed for these exploratory endpoints.

4.2.6.7 Change from Baseline in Ambulatory Night-Time Average SBP at Week 12 as Measured by ABPM

This exploratory endpoint is defined for 2 mg baxdrostat and 1 mg baxdrostat combined. The analysis of this endpoint will be conducted using a similar approach as for the exploratory endpoint, change from baseline in mean ambulatory 24-hour average SBP at Week 12 as measured by ABPM (Section 4.2.6.6), but only considering night-time average SBP measured by ABPM.

4.2.6.8 Change from Baseline in Ambulatory Day-Time Average SBP at Week 12 as Measured by ABPM

This exploratory endpoint is defined for 2 mg baxdrostat and 1 mg baxdrostat combined. The analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the secondary endpoint, change from baseline in mean ambulatory 24-hour average SBP at Week 12 as measured by ABPM (Section 4.2.6.6), but only considering day-time average SBP measured by ABPM.

4.2.6.9 Achieving Ambulatory 24-Hour Average SBP of < 130 mmHg at Week 12 as Measured by ABPM

This exploratory endpoint is defined for 2 mg baxdrostat and 1 mg baxdrostat combined. The analysis of this endpoint will be conducted using a similar approach as for the exploratory endpoint, change from baseline in mean ambulatory 24-hour average SBP at Week 12 as measured by ABPM (Section 4.2.6.6). This analysis will only include participants with baseline SBP of 130 mmHg or higher as measured by ABPM.

Derivation

The endpoint for the analysis will be derived as a categorical variable according to,

- If mean ambulatory 24-hour average SBP at Week 12 < 130 mmHg (responder) then equal to 1
- If mean ambulatory 24-hour average SBP at Week 12 ≥ 130 mmHg (non-responder) then equal to 0
- If mean ambulatory 24-hour average SBP at Week 12 is missing, then set to missing.

The treatment effect will be assessed by the population level summary statistic of OR of baxdrostat (2 mg or 1 mg combined) versus placebo.

Analysis

The analysis of the exploratory endpoint will be analysed using a logistic regression model which will include baseline ambulatory 24-hour average SBP value as a covariate and treatment and HTN category at baseline (uHTN, rHTN) as factors, based on the ABPM analysis set. The treatment effect will be estimated by OR, SE and 95% CI. The p-value will also be presented. In accordance with the primary estimand and strategies for intercurrent events, the primary analysis will include all available measurements regardless of treatment discontinuation and initiation of rescue therapy. There will be no imputation of missing data. The logistic model will be fitted using PROC LOGISTIC in SAS.

4.2.6.10 Change from Baseline in Ambulatory 24-Hour Average DBP at Week 12 as Measured by ABPM

This exploratory endpoint is defined for 2 mg baxdrostat and 1 mg baxdrostat combined. The analysis of this endpoint will be conducted using a similar approach as for the exploratory endpoint, change from baseline in mean ambulatory 24-hour average SBP at Week 12 as measured by ABPM (Section 4.2.6.6), but replacing mean ambulatory 24-hour average SBP measurements with mean ambulatory 24-hour average DBP measurements and with change from baseline in mean ambulatory 24-hour average DBP at Week 12 as measured by ABPM as the response variable.

4.2.6.11 Achieving Seated SBP < 140 mmHg at Week 12

This exploratory endpoint is only applicable for the CSP for EU and is defined for 2 mg baxdrostat and 1 mg baxdrostat separately. The analysis of this endpoint will be conducted using a similar estimand, estimator, and presentation as for the primary analysis of the secondary endpoint, achieving Seated SBP < 130 mmHg at Week 12 (Section 4.2.5). This analysis will only include participants with baseline SBP of 140 mmHg or higher.

4.3 Pharmacodynamic Endpoints

4.3.1 Definitions and Derivations

Pharmacodynamic 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 (PRA) and/or plasma renin concentration (PRC).
- Calculation of aldosterone/PRA ratio and/or aldosterone/PRC ratio.
- Proteomic panel (Olink®).

Proteomic panel (Olink®) data will not be available at the time of PDL analysis and therefore will not be included. These data will be incorporated into the second (ie, final) CDL analysis.

Pre-dose blood samples for PD analysis will be collected at Visit 3, 5, 7, 9 and 11.

4.3.2 Analysis

For the distinct types of laboratory parameters, the following summaries over time per timepoint will be provided for 12-week DB period (on-treatment and on-study) and 24-week period (on-study) using the Safety Analysis Set; assessments as per analysis visit windows (see Section 3.3.2) will be used:

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

For the distinct types of laboratory parameters measured in the DB RWD period (Week 24 to Week 32) summaries over time per timepoint will be provided up to 32 weeks from RWD baseline at week 24, based on the RWD analysis set for on-study analysis period.

4.3.3 Presentation

The outputs for PD variables will follow Clinical Laboratory, Blood Sample, outputs in Section 4.6.3.3, where applicable. Analysis of PD with respect to baxdrostat concentration may be conducted in separate reports.

4.4 Pharmacokinetics

4.4.1 Definitions and Derivations

Evaluating the PK of baxdrostat is an exploratory objective. Pharmacokinetic blood samples will be collected for measurement of plasma concentrations pre-dose at Visit 5, 7, 9, and 11. 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.

4.4.2 Presentation

Descriptive analysis for PK concentrations in plasma will be summarised by treatment and visit. For each PK parameter the following statistics will be derived: number of subjects (n), mean, SD, geometric mean, geometric CV%, min, median and max. Listings on individual level based on the PK analysis set.

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. In addition, extra evaluation will be done for the following AESI: hyperkalaemia, hyponatraemia and hypotension events that require medical intervention, and for pre-specified safety categories MACE and MACE-Plus events. An EAC will provide external independent assessment of blinded data to confirm the diagnosis and causality of the MACE and MACE-Plus events. Exposure to study treatment will be described.

Table 9 Safety Analyses

Type	Safety Endpoint	Details in section
General Safety Objective: To assess the safety and tolerability of baxdrostat 1 or 2 mg as compared to placebo in patients with uHTN and 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 (complete list of parameters is presented in Section 4.6.3), change from baseline and time to first treatment emergent abnormality.	4.6.3, 4.6.4
Vital signs	Observed vital sign value (including blood pressure, heart rate and body weight), change from baseline, and time to first treatment emergent abnormality.	4.6.5
ECG	Observed ECG parameter, change from baseline and time to first treatment emergent abnormality.	4.6.6
Other	Occurrence and time to first event for AESIs (hyperkalaemia, hyponatraemia and hypotension events that require medical intervention). Occurrence for pre-specified safety categories (MACE and MACE-Plus).	4.6.7

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.

The safety estimand is primarily defined for the 12-week DB period (Week 0 to Week 12). For analysis periods in Section 3.3.1.4 attributes of the safety estimand will be utilised where applicable.

The general safety objective will be assessed through an estimand defined by the following attributes (Hedman et al 2024):

Population: Patients with HTN as defined by the inclusion and exclusion criteria. Implemented through the use of the Safety Analysis Set.

Treatment: 2 mg baxdrostat QD on a stable regimen of background antihypertensive medication or 1 mg baxdrostat QD on a stable regimen of background antihypertensive medication, alternative treatment condition is placebo QD and stable regimen of background medication.

Intercurrent events (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 medication: These ICEs will be ignored, that is, handled using a treatment policy approach.
- Death: This ICE will be handled hypothetically as if it cannot happen, implemented by censoring time to event data at death and not imputing any data after death.

Population level summaries and estimators for respective analysis:

- 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 subjects, included in the analysis set used for safety, are followed up regardless of study intervention compliance and adherence to the study protocol (for planned study periods and SFU).

AEs and safety parameters will be evaluated based on the safety analysis set (see Section 3.2) by treatment group. Treatment group in safety analysis set will be allocated as per actual treatment and not randomised treatment (see section 4.1.2.1).

The following analysis periods will be included in the safety analyses (unless stated otherwise): 12-week DB period, 24-week period, 52-week period, DB RWD period, and 42-week period.

All analyses will be conducted with the on-study analysis approach (see Section 3.3.1) for all analysis periods. For the 12-week DB period all analyses will be conducted also with the on-treatment analysis approach with exception of extreme value analyses and potential liver injury analyses.

Hazard ratios 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. 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 Kaplan-Meier estimator. The probability of the event of interest occurring before predefined timepoint will be estimated by the Kaplan-Meier estimator at the below defined timepoint for each respective analysis period by treatment group, and the treatment group difference in Kaplan-Meier estimate (main summary measure) with 95% CI will be estimated at the same timepoint.

For AE and AESI, the midpoint of the SoA visit window for the targeted visit in the analysis period will be used for KM estimation. Since laboratory, vital signs and ECG parameters are only assessed at visits, the upper limit of the SoA visit window for the targeted visit in the analysis period will be used for KM estimation. This results in the following timepoints for Kaplan-Meier estimation:

- 12-week DB period: Week 12

  - For AE and AESI: SoA study day 85
  - For laboratory, vital signs and ECG parameters: SoA study day 89
- DB RWD period: Week 32
  - For AE and AESI: study day [a] 57
  - For laboratory, vital signs and ECG parameters: study day [a] 61
- 24-week period: Week 24
  - For AE and AESI: SoA study day 169
  - For laboratory, vital signs and ECG parameters: SoA study day 173
- 52-week period: Week 52
  - For AE and AESI: SoA study day 365
  - For laboratory, vital signs and ECG parameters: SoA study day 369
- 42-week period: Week 52
  - For AE and AESI: study day [b] 281
  - For laboratory, vital signs and ECG parameters: study day [b] 285

[a] Study day is anchored on date of randomisation to DB RWD period, and the date of randomisation to DB RWD period is considered as study day 1.
[b] Study day is anchored on date of randomisation to Open-label 12 weeks period, and the date of randomisation to Open-label 12 weeks period is considered as study day 1.

Time to event definition: For subjects 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.

As a general rule, for subjects who do not present the defined event in the defined analysis period, time to event is censored at the subject's last timepoint in the defined analysis period. This applies to all analysis periods that end with SFU (52-week period, 42-week period, and cohort 2 in 24-week period), and to Kaplan-Meier curve estimation in all analysis periods. It will also be applied for Kaplan-Meier estimation at the above defined timepoints of AE and AESI events.

An exception to this general rule is for analysis periods that end in the visit targeted for Kaplan-Meier estimation (12-week DB period, DB RWD period, and for Cohort 1 the 24-week period) for subjects with last visit that falls within the visit windows of ±4 days as specified in the CSP SoA. For the analysis of laboratory, vital signs and ECG parameters, these subjects will be censored at the timepoints defined above. For example, a subject who is event free during the 12-week DB period and has Week 12 visit at day 81 will be censored at day 89 for the analysis of laboratory, vital signs and ECG parameters. This

special censoring rule is to mitigate potential heavy censoring at these timepoints in the context of the study design and improve the precision of the KM estimates.

Subgroup analyses of AEs and other safety events will be performed, per definition in the presentation section, with the same approach as for the overall study population but within each subgroup category. Unless otherwise specified, all subgroup variables will be defined based on data collected at the time of the first randomisation (ie, the DB period randomisation).

The subgroups and categories that will be used are;

- Age category (< 65, ≥ 65 - < 75, ≥75),
- eGFR at baseline (mL/min/1.73m^2) group (< 60, ≥ 60),
- HTN at baseline (uHTN, rHTN),
- Sex (Male, Female),
- Race (Asian, Black or African American, and White).
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino),
- Geographical region (Americas, AMEA, Europe).

Presentation

For the 12-week DB period (SoA Week 0 to Week 12) AEs and safety parameters will be presented based on the Safety Analysis Set (Section 3.2) by treatment group. Both the On-treatment analysis period and the On-study analysis period will be presented unless otherwise stated (Section 3.3.1.4).

For the DB RWD period (SoA Week 24 to Week 32) AEs and safety parameters will be presented based on the RWD set by treatment group. Only the On-study analysis period will be presented (Section 3.3.1.4).

For the 24-week period (SoA Week 0 to Week 24) AEs and safety parameters will be presented based on the Safety Analysis Set for the On-study analysis period by treatment group. This analysis will exclude participants who either switch from baxdrostat 1 mg to SoC or switch from placebo to baxdrostat 2 mg as a result of the second randomisation at Week 12 (Visit 7).

For the 52-week period (SoA Week 0 to Week 54) AEs and safety parameters will be presented for participants in Cohort 1 based on the Safety Analysis Set for the On-study analysis period. This analysis will exclude participants who either switch from baxdrostat 1 mg to SoC or switch from placebo to baxdrostat 2 mg as a result of the second

randomisation at Week 12 (Visit 7), and those who switch from baxdrostat 2 mg to placebo as a result of the third randomisation at Week 24 (Visit 9).

For the 42-week period (SoA Week 12 to Week 54) safety outputs will be presented for On-study analysis period which will include participants on baxdrostat 2 mg and SoC across periods. However, participants receiving placebo in the DB RWD period will be included in the baxdrostat 2 mg group in the 42-week period analysis. Furthermore, only participants excluded from 24-week period and 52-week period will be included in the 42-week period analysis.

For presentations using data cumulatively over a defined analysis period, comparisons between treatments 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 illustration of precision of the estimate. Their coverage should not be interpreted as a proof of an existence, or an absence, of a safety signal.

Preliminary long-term safety data analysis at PDL

For the 24-week and 52-week periods, participants will be included according to above description, with the additional restrictions:

- 24-week period:
  - Participants who attended Visit 9 (Week 24) or a later visit; or
  - Participants who withdrew from the study before Visit 9 and were randomised at least 168 days before the PDL date.
- 52-Week period:
  - Participants who attended Visit 13 (Week 52) or the SFU visit (Week 54).
  - Cohort 1 participants who withdrew from the study and were randomised at least 364 days before the PDL date.

Preliminary 42-week period safety data analysis at PDL

For the 42-week period, participants will be included according to above description, with the additional restrictions:

- 42-week period:
  - Cohort 1 participants who attended Visit 13 (Week 52) or the SFU visit (Week 54).
  - Cohort 1 participants who withdrew from the study and were randomised at least 364 days before the PDL date.

- Cohort 2 participants who attended Visit 9 (Week 24) or the SFU visit (Week 26).
- Cohort 2 participants who withdrew from the study and were randomised at least 168 days before the PDL date.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Total exposure (days) is defined as the number of days from the date of first dose of IMP 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

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

Cumulative exposure over time for subjects with exposure of at least 12, 24, 32 and 52 weeks will be derived.

Exposure will be defined for each analysis period as applicable. Exposure is only defined for baxdrostat or placebo and is not applicable for participants receiving SoC.

4.6.1.2 Presentation

Total and actual exposures as well as cumulative exposure over time will be summarised by treatment and analysis period.

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 Appendix B in CSP.

All AEs will be classified by SOC and PT according to a MedDRA version. The MedDRA version will be up-versioned to the latest version, or remain one version behind the latest version of MedDRA during the study until the time of CDL.

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 a reported AE with a 'Fatal' outcome and with an onset date within the defined analysis period. The onset date of the AE determined whether an AE belongs to 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 "IMP permanently discontinued" and with an onset date within the defined analysis period. The onset date of the AE determined whether the AE leading to discontinuation of IMP belongs to the analysis period, irrespective of date of discontinuation 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 subject 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:

- Number and percentage of subjects who experienced an event, by treatment group.
- Kaplan-Meier risk estimate in percent (KM%) at Week 12, Week 24 and Week 52 (at specific days as defined for Safety Estimand above) from baseline, including

only patients with continuous baxdrostat (2 mg or 1 mg) versus continuous placebo/SoC, by treatment group.

- Difference between treatment groups in KM% at Week 12, Week 24 and Week 52 (at specific days as defined for Safety Estimand above) from baseline together with 95% CI.
- Hazard ratio between treatment groups together with 95% CI, based on a Cox proportional hazards regression model with a factor for treatment group.

For the distinct types of AEs collected in the DB RWD period (Week 24 to Week 32) summaries/analyses will be provided based on the RWD analysis set. The RWD baseline (Week 24) will be used for KM estimates, difference between treatment groups in KM% and HR at specific day as defined for Safety estimand as above.

Missing data

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

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 10 Brief Output Description for Adverse Events

Overall summary of AE; KM% table[A1] of categories: Any SAE, Any SAE with outcome death, Any AE, Any AE leading to permanent discontinuation of IP, Any intensity.
Any AE by SOC and PT; KM% table[A1] for each respective category: Any AE, Any SAE, Any SAE leading to discontinuation of IP[a], Any possibly related AE[b], Any possibly related SAE[a]. Dot plot of KM% and forest plot[A2] of comparisons of AE
Any AE per subgroup[c] level by SOC and PT[d]; KM% table[A1].
AEs with KM% > 1%[a]; KM% table[A1], including all PTs with a KM% higher than 1%, presented in descending KM% value of baxdrostat 2 mg/baxdrostat .
AE maximum intensity by SOC and PT[a]; 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; An AE listing will cover details for each individual AE. A SAE listing covering SAE and SAE with outcome death during screening period.
Narratives; Will be produced for all deaths, AEs leading to discontinuation of IMP, SAEs 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 with 95% CI, HR with 95% CI.
[A2] The KM% forest plot presents KM% per treatment group, difference in KM% between treatment groups with 95% CI, HR with 95% CI.
[a] Output only presented for 12-week DB period, 24-week period and 52-week period.
[b] Output only presented for 12-week DB period.
[c] Subgroups as defined in Section 4.6.
[d] Output only presented for 12-week DB period and 52-week period.
Possibly related, as assessed by investigator.
AE, adverse event; HR, hazard ratio; IMP, investigational medical product; KM, Kaplan-Meier; PT, preferred term; SAE, serious adverse event; SOC, System Organ Class.

4.6.3 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 and Chemistry. Safety lab (whole panel or creatinine, K^+ and Na^+) will be performed by central lab at all visits. Clinical laboratory safety tests are summarised in CSP Table 2, Table 4, and Table 8.

A treatment emergent abnormality is defined as: A switch in parameter from not-abnormal at baseline to abnormal at post-baseline assessments accordingly 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 <4.0 at baseline, ≥4 to <4.5 at baseline or ≥4.5 to ≤5 at baseline and
  - >5.0 post-baseline
  - >5.5 post-baseline
  - >6.0 post-baseline

  - >6.5 post-baseline
- Serum potassium (mmol/L): Subjects who have <4.0 at baseline, ≥4 to <4.5 at baseline or ≥4.5 to ≤5 at baseline and <3.5 post-baseline.
- Serum sodium (mmol/L); <125, <130 and <135.
- eGFR (mL/min/1.73m2):
  - ≥ 30 % decrease from baseline
  - ≥ 50% decrease from baseline
  - Participants who have ≥ 60 at baseline
    - < 45 post-baseline
    - < 30 post-baseline
  - Participants who have < 60 at baseline
    - < 45 post-baseline
    - < 30 post-baseline

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.

For the 12-week double blind treatment period, potassium measurements of > 5.5 mmo/L and > 6.0 mmol/L based on central lab will be further assessed as follows:

- For central lab potassium values of > 6.0 mmo/L, the confirmation status will be assessed based on local lab potassium from the same day. Specifically, if the local potassium value is >6 mmo/L, then central potassium value is classified as "Confirmed"; if the local potassium value is ≤ 6 mmo/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".
- For central lab potassium values of >5.5 to ≤ 6.0 mmo/L, the sustainment status will be assessed based on the subsequent central lab measurement taken within 7 days. Specifically, if the subsequent central potassium value was >5.5 mmo/L, then the central potassium is classified "Sustained"; if the subsequent central potassium value was ≤5.5 mmo/L, then central potassium is classified "Not Sustained"; if the subsequent central potassium value is not available, then central potassium is classified "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.

4.6.3.2 Analysis

For the distinct types of treatment emergent abnormalities and worsening from baseline respectively, the corresponding summaries/analyses as specified for AEs (in Section 4.6.2.2) will be provided based on the Safety Analysis Set, including both planned and unplanned assessments.

For the distinct types of laboratory parameters, the following summaries over time per timepoint will be provided up to 12, 24 and 52 weeks after baseline, based on the Safety Analysis Set; assessments as per analysis visit windows (see Section 3.3.2) will be used:

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

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 for the On-study analysis period and will include both planned and unplanned assessments.

For the distinct types of laboratory parameters measured in the DB RWD period (Week 24 to Week 32) summaries over time per timepoint will be provided up to 32 weeks from RWD baseline at week 24, based on the RWD analysis set.

The following categories will be used for the subgroups for the distinct types of treatment emergent abnormalities. Unless otherwise specified, all subgroup variables will be defined based on data collected at the time of the first randomisation (ie, the DB period randomisation).

- eGFR at baseline (mL/min/1.73m^2); <60, ≥60.
- Diabetes status at baseline; Yes, No.
- Age category (years); <65, ≥65 - <75, ≥75.

Missing data

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

- In analyses of occurrence of treatment emergent abnormalities, for subjects who have a non-missing post-baseline value and a missing baseline value for a parameter, the missing baseline value is assumed normal.
- Safety assessment values of the form of "< x" (ie, below the lower limit of quantification) or "> x" (ie, 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 Presentation

The following outputs will be presented as described in below table.

Table 11 Brief Output Description for Clinical Chemistry and Blood Sample

Box plots of observed values from baseline, by treatment group over time.
Box plots of change from baseline, by treatment group over time .
Treatment emergent abnormalities by predefined criteria; KM% table[A1]. Treatment emergent abnormalities by predefined criteria per subgroup[a] levels; 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 on-treatment ALT and AST versus maximum on-treatment bilirubin for the total of subjects from 1st randomisation to SFU, only on-study. Scatter plot of maximum post-baseline total bilirubin on maximum post-baseline value of ALT and AST, or the total of subjects from 1st randomisation to SFU only on-study.
Shift plot of observed maximum post-baseline value on observed baseline by treatment group, only on-study.
Shift plot of observed minimum post-baseline value on observed baseline by treatment group, only on-study.
Scatter plot of observed maximum post baseline serum potassium value on baseline eGFR by treatment group, only on-study.
Scatter plot of observed maximum post baseline serum potassium value on baseline hba1c by treatment group, only on-study.
Scatter plot of observed maximum post baseline serum potassium value on baseline age by treatment group, only on-study.
Spaghetti plot of individual subject level data over time for serum potassium above predefined levels.

Key subject information; Tables with key information for subjects with treatment emergent abnormalities or potential Hy's law. 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.
Listings; 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. Central lab potassium values of >5.5 to ≤ 6.0 mmol/L in the 12-week double blind treatment period including the subsequent central lab values within 7 days, to facilitate assessment of the sustainment status.

[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 with 95% CI, HR with 95% CI.
[a] Subgroups as defined in Section 4.6.3.2.
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 CSP Table 2, Table 4, and Table 8. Only baseline values are collected.

4.6.4.2 Analysis

N/A

4.6.4.3 Presentations

The individual subject urine sample data will be listed.

4.6.5 Vital Signs

4.6.5.1 Definitions and Derivations

Vital sign parameters that will be analysed and presented include mean seated SBP, mean seated DBP, seated pulse rate and BMI. 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 4.6.3.1.

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

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

4.6.5.2 Analysis

The analyses will follow the Clinical Laboratory, Blood Sample, analyses in Section 4.6.3.2.

4.6.5.3 Presentation

The following outputs will be presented as described in below table.

Table 12 Brief Output Description for Vital Signs

Box plots of observed values from baseline, by treatment group over time.
Box plots of change from baseline, by treatment group over time.
Treatment Emergent Abnormalities; 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 with 95% CI, HR with 95% CI.

4.6.6 Electrocardiogram

4.6.6.1 Definitions and Derivations

ECG parameters that will be analysed and presented include QRS interval, heart 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 4.6.3.1.

The QT interval will be corrected according to the Fridericia's formula.

The following definitions of abnormalities will be used for specific parameters:

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

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

4.6.6.2 Analysis

The analyses will follow the Clinical Laboratory, Blood Sample, analyses in Section 4.6.3.2.

4.6.6.3 Presentation

The following outputs will be presented as described in below table.

Table 13 Brief Output Description for Electrocardiogram

Box plots of observed values from baseline; by treatment group over time.
Box plots of change from baseline, by treatment group over time.
Bar chart of overall assessment of ECG, over time.
Treatment Emergent Abnormalities; KM% table[A1].
Table for QTcF value post-baseline (ms) > 450, > 480 and > 500 and QTcF increase by more than 30 or 60 ms, by treatment group over time
Shift plots of observed baseline versus post-baseline values by treatment group over time, only 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 with 95% CI, HR with 95% CI.

4.6.7 Other Safety Assessments

4.6.7.1 Definitions and Derivations

Other safety parameters include:

- AESI: hyperkalaemia that requires medical intervention, hyponatraemia that requires medical intervention, and hypotension events that requires medical intervention.
- Pre-specified safety categories: MACE (MACE and MACE-Plus) as confirmed by an independent EAC.

Any safety parameters can be, or contribute to, an AE. For these data, the process stated for AE will be followed (Section 4.6.2.1). In addition, the following additional evaluations will be performed for the above list of other safety parameters.

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 and Pre-specified safety categories mapping table.

Adverse event of special interest

For AESI, the definitions and derivations will follow those of AEs in Section 4.6.2.1.

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 PTs: Hyperkalaemia, Blood Potassium increase.

Contributing factors as reported by the investigators:

- Medication(s) other than study drug or baseline ACEi/ARB (for example, new or increased ACEi/ARB dose; existing, new, or increased dose of other medications contributing to hyperkalaemia risk),
- Hypovolemia without increase in creatinine,
- Diet/Supplements (for example salt substitute),
- Acute or subacute kidney injury,
- Acidosis,
- Pseudohyperkalaemia, phlebotomy technique, or sample haemolysis.

Concomitant medications initiated in relation to this AESI of particular interest:

- High-Ceiling Diuretics (C03C),
- Insulins and analogues for injection, fast-acting (A10AB),
- Drugs for treatment of hyperkalaemia and hyperphosphatemia (V03AE).

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 PTs: Hyponatraemia, Blood Sodium decrease.

Contributing factors as reported by the investigators:

- Medication(s) other than study drug (for example newly introduced medicine or change of dose),
- Hypovolemia,
- Hyperglycaemia,
- Hypervolemia (for example due to heart failure),
- Syndrome of inappropriate antidiuretic hormone (including idiopathic SIADH or SIADH due to for example due to surgery, pulmonary disease, medications),

- Polydipsia and/or decreased solute intake.

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 PTs Hypotension, Blood pressure decreased, Blood pressure systolic decreased.

Contributing factors as reported by the investigators:

- Medication(s) other than study drug (for example newly introduced medicine or change of dose),
- Hypovolemia,
- Heart failure or other cardiovascular contributor(s).

Additional definitions

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):

- 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

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.

Pre-specified safety categories

MACE and MACE-plus are classified using PT classification and as applicable, SMQ classification. The MedDRA version will be up-versioned to the latest version, or remain one version behind the latest version of MedDRA during the study until the time of CDL.

An EAC will be established in the study to provide an external independent assessment of blinded data to confirm the diagnosis and causality of MACE and MACE-Plus events, that occur from randomisation until the end of the SFU. Events for adjudication will be selected from all reported AEs in the study. The EAC will adjudicate the following:

- All death cases.
- Myocardial infarction, defined as any non-fatal case that is coded to a PT included in the SMQ "Myocardial infarction" (broad scope).
- Stroke, defined as any non-fatal case that is coded to a PT included in the SMQ "Central nervous system haemorrhages and cerebrovascular conditions" (narrow scope).
- Heart failure, defined as any non-fatal case that is coded to a PT included in the SMQ "Cardiac Failure" (broad scope) and classified by the investigator as serious.

Confirmed MACE

Confirmed MACE will be defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke confirmed by the EAC.

Confirmed MACE-plus

Confirmed MACE-plus will be defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke and hospitalisation for heart failure confirmed by the EAC.

4.6.7.2 Analysis

The analyses will follow the AE analyses in Section 4.6.2.2.

4.6.7.3 Presentation

Outputs presenting 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 14 Brief Output Description for Adverse Event of Special Interest

AESIs mapping table.
KM% table[A1] per AESI event[a] including contributing factors and the defined AE and SAE categories

Figure of KM% curve per AESI event by treatment.
Medications table for AESI Hyperkalaemia event that requires medical intervention[a].
Overall summary of AESI events[b].

A1 The KM% table presents number and percentage of subjects with at least one event per treatment group, KM% per treatment group with 95% CI, difference in KM% between treatment groups with 95% CI, HR with 95% CI.
[a] Output presented for 12-week DB period, 24-week period and 52-week period.
[b] Output presented for DB RWD period and 42-week period.

Table 15 Brief Output Description for Pre-Specified Safety Categories

Pre-specified safety categories mapping table.
Pre-specified safety categories key subject information.

5 INTERIM ANALYSIS

No interim analysis for efficacy or futility is planned for this study. However, two CDLs are planned to be conducted. The first CDL (primary data lock, PDL) and unblinding will occur after participants in both cohorts have completed the 12-week DB period and participants in Cohort 1 have completed the DB RWD period. The final analysis of efficacy, short-term (12 week) safety and initial analysis of long-term (24, 42 and 52 weeks) safety will be conducted based on the data from the first CDL. The data may support potential regulatory submissions. The second CDL will occur when all participants in Cohort 1 and Cohort 2 have completed the study, including the Safety Follow up Visit. The final analysis of long-term safety will be based on the data from the second CDL.

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