STATISTICAL ANALYSIS PLAN	
Study Code	D6970C00011
Edition Number	3.0
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A Randomised, Double-blind, Placebo-controlled Study to Evaluate Cortisol Reserve in Response to Adrenocorticotropic Hormone Stimulation Test Following Treatment with Baxdrostat for 8 Weeks in Participants with Uncontrolled Hypertension

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LIST OF ABBREVIATIONS

Abbreviation or Specialised Term	Definition
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
AESI	Adverse Events of Special Interest
AI	Adrenal Insufficiency
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
gCV	Geometric Coefficient of Variance
IPD	Important Protocol Deviation
K^+	Potassium
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
Na^+	Sodium
NC	Not Calculable
NQ	Non-Quantifiable
NR	Not Reportable
NS	No Sample
PK	Pharmacokinetics
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFL	Tables, Figures, Listings
ULN	Upper Limit of Normal
WHO	World Health Organization

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	7/15/2024	Initial approved SAP	N/A	N/A
1	8/28/2024	Amendment of "Version 2.0 of the CSP dated 05 June 2024" to "Version 3.0 of the CSP dated 26 August 2024".	Yes	CSP Amendment.
3.2, 4.1, 4.2, 4.5.	8/28/2024	Amendment of "Pharmacodynamic analysis set" to "Full analysis set", and revision of the corresponding definition (deletion of "Treatment classification is based on the study treatment that participants were randomly assigned to.").	Yes	Correction of analysis set (as per CSP Version 3.0).
4.1.6.1, Appendix B.	8/28/2024	List of WHO Drug codes for antihypertensive medications and Preferred Terms for concomitant diabetes, chronic kidney disease, and cardiovascular diseases added as Appendix B. Reference to Appendix B added to Section 4.1.6.1.	NA	To provide additional clarification.
Table 1, 4.2.1.2, 4.2.2.2.	8/28/2024	Amendment of cortisol cut-off amount from "≤ CCI µg/dL" to "< CCI µg/dL" for baseline, Week 8, and unscheduled visit for the repeat post- CCI minute ACTH stimulation test.	Yes	To CCI [redacted]
Table 1, 4.2.1.2, 4.2.2.2.	8/28/2024	Amendment of abnormal cortisol level definition to this effect that cortisol level at CCI minutes after ACTH stimulation that is < CCI µg/dL at baseline and Week 8 is considered abnormal, indicating impaired cortisol reserve. An abnormal cortisol level after ACTH stimulation test at baseline, results in the participant's discontinuation of the study intervention. At Week 8, in the rare incidence of an abnormal ACTH stimulated cortisol level, the participant is asked to remain on treatment and to undergo repeat ACTH stimulated cortisol measurements during an unscheduled visit which includes cortisol measurements CCI minutes	Yes	To CCI [redacted]

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
		after ACTH stimulation test (with CCI µg/dL cut-off) and CCI minutes after ACTH stimulation test (with CCI µg/dL cut-off). To be considered an abnormal repeat ACTH stimulated cortisol result, post-ACTH cortisol must be < CCI µg/dL at CCI minutes post-ACTH stimulation and < CCI µg/dL at CCI minutes post-ACTH stimulation. If only one of the two results is abnormal, the overall test is considered normal. The results from the repeat test supersede the original Week 8 results.		
Table 1, 4.2.1.4, 4.2.2.4.	8/28/2024	Addition of clarification stating that, if performed, the results of the repeat ACTH stimulation test at the unscheduled visit are used for the analysis; and that participants with abnormal cortisol levels at baseline are reported separately.	Yes	To provide clarification (as per CSP Version 3.0).
Table 1, 4.2.1.4, 4.2.2.4, 4.2.3.2.	8/28/2024	Update of the intercurrent event strategy. Addition of clarification that "CCI [redacted] The data collected after the other intercurrent events are included in the data analyses (Treatment Policy Strategy)".	Yes	To improve estimand strategy and provide clarification (as per CSP Version 3.0).
Table 1, 4.2.3.2	8/30/2024	Addition of clarification that the incidence of clinical AI events is evaluated in participants with normal stimulated cortisol at baseline (participants with abnormal stimulated cortisol at baseline are reported separately).	NA	To provide additional clarification and improve the evaluation of the incidence of clinical AI event.
4.5.6.1	8/28/2024	Vital sign categorisation as low, normal, or high added.	NA	To provide additional clarification.

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Appendix A	8/30/2024	Update of the analysis visit window for serum cortisol at Week 8 timepoint from “Day 2 to End of Treatment” to “Day 26 to End of Treatment”.	NA	To improve ACTH stimulation cortisol analysis, including participants with at least 4 weeks of treatment.
4.2.3	09/11/2024	Addition of a separate paragraph for AI events definitions, derivations and presentation.	NA	To provide additional clarification.
4.5.3.1	09/11/2024	Addition of clarification that central laboratory results are used for the analyses, local laboratory results are listed only.	NA	To provide additional clarification.
3.3.1	09/12/2024	Amendment of the baseline definition from “last non-missing value prior to or on the date of randomisation visit” to “last non-missing value prior to the administration of the first dose of study treatment”.	Yes	To be consistent with the CSP.
3.3.1	09/12/2024	Amendment of the on-treatment analysis period definition from “The on-treatment analysis period starts on the date of Randomisation Visit and ends on the earliest of the date of last dose of study treatment or the end of the on-study analysis period” to “The on-treatment analysis period starts on the date of first administration of study treatment and ends on the earliest of 10 days following the date of last dose of study treatment or the end of the on-study analysis period”.	No	To provide additional clarification and improve the evaluation of safety data, adding a window of 10 days after the last dose of study treatment.
4.1.1.1	09/12/2024	Amendment of the definitions and derivations for participant disposition and completion status, removing the following sentence: “Participants who die after randomisation without having withdrawn consent are considered having completed the study”.	NA	Correction to ensure consistency with the data recorded in the CRF.

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
4.1.1.2	09/12/2024	Addition of reason for study withdrawal to the disposition table.	NA	To provide additional information.
4.5.3.2, 4.5.6.2, 4.5.7.2	09/18/2024	Addition of clarification that separate summaries are presented for the on-treatment and on-study periods.	NA	To provide additional information.
4.5.2.2	09/27/2024	Addition of AE possibly related to study treatment and SAE possibly related to study treatment to the overall summary of AEs, and to the list of tables by SOC and PT.	No	To provide additional information.
Appendix B	10/29/2024	List updated including missing PTs.	NA	To provide additional information.
4.5.7.2	10/31/2024	Amendment of the list of ECG variables for which summary tables of absolute values and changes from baseline are provided, removing "ECG heart rhythm".	NA	Correction.

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D6970C00011 supporting the CSR. The CSP and the CRF are available for details of study conduct and data collection. This SAP is based on Version 3.0 of the CSP dated 26 August 2024. In the event of future amendments to the CSP, this SAP may be modified to account for changes relevant to the statistical analysis.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

There are no changes to the analyses currently planned in the CSP.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

No interim analyses are planned for this study.

The data cut-off for the final analysis is planned to occur when approximately 45 participants randomised have completed a treatment period of up to about 10 weeks plus a safety follow-up period of 2 weeks after last dose. Final analysis results are used to write the CSR after the final database lock.

The study remains blinded until the final database lock.

3.2 Analysis Populations

There are 4 analysis sets defined for this study as follows.

Screened set

The Screened set consists of all participants who sign the informed consent form.

Randomised/assigned to study intervention set

The Randomised set consists of all randomised participants. This population is used for the purpose of participant disposition.

Full analysis set

The Full analysis set consists of all randomised participants who received at least one dose of study treatment. This population is the primary population for all endpoints.

Pharmacokinetic analysis set

The PK analysis set consists of all randomised participants who had at least one evaluable pre-dose plasma concentration data for PK analysis and who received active treatment.

3.3 General Considerations

3.3.1 General Study Level Definitions

The below mentioned general principles are followed throughout the study:

- Summary tables are produced by treatment group (2 mg baxdrostat and placebo).
- Descriptive statistics are used for all variables, as appropriate. Continuous variables are summarised by the number of observations, mean, standard deviation, median, upper and lower quartiles where indicated, minimum, and maximum. Categorical variables are summarised by frequency counts and percentages for each category.
- If data are available for less than 3 participants, no summary statistics other than minimum, maximum and number of observations are presented.
- Unless otherwise stated, percentages are calculated out of the population total for the corresponding treatment group.
- For continuous data, the mean, median, upper and lower quartiles and standard deviation are rounded to 1 additional decimal place compared to the original data. Minimum and maximum are displayed with the same accuracy as the original data.
- Derived variables are rounded to 1 more decimal place compared to the least number of decimal places among the raw data used for calculation, provided the scale of the data is not changing.
- For categorical data, percentages are rounded to 1 decimal place with the exception of 100% which is presented as a whole number. No percentages are presented for zero counts.
- SAS® Version 9.4 (or higher) and other validated software (as appropriate) are used for the analyses.
- The baseline value for statistical analysis is the last non-missing value prior to the administration of the first dose of study treatment unless otherwise specified. The following are applied:
  - If there is only one visit eligible to assess participant status at baseline and it is on the date of first administration of study treatment without time recorded for the assessment, then it should be assumed it is a baseline assessment unless the CSP

suggests otherwise. This value should be a non-missing assessment to qualify as baseline.

  - If there are more than one assessment equally eligible to assess participant status at baseline (eg, several assessments on the date of first administration of study treatment and occurring either at the same time or with no time collected), the average of the non-missing values should be taken as the baseline value. For non-numeric assessment, the most normal assessment should be selected as baseline.

- In all summaries, change from baseline endpoints are calculated as the post-treatment value minus the value at baseline. The percentage change from baseline is calculated as (post-baseline value - baseline value)/baseline value × 100. If either a post-baseline value or the baseline value is missing, the corresponding timepoint change from baseline and percent change from baseline values are also set to missing.
- For the purposes of summarising safety data assessed at visits, separate summaries are presented for the on-treatment and on-study periods. The on-study analysis period starts on the date of first administration of study treatment and ends on the date of last clinical event assessment, unless the participant dies while under follow-up, then the date of death is taken as the end of the period. If a participant withdraws consent to continue in the study, then the on-study analysis period ends on this date at the latest. The on-treatment analysis period starts on the date of first administration of study treatment and ends on the earliest of 10 days following the date of last dose of study treatment or the end of the on-study analysis period.

3.3.2 Visit Window

For safety and AM/routine serum cortisol assessments, visit windows are defined for any presentations that summarise values by visit. The following conventions apply:

- Study day reference is date of first dose of study treatment as Day 1.
- The time windows are exhaustive so that data recorded at any timepoint (scheduled or unscheduled) has the potential to be summarised. Inclusion within the time window is based on the actual date and not the intended date of the visit.
- The windows for the visits following baseline are constructed in such a way that the upper limit of the interval falls halfway between the 2 visits (the lower limit of the first post-baseline visit is Day 2). If an even number of days exists between 2 consecutive visits, then the upper limit is taken as the midpoint value minus 1 day. Visit windows are reported in Appendix A.

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded is used (regardless of where it falls in an interval).
- Listings display all values contributing to a timepoint for a participant.
- For visit based summaries, if there is more than one value per participant within a time window then the closest value to the scheduled visit date is summarised, or the earlier, in the event the values are equidistant from the nominal visit date. The listings highlight the value for the participant that contributed to the summary table, wherever feasible. **Note:** in summaries of extreme values, all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date.
- For summaries at a participant level, all values are included, regardless of whether they appear in a corresponding visit-based summary, when deriving a participant level statistic such as a maximum.

3.3.3 Handling of Unscheduled Visits

For analyses not based on any particular study visit, all data are listed and/or analysed, including any repeated or unscheduled visits, unless otherwise specified.

For the analyses based on particular study visit, refer to Section 3.3.2 for the visit determination and scheduled/unscheduled visit handling.

3.3.4 Multiplicity/Multiple Comparisons

Not Applicable.

3.3.5 Handling of Protocol Deviations in Study Analysis

Only IPDs are listed and tabulated in the CSR. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

Important protocol deviations may include, but are not limited to the following:

- Written informed consent not obtained prior to mandatory study specific procedures, sampling and analyses.
- Participants randomised who received an alternative protocol-specified therapy to that which they were randomised.
- Those who met the criteria for discontinuation of protocol-specified therapy during the study, but remained on the protocol-specified therapy.

- Site procedure for unblinding the participant was not compliant with CSP.
- Received concomitant medication defined in the CSP as prohibited.

None of the deviations will lead to participants being excluded from any analysis populations described in this SAP. If a deviation is serious enough to have a potential impact on the primary analysis, sensitivity analyses may be performed. A list of all protocol deviations is reviewed and decisions regarding how to handle these deviations are documented by the study team physician, clinical pharmacology scientist and statistician at the time of the blind planned analysis review meeting prior to final database lock.

3.3.6 Missing Data

Missing safety data are generally not to be imputed. However, safety assessments of the form of "< x" (ie, below the lower limit of quantification) or "> x" (ie, above the upper limit of quantification) are imputed as "x" in the calculation of summary statistics but are displayed as "< x" or "> x" in the listings.

For missing start dates for AEs and medications/procedures, the following rules are applied:

- Missing day: Impute the 1st of the month unless the month is the same as month of the first dose of study treatment and the end date is on or after the first dose of study treatment or ongoing then impute first dose date.
- Missing day and month: Impute 1st January unless year is the same as first dose date and the end date is on or after the first dose of study treatment or ongoing then impute first dose date.
- Completely missing date: Impute first dose date unless the end date is prior to this in which case impute the date the participant was enrolled.

An imputed start date of an AE/medication/procedure must be prior to the end date of the AE/medication/procedure.

For missing stop dates of AEs or medications/procedures, the following rules are applied:

- Missing day: Impute the last day of the month unless month is the same as month of study discontinuation, then impute as study discontinuation date.
- Missing day and month: Impute 31st December unless year is the same as year of study discontinuation then impute study discontinuation date.

- Completely missing: If an AE/medication has a completely missing end date then it is treated as ongoing.

For missing stop dates of fatal AEs, the end date is imputed with the date of death.

If a participant is known to have died where only a partial death date is available, then the date of death is imputed according to the rules for imputing AE start dates unless this date is before the last date the participant is known to be alive then the date of death is imputed as the date the participant was last known to be alive + 1.

If death has been recorded but the date is entirely missing, then date of death is imputed as the date the participant was last known to be alive + 1.

The imputation of dates for AEs and medications are used to determine if an AE is treatment emergent and whether a medication is concomitant. Flags are retained in the analysis datasets indicating where any programmatic imputation is applied, and in such cases, no durations are calculated.

Other rules for handling missing data are described under the derivation rules for that particular variable.

4 STATISTICAL ANALYSIS

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

4.1 Study Population

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

All summary tables are based on the Full analysis set with the exception of the disposition and analysis set tables.

4.1.1 Participant Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Participants enrolled/screened is defined as informed consent received. Participants who fail to meet the eligibility criteria are termed as ‘screen failures’. Participants completed treatment are defined as randomised participants who did not permanently discontinue

study treatment for other reasons than death. Participants completed study are defined as randomised participants who did not withdraw from the study, and are not lost to follow-up.

4.1.1.2 Presentation

Participant disposition including screen failures and reason for screen failure is listed and summarised based on all participants screened by treatment group and for all participants combined as defined by the current relevant TFL standards. The number and percentage of participants for the following are summarised if applicable:

- Participants screened.
- Screen failures.
- Reason for screen failures.
- Participants randomised.
- Participants randomised, but who were not treated.
- Reason for not being treated.
- Participants who started treatment.
- Participants who completed treatment.
- Participants who discontinued treatment.
- Reason for treatment discontinuation.
- Participants who completed study.
- Participants who withdrew from study.
- Reason for study withdrawal.

The number of participants by country and site is also summarised in a separate table.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

For the definitions of each analysis set, refer to Section 3.2.

4.1.2.2 Presentation

The analysis sets are summarised by treatment group and for all participants combined. Any exclusions from analysis sets are listed.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Protocol deviations are collected, reviewed, and reconciled throughout the study. Important protocol deviations are identified from the complete set of protocol deviations.

A set of pre-determined IPDs are listed in the protocol deviation assessment plan. The protocol deviation assessment plan also indicates which IPDs are identified by programmatic checks.

The examples of the categories are shown in Section 3.3.5.

4.1.3.2 Presentation

A summary table is produced by treatment group and for all participants combined, showing the number and percentage of participants with any IPD and by category of IPD, which includes the individual IPDs as detailed in the protocol deviations plan.

The individual participant data for IPDs is also listed.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Age is grouped accordingly in the following categories: < 65 and ≥ 65 years. Each race category counts participants who selected only that category.

4.1.4.2 Presentation

Demographics are listed and summarised by treatment group and for all participants combined as defined by the current relevant TFL standards. The following are summarised: age, age group, sex, race, and ethnicity.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

The BMI is be calculated as

$$\text{BMI } (kg/m^2) = \text{Weight } (kg)/\{\text{Height } (m)\}^2$$

Body mass index is categorised into BMI groups of < 18.5, ≥ 18.5 - < 25.0, ≥ 25.0 - < 30.0 and ≥ 30.0.

4.1.5.2 Presentation

Baseline characteristics are listed and summarised by treatment group and for all participants combined as defined by the current relevant TFL standards. The following are summarised: height, weight, BMI, and BMI group.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

The number of antihypertensive medications is derived from the concomitant medication form using the latest WHO Drug Dictionary version. Concomitant diabetes, chronic kidney

disease and cardiovascular diseases are derived from the medical history and concomitant disease form using the latest MedDRA version. Corresponding terms/codes are reported in Appendix B.

4.1.6.2 Presentation

The following disease characteristics at screening are summarised: systolic and diastolic blood pressure, number of antihypertensive medications, concomitant diabetes, chronic kidney disease and cardiovascular diseases.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history and relevant surgical history are coded using the latest MedDRA version.

Any medical history which is ongoing at time of informed consent is considered an ongoing condition, otherwise it is considered past medical history.

4.1.7.2 Presentation

Medical history and concomitant disease, and surgical history are summarised by treatment group and for all participants combined as defined by the current relevant TFL standards.

Summaries on participants' medical and surgical history by SOC and PT are produced.

A listing of medical history is also provided.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

All therapies (drug and non-drug, including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements), that are used from the time of informed consent up until the Safety Follow-Up Visit are recorded in the eCRF.

Medications are coded using the latest WHO Drug Dictionary version. The version used is indicated in the data summaries and listings.

For the purpose of inclusion in prior and/or concomitant medication or therapy summaries, incomplete medication start and stop dates are imputed as detailed in Section 3.3.6.

Prior and concomitant medications are defined based on imputed start and stop dates as follows:

- Prior medications are those taken prior to study treatment with a stop date prior to the first dose of study treatment.

- Concomitant medications are those with a stop date on or after the first dose date of study treatment, and must have started prior to or during treatment so there is at least one day in common with the study treatment.

4.1.8.2 Presentation

The number and percentage of participants who took prior and concomitant medications are summarised by ATC code (level 4) and the generic name/term coded by WHO Drug Dictionary.

A listing of prior and concomitant medications is also provided.

4.1.9 Study Treatment Compliance

4.1.9.1 Definitions and Derivations

Study treatment compliance is calculated as follows:

$$\text{Study treatment compliance (\%)} = \frac{\text{Number of doses taken during treatment period}}{\text{Number of doses planned during treatment period}} \times 100$$

The planned dose is one tablet per day.

Study treatment compliance is grouped accordingly to the following categories: $< 80\%$ and $\geq 80\%$.

4.1.9.2 Presentation

Study treatment compliance is summarised by treatment group and for all participants combined as defined by the current relevant TFL standards.

Compliance is summarised by descriptive statistics and is presented by the number and percentage of participants whose compliance falls under predefined categories of compliance.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, and other endpoints including sensitivity and supportive analyses.

An overview of the endpoint analyses is provided in Table 1.

Table 1 Overview of the Endpoint Analyses

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To characterise the total serum cortisol before and after ACTH stimulation test at baseline and Week 8.					
Primary	Individual serum cortisol level before and after ACTH stimulation test at baseline and Week 8. If applicable, the unscheduled visit results are included.	Full analysis set, excluding participants with abnormal ACTH stimulated cortisol (< CCI µg/dL at CCI minutes) at baseline	Included in the analysis regardless of study treatment discontinuation, use of antihypertensive rescue therapy and other intercurrent events that do not interfere with cortisol production (Treatment Policy Strategy); CCI [redacted]	Descriptive statistics	4.2.1
Objective 2: To evaluate the total serum cortisol response after ACTH stimulation test at Week 8.					
Secondary	Incidence of abnormal stimulated cortisol at Week 8 in the baxdrostat and placebo groups. In the event that the routine stimulated cortisol at Week 8 is abnormal (< CCI µg/dL at CCI minutes), an abnormal result for repeat	Same as for primary analysis	Same as for primary analysis	Descriptive statistics	4.2.2

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
	stimulated cortisol is defined as <CCI µg/dL at CCI minutes AND <CCI µg/dL at CCI minutes.				
Objective 3: To evaluate the CCI					
Exploratory	CCI	Same as for primary analysis	Same as for primary analysis	Descriptive statistics	4.2.3
Objective 4: To assess the pharmacokinetics of baxdrostat.					
Exploratory	Plasma concentrations of baxdrostat	PK analysis set	NA	Descriptive statistics	4.3
Objective 5: To explore how CCI					
The results of these CCI will be reported outside the CSR in a separate study summary.					
Objective 6: To assess the safety and tolerability of baxdrostat as compared to placebo.					
Safety	AEs/SAEs, vital signs, clinical laboratory findings, ECGs, and exposure.	Full analysis set	NA	Descriptive statistics	4.5

4.2.1 Primary Endpoint - Individual Cortisol Level Before and After ACTH Stimulation Test at Baseline and Week 8

4.2.1.1 Definition

The primary endpoint is the cortisol level before and after ACTH stimulation test at baseline and Week 8.

4.2.1.2 Derivations

An ACTH stimulation test using 250 µg ACTH is performed at baseline and Week 8 (End of Treatment), with serum cortisol level measured before and CCI minutes after ACTH stimulation test. In the event of abnormal stimulate cortisol results at Week 8 (ie, <CCI µg/dL at CCI minutes), cortisol response to ACTH stimulation testing is assessed

CCI minutes and CCI minutes after ACTH stimulation at an unscheduled visit. An abnormal result is defined as abnormal repeat stimulated cortisol (< CCI µg/dL at CCI minutes AND < CCI µg/dL at CCI minutes) obtained in the event that the routine stimulated cortisol at Week 8 is abnormal (< CCI µg/dL at CCI minutes). If only one of the two repeat results is abnormal, the overall test is considered normal. The results from the repeat test supersede the original Week 8 results.

4.2.1.3 Handling of Dropouts and Missing Data

No imputation is performed for missing data.

4.2.1.4 Primary Analysis of Primary Endpoint

Cortisol values prior to ACTH stimulation testing and after CCI minutes, both at baseline and at Week 8, are listed for the Full analysis set population by treatment group. Cortisol response to ACTH stimulation test is also described on individual level via line plot of serum total cortisol values prior to ACTH stimulation testing and after CCI minutes, both at baseline and at Week 8, for each treatment group. If performed, the results of the repeat ACTH stimulation test at the unscheduled visit are also included in the analysis.

Participants with abnormal cortisol levels at baseline, ie cortisol level at CCI minutes after ACTH stimulation testing < CCI µg/dL, are not considered in the primary analysis and are listed and plotted separately.

CCI [redacted] The data collected after the other intercurrent events are included in the data analyses (Treatment Policy Strategy).

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

No sensitivity analyses of cortisol response to ACTH stimulation test are performed.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

No supplementary analyses of cortisol response to ACTH stimulation test are performed.

4.2.1.7 Subgroup Analyses of the Primary Endpoint

No subgroup analyses of cortisol response to ACTH stimulation test are performed.

4.2.2 Secondary Endpoint - Incidence of Abnormal Stimulated Cortisol at Week 8

4.2.2.1 Definition

The secondary endpoint is the incidence of abnormal stimulated cortisol at Week 8 in the baxdrostat and placebo groups.

4.2.2.2 Derivations

Refer to Section 4.2.1.2.

4.2.2.3 Handling of Dropouts and Missing Data

Refer to Section 4.2.1.3.

4.2.2.4 Primary Analysis of Secondary Endpoint

The incidence of abnormal stimulated cortisol (ie, total serum cortisol below the pre-specified threshold after CCI minutes) at Week 8 is summarised for the Full analysis set population, excluding participants with abnormal stimulated cortisol at baseline, by treatment group. Participants with abnormal stimulated cortisol at baseline (< CCI µg/dL at CCI minutes) are reported separately. If performed, the results of the repeat ACTH stimulation test at the unscheduled visit are used for the analysis.

CCI [redacted] The data collected after the other intercurrent events are included in the data analyses (Treatment Policy Strategy).

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

No sensitivity analyses of the incidence of abnormal stimulated cortisol at Week 8 are performed.

4.2.2.6 Supplementary Analyses of the Secondary Endpoint

No supplementary analyses of the incidence of abnormal stimulated cortisol at Week 8 are performed.

4.2.2.7 Subgroup Analyses of the Secondary Endpoint

No subgroup analyses of the incidence of abnormal stimulated cortisol at Week 8 are performed.

4.2.3 CCI [redacted]

4.2.3.1 Definitions and Derivations

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

4.2.3.2 Presentation

CCI [redacted] in participants with normal stimulated cortisol at baseline are summarised by SOC and PT, where sorting is by internationally agreed order for SOC, and alphabetically for PT within SOC. Participants with abnormal stimulated cortisol at baseline (< CCI [redacted] µg/dL at CCI [redacted] minutes) are reported separately.

CCI [redacted] The data collected after the other intercurrent events are included in the data analyses (Treatment Policy Strategy).

Separate summaries are presented for the on-treatment and on-study periods, as defined in Section 3.3.1.

4.3 Pharmacokinetics

Plasma concentration descriptive statistics

Evaluating the PK of baxdrostat is an exploratory objective. Pharmacokinetic blood samples are collected for measurement of plasma concentrations pre-dose at Visit 5. For participants who are discontinued from study treatment due to hyperkalaemia, a PK sample should be collected at the end of treatment visit.

Summary statistics (n, n < LLOQ, arithmetic mean, standard deviation, geometric mean, gCV%, minimum, median and maximum) are produced for plasma concentrations of baxdrostat at the scheduled PK sampling timepoints. A listing on individual level is also provided.

Participants with protocol deviations seriously impacting PK results are excluded from the summary tables.

If data permit, additional PK or PK/pharmacodynamic analyses may be performed. Any such analyses will be described in a separate data analysis plan and the results will be provided in a separate report.

Handling of Non-Quantifiable Concentrations

Individual concentrations below the LLOQ of the bioanalytical assay are reported as NQ in the listings with the LLOQ defined in the footnotes of the relevant tables and listings. Individual plasma concentrations that are Not Reportable are reported as NR and those that are missing are reported as NS in the listings. Plasma concentrations that are NQ, NR or NS are handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS are excluded from the summary tables.
- At a timepoint where less than or equal to 50% of the concentration values are NQ, all NQ values are set to the LLOQ, and all descriptive statistics are calculated accordingly.
- At a timepoint where more than 50% (but not all) of the values are NQ, the geometric mean and gCV% are set to NC. The maximum value is reported from the individual data, and the minimum and median are set to NQ.
- If all concentrations are NQ at a timepoint, no descriptive statistics are calculated for that timepoint. The geometric mean, minimum, median, and maximum are reported as NQ and the gCV% as NC.
- The number of values below LLOQ (n < LLOQ) are reported for each timepoint together with the total number of collected values (n).

Three observations > LLOQ are required as a minimum for a plasma concentration to be summarised. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

Precision and Rounding Rules for Pharmacokinetic Data

Pharmacokinetic concentration data listings present to the same number of significant figures as the data received from the bioanalytical laboratory (usually but not always to 3 significant figures) and against the same units as received.

Pharmacokinetic concentration descriptive statistics present 4 significant figures with the exception of the minimum and maximum which present 3 significant figures and n and n < LLOQ which present as integers.

4.4 Immunogenicity

Not Applicable.

4.5 Safety Analyses

The domain safety covers exposure, AEs, clinical laboratory, vital signs, and ECG.

Tables and listings are provided for the Full analysis set.

4.5.1 Exposure

4.5.1.1 Definitions and Derivations

In the assessment of the treatment exposure, interruptions are considered.

When there is no interruption, treatment exposure duration (in days) is calculated as follows:

Treatment exposure duration (days) = min (last dose date, date of death, date of data cut-off) – first dose date + 1.

When there is any interruption, treatment exposure duration is calculated as follows:

For each interruption, the duration of interruption is calculated as follows:

(first dose date after the interruption – first day of interruption date).

The treatment exposure duration (in days) is calculated as follows:

Treatment exposure duration (days) = min (last dose date, date of death, date of data cut-off) – first dose date + 1 – (sum of interruptions).

4.5.1.2 Presentation

The treatment exposure duration (in days) is listed and summarised by treatment group.

4.5.2 Adverse Events

4.5.2.1 Definitions and Derivations

The latest MedDRA version is used to code AEs.

Missing start and stop dates for AEs are to be handled using the rules described in Section 3.3.6.

Adverse events of special interest

For this study, AESIs include the following: hyperkalaemia, hyponatraemia and hypotension events [redacted]. These events consist of high K^+ (> [redacted] mmol/L) in blood, abnormally low Na^+ concentration (< [redacted] mmol/L) in blood and abnormally low blood pressure (< [redacted] mmHg), respectively, that requires medical intervention. These AESIs are confirmed by a clinician. During the study, additional AESIs may be identified by AstraZeneca.

4.5.2.2 Presentation

All AEs are summarised descriptively by count (n) and percentage (%) for each treatment group.

An overall summary of the event counts and the number and percentage of participants in each category below are presented. Each AE category is separately summarised by SOC and PT, where sorting is by internationally agreed order for SOC, and alphabetically for PT within SOC:

- Any AE.
- Any SAE.
- Any SAE with outcome of death.
- Any AE leading to discontinuation of study treatment.
- Any AE possibly related to study treatment.
- Any SAE possibly related to study treatment.

Separate tables for AESIs, AEs taking into consideration maximum intensity, and by decreasing frequency on PT level are provided.

Additionally, the most common AEs, which are those AEs that occur in at least 5% (where no rounding is applied, ie an AE with frequency 4.9% does not appear if the cut-off is 5%) of participants in any treatment group, are summarised by PT, by decreasing frequency

based on the total number of AEs across treatment groups. This cut-off may be modified after review of the data.

Key participant information is provided in 3 separate tables for all SAEs, SAEs with an outcome of death and all AEs leading to treatment discontinuation.

Separate summaries are presented for the on-treatment and on-study periods, as defined in Section 3.3.1.

All AEs are listed, and the time to onset of the AE from date of first dose is presented in the listing.

4.5.3 Clinical Laboratory, Blood Sample

4.5.3.1 Definitions and Derivations

Blood samples for determination of clinical chemistry and haematology are collected as described in the SoA and in Table 7 of the CSP.

Central laboratory results are used for the analyses. Local laboratory results are listed only.

The rules described in Section 3.3 of this document considering definition of baseline, visit windows and how to handle multiple records and missing data are followed.

Change from baseline in haematology and clinical chemistry variables are calculated for each post-dose visit.

Absolute values are compared to the reference range and classified as low (below range), normal (within range or limits of range) and high (above range).

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/local lab and defined as > ULN or < LLN, where applicable.

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

- Serum potassium: > CCI mmol/L.
- Serum potassium: > CCI mmol/L.
- eGFR: ≥ CCI
- eGFR: > CCI

In addition, the highest post-baseline serum potassium (mmol/L), categorised by ≤ 5.0, > 5.0 - ≤ 5.5, > 5.5 - < 6, ≥ 6 - < 6.5, ≥ 6.5, and the lowest post-baseline serum sodium (mmol/L), categorised by < 125, ≥ 125 - < 130, ≥ 130 - < 135, are cross-tabulated by baseline eGFR (mL/min/1.73m^2) ≥ 45 - ≤ 60, > 60, by treatment group.

4.5.3.2 Presentations

Laboratory parameters are presented for each treatment group using summary statistics.

For all continuous laboratory assessments, absolute value and change from baseline are summarised using descriptive statistics at each scheduled assessment time.

Treatment emergent abnormalities by predefined criteria are presented.

Shift tables from baseline to maximum and minimum post-randomisation value are provided. Percentages are to be based on the number of participants with a baseline and a post-randomisation value.

Key participant information is presented for participants with treatment-emergent changes in laboratory parameters outside predetermined criteria.

If potential cases of Hy's Law are identified during the course of the study, liver biochemistry test results over time for participants with elevated ALT (ie, ≥ 3 x ULN) or AST (ie, ≥ 3 x ULN), and elevated total bilirubin (ie, ≥ 2 x ULN) and in which the elevation in transaminases precede or coincide with (that is, on the same day as) the elevation in total bilirubin are summarised and listed.

Separate summaries are presented for the on-treatment and on-study periods, as defined in Section 3.3.1.

All laboratory data are listed. Flags are applied to values falling outside reference ranges.

4.5.4 Clinical Laboratory, Urinalysis

4.5.4.1 Definitions and Derivations

Urine samples for determination of urinalysis are collected as described in the SoA of the CSP.

4.5.4.2 Presentations

This data is listed only, no summary tables are produced.

4.5.5 Other Laboratory Evaluations

4.5.5.1 Definitions and Derivations

Not Applicable.

4.5.5.2 Presentations

Not Applicable.

4.5.6 Vital Signs

4.5.6.1 Definitions and Derivations

Vital signs are assessed at timepoints as specified in the SoA of the CSP. The following vital signs are measured: systolic and diastolic blood pressure, pulse rate and body weight.

The rules described in Section 3.3 of this document considering definition of baseline, visit windows and how to handle multiple records are followed. Additionally, for multiple results taken at the same timepoint the multiple results are averaged before analysis.

Treatment emergent vital sign abnormalities are categorised as follows:

- Systolic blood pressure: < [redacted] mmHg.
- Diastolic blood pressure: < [redacted] mmHg.
- Pulse rate: < [redacted] bpm, > [redacted] bpm.

Vital signs are categorised as low, normal, or high as follows:

- Diastolic blood pressure: low < [redacted] mmHg, normal ≥ [redacted] mmHg - < [redacted] mmHg, high ≥ [redacted] mmHg.
- Systolic blood pressure: low < [redacted] mmHg, normal ≥ [redacted] mmHg - < [redacted] mmHg, high ≥ [redacted] mmHg.

4.5.6.2 Presentations

Vital sign parameters are presented for each treatment group using summary statistics.

Absolute values and change from baseline for diastolic and systolic blood pressure, pulse rate and weight are summarised over time.

In addition, the number and percentage of participants with treatment emergent vital sign abnormalities falling into the categories defined in Section 4.5.6.1 are summarised. Key participant information is also presented for participants with treatment emergent vital sign abnormalities by predetermined criteria.

Shift tables from baseline to maximum and minimum post-randomisation value are provided. Percentages are to be based on the number of participants with a baseline and a post-randomisation value.

Separate summaries are presented for the on-treatment and on-study periods, as defined in Section 3.3.1.

All vital sign data are listed.

4.5.7 Electrocardiogram

4.5.7.1 Definitions and Derivations

Resting 12-lead ECGs are recorded at timepoints specified in the SoA of the CSP.

The following ECG variables are collected: ECG heart rate, ECG heart rhythm, PR duration, QRS duration, QT interval, QTcF interval, RR duration and overall ECG evaluation.

The rules described in Section 3.3 of this document considering definition of baseline, visit windows and how to handle multiple records are followed.

The overall evaluation of an ECG is either “normal” or “abnormal” with abnormalities categorised as either “clinically significant” or “not clinically significant”.

The QT interval corrected for heart rate using Fridericia’s correction (QTcF) is calculated as follows (where QT and RR are in seconds):

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

4.5.7.2 Presentations

ECG parameters are presented for each treatment group using summary statistics.

A summary table of absolute values and change from baseline for ECG heart rate, PR duration, QRS duration, QT duration, QTcF duration and RR duration are presented over time. A shift table of baseline overall assessment versus each post-screening timepoint is provided where percentages are based on the number of participants with a baseline and post-screening assessment.

Separate summaries are presented for the on-treatment and on-study periods, as defined in Section 3.3.1.

All ECG data are listed.

4.5.8 Other Safety Assessments

4.5.8.1 Definitions and Derivations

Not Applicable.

4.5.8.2 Presentations

Not Applicable.

5 INTERIM ANALYSIS

No interim analyses are planned for this study due to the short duration of the study.

6 REFERENCES

Not Applicable.

7 APPENDIX

Appendix A Visit Windows

Visit windows for safety and AM/routine serum cortisol assessments are reported in Table A1.

Table A1 Visit Windows for Safety Assessments

		Window (days)			
Timepoint	**Planned study day**	**Creatinine, eGFR, K^+, Na^+**	**Vital signs, haematology and clinical chemistry (excluding creatinine, eGFR, K^+, Na^+)**	**ECG**	**AM (for Screening)/Routine Serum cortisol**
Screening	(− 28 to – 1)	NA	NA	NA	− 28 days to – 1 day before Day 1
Baseline	1	See Section 3.3.1	See Section 3.3.1	See Section 3.3.1	See Section 3.3.1
Week 1	8	2 to 12	NA	NA	NA
Week 2	16	13 to 22	NA	NA	NA
Week 4	29	23 to 43	2 to 43	NA	NA
Week 8/End of Treatment	57	44 to End of Treatment	44 to End of Treatment	2 to End of Treatment	26 [a] to End of Treatment
Safety Follow-Up	14 days from last dose	> End of Treatment [b] to last visit during the Safety Follow-Up	> End of Treatment [b] to last visit during the Safety Follow-Up	> End of Treatment [b] to last visit during the Safety Follow-Up	NA

[a] Lower limit of visit window for serum cortisol at Week 8 timepoint is set to Week 4 (ie, Day 29 ± 3).

[b] If the End of Treatment Visit is conducted > 10 days after the last administered dose, all assessments required at End of Treatment and Safety Follow-Up Visits are to be conducted within the same visit.

Appendix B WHO Drug Codes for Antihypertensive Medications and Preferred Term for Concomitant Diabetes, Chronic Kidney Disease and Cardiovascular Diseases

WHO Drug codes for antihypertensive medications:

- C02AB
- C02AC
- C02CA
- C02DB
- C02DD
- C02LB
- C02LC
- C02LE
- C03AA
- C03BA
- C03CA
- C07AA
- C07AB
- C07AG
- C07BA
- C07BB
- C07BG
- C07CA
- C07CB
- C07CG
- C07DA
- C07DB
- C07EA
- C07EB
- C07FB
- C07FX
- C08CA

- C08DA
- C08DB
- C08GA
- C09AA
- C09BA
- C09BB
- C09BX
- C09CA
- C09DA
- C09DB
- C09DX

Preferred Terms for concomitant diabetes:

- Diabetes mellitus inadequate control
- Diabetes mellitus
- Type 1 diabetes mellitus
- Diabetes mellitus management
- Type 2 diabetes mellitus
- Diabetic neuropathy
- Diabetic retinopathy
- Diabetic eye disease
- Diabetic complication
- Diabetic vascular disorder
- Diabetic nephropathy
- Insulin resistant diabetes
- Insulin-requiring type 2 diabetes mellitus
- Latent autoimmune diabetes in adults
- Monogenic diabetes
- Type 3 diabetes mellitus
- Diabetic microangiopathy

Preferred Terms for concomitant chronic kidney disease:

- Benign renal neoplasm
- Cardiorenal syndrome
- Chronic kidney disease
- Congenital renal disorder
- Diabetic complication renal
- Diabetic nephropathy
- Oedema due to renal disease
- Postrenal failure
- Prerenal failure
- Renal amyloidosis
- Renal aplasia
- Renal arteriosclerosis
- Renal artery arteriosclerosis
- Renal disorder
- Renal dysplasia
- Renal failure
- Renal glycosuria
- Renal hypertrophy
- Renal hypoplasia
- Renal impairment
- Renal ischaemia
- Renal milk of calcium cyst
- Renal salt-wasting syndrome
- Renal tubular disorder
- Renal vasculitis
- Renal vessel disorder
- Renal-limited thrombotic microangiopathy

Preferred Terms for concomitant cardiovascular diseases:

- Accessory cardiac pathway
- Acquired cardiac septal defect
- Arrhythmia
- Athletic heart syndrome
- Atrial fibrillation
- Atrial tachycardia
- Benign cardiac neoplasm
- Benign pericardium neoplasm
- Bradycardia
- Bundle branch block right
- Cardiac amyloidosis
- Cardiac aneurysm
- Cardiac autonomic neuropathy
- Cardiac contractility decreased
- Cardiac disorder
- Cardiac dysfunction
- Cardiac failure
- Cardiac failure chronic
- Cardiac failure congestive
- Cardiac failure high output
- Cardiac fibrillation
- Cardiac fibroma
- Cardiac flutter
- Cardiac function disturbance postoperative
- Cardiac haemangioma benign
- Cardiac hypertrophy
- Cardiac myxoma
- Cardiac neoplasm unspecified
- Cardiac neurofibroma
- Cardiac perfusion defect

- Cardiac polyp
- Cardiac pseudoaneurysm
- Cardiac sarcoidosis
- Cardiac septal defect
- Cardiac septal defect residual shunt
- Cardiac valve disease
- Cardiac valve fibroelastoma
- Cardiac valve replacement complication
- Cardiac valve sclerosis
- Cardiac valve thickening
- Cardiac ventricular disorder
- Cardiac ventricular scarring
- Congenital heart valve disorder
- Congenital supraventricular tachycardia
- Coronary artery disease
- Dextrocardia
- Endocardial disease
- Heart alternation
- Heart block congenital
- Heart disease congenital
- Heart failure with midrange ejection fraction
- Heart failure with preserved ejection fraction
- Heart failure with reduced ejection fraction
- Heart valve calcification
- Heart valve incompetence
- Heart valve stenosis
- Hypertensive heart disease
- Inherited cardiac conduction disorder
- Intracardiac mass
- Junctional ectopic tachycardia
- Kyphoscoliotic heart disease

- Laevocardia
- Myocardial bridging
- Myocardial fibrosis
- Myocardial hypoperfusion
- Myocardial infarction
- Myocardial ischaemia
- Myocardial necrosis
- Myocardial stunning
- Oedema due to cardiac disease
- Pericardial disease
- Pericardial fibrosis
- Peripheral arterial occlusive disease
- Prosthetic cardiac valve regurgitation
- Rebound tachycardia
- Rheumatic heart disease
- Silent myocardial infarction
- Sinus bradycardia
- Sinus tachycardia
- Subendocardial ischaemia
- Supraventricular bradycardia
- Supraventricular extrasystoles
- Supraventricular tachycardia
- Tachycardia
- Tachycardia paroxysmal
- Cardiovascular disorder
- Cardiovascular insufficiency
- Cardiovascular somatic symptom disorder
- Cardiovascular symptom
- Congenital cardiovascular anomaly
- Coronary vascular graft occlusion
- Coronary vascular graft stenosis

- Diabetic complication cardiovascular
- Microvascular coronary artery disease
- Cerebrovascular arteriovenous malformation
- Cerebrovascular disorder
- Cerebrovascular insufficiency
- Cerebrovascular stenosis
- Congenital cerebrovascular anomaly
- Hypertensive cerebrovascular disease
- Vascular calcification
- Vascular cognitive impairment
- Vascular dementia
- Vascular encephalopathy
- Vascular fragility
- Vascular headache
- Vascular stenosis
- Vascular wall hypertrophy

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