Clinical Study Protocol	
Study Intervention	Baxdrostat
Study Code	D6970C00011
Version	3.0
Date	26 August 2024
IND Number	146112

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

Sponsor Name: AstraZeneca AB

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Regulatory Agency Identifier Number: IND 146112

This protocol has been subject to a peer review according to AstraZeneca standard procedures. The protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Standard - Bioethics and in compliance with prevailing laws and regulations.

Version Scope: Global

Brief Title: A Study to Evaluate Cortisol Reserve in Response to Adrenocorticotropic Hormone Stimulation Test Following Baxdrostat Treatment Compared to Placebo in Participants with Uncontrolled Hypertension

Study Phase: Phase II

Study Clinical Lead Name and Contact Information will be provided separately.

Study Clinical Lead is responsible for the clinical integrity of the study (for example, the study physician or scientist).

SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Clinical Study Protocol Version 3.0 (Amendment 2.0)	26-August-2024
Clinical Study Protocol Version 2.0 (Amendment 1.0)	05-June-2024
Clinical Study Protocol Version 1.0	05-March-2024

Clinical Study Protocol (CSP) Version 3.0, 26 August 2024

Overall Rationale for the Modification:

The primary rationale for this amendment is CCI [redacted] and to correct and/or clarify details related to some procedures, statistical analysis details, and tests as listed below. Additionally, some minor editorial and typographical corrections have been made throughout this protocol which have not been listed in the summary of change.

Summary of Changes:

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis; Section 1.3, Schedule of Activities; Section 4.1, Overall Design.	Addition of Table 3 "Schedule of Cortisol Measurements" and providing description of different cortisol measurements during the study throughout.	To provide additional clarification.
Section 1.3, Schedule of Activities.	Addition of clarification to Table 1 footnote "b" to read "In rare incidence that participant has abnormal ACTH stimulated cortisol level, the participant will be asked to remain on treatment and to undergo repeat ACTH stimulated cortisol measurements during an unscheduled visit. See Footnote "g". If applicable, the repeat tests shall be rescheduled as soon as possible to keep the duration of the treatment within 10 weeks. The IMP will be discontinued immediately following the completion of the repeated ACTH stimulation test".	To provide additional clarification.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities.	Amendment to Table 1 footnote "g" to read "If the cortisol level is abnormal at EoT (Visit 6, Week 8), the test will be repeated during an unscheduled visit (prior to ACTH stimulation test, CCI minutes after ACTH stimulation test, and CCI minutes after ACTH stimulation test) for confirmation. See Table 3 for more details."	To clarify and align the language around the unscheduled visit throughout.
Section 1.3, Schedule of Activities.	Addition for clarification to Table 1 footnote "h" that "Participants must have a morning cortisol (measured at 08:00 AM ± 2 hours) ≥ CCI µg/dL, determined as per central laboratory to be eligible for the study".	To provide additional clarification.
Section 1.1, Synopsis; Section 4.1, Overall Design.	Addition of clarification note "10 weeks is not the targeted duration of the treatment period, but only intends to provide flexibility in case of unforeseen event. The last date of treatment can be later than the EoT Visit date." Deletion of duplicated sentence "this period can be extended up to 10 weeks if waiting for ACTH results."	To clarify and to provide the needed time flexibility in case of an unforeseen event such as waiting for ACTH stimulation test results.
Section 1.1, Synopsis; Section 4.1, Overall Design.	Addition for clarification that "If applicable, the repeat tests shall be rescheduled as soon as possible to keep the duration of the treatment within 10 weeks" AND that "The IMP will be discontinued immediately following the completion of the repeated ACTH stimulation test."	To provide clarification on the duration of treatment.
Section 1.1, Synopsis; Section 4.1, Overall Design.	Amendment of cortisol cut-off amount from "≤ CCI µg/dL" to "< CCI µg/dL" for baseline (Visit 2), EoT Visit (Visit 6), and Unscheduled Visit for the repeat post CCI minute ACTH stimulation test.	CCI
Section 1.1, Synopsis; Section 4.1, Overall Design; Section 7.1, Discontinuation of Study Intervention.	Addition of clarification that "In case of abnormal ACTH stimulated cortisol values at baseline, participant discontinues the study intervention and follows steps as described in the protocol."	To provide clarification.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis; Section 4.1, Overall Design; Section 8.6.2, ACTH Stimulation Test and Cortisol Level Measurement.	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 (Visit 2) and EoT (Visit 6, Week 8) will be considered abnormal, indicating impaired cortisol reserve. An abnormal cortisol level after ACTH stimulation test at baseline (Visit 2), will result in the participant's discontinuation of the study intervention. At EoT (Visit 6, Week 8), in the rare incidence of an abnormal ACTH stimulated cortisol level, the participant will be asked to remain on treatment and to undergo repeat ACTH stimulated cortisol measurements during an unscheduled visit which includes cortisol measurements CCI minutes 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 will be considered normal. The results from the repeat test will supersede the original Week 8 results.	CCI
Section 1.1, Synopsis; Section 9.4.2.1, Primary and Secondary Endpoints.	Amendment of the incidence of abnormal stimulated cortisol to read "serum total cortisol **below** the pre-specified threshold after CCI minutes."	To correct a typographical error.
Section 1.1, Synopsis; Section 9.4.2.1, Primary and Secondary Endpoints.	Addition of clarification that "Those discontinued participants will be listed and plotted separately. If performed, the results of the repeat ACTH stimulation test at the unscheduled visit will be used for the analysis".	To provide clarification.
Section 3.0, Objectives, Endpoints, and Estimands.	Update of the primary estimand treatment condition and intercurrent events and strategies.	To improve estimand strategy.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis; Section 9.4.2.1, Primary and Secondary Endpoints.	Addition of clarification that CCI [redacted] The data collected after the other intercurrent events will be included in the data analyses (Treatment Policy Strategy)".	To provide clarification.
Section 5.2, Exclusion Criteria; Section 6.9.1, Prohibited Concomitant Medications; Section 6.9.2., Restricted Concomitant Medications.	Amendment of exclusion criterion number 25 to read "Treatment with medications that CCI [redacted] within 8 weeks prior to Screening." AND expansion of the list of prohibited medications to include "CCI [redacted] CCI [redacted] and Once enrolled, treatment with any form of CCI [redacted] therapy or on over the counter CCI [redacted] while enrolled in the study, treatment with CCI [redacted] at any dose". Removed repetition of prohibited medications from Section 6.9.2.	To define concomitant medications CCI [redacted]
Section 8.1, Administrative and General/Baseline Procedures.	Addition of "Cortisol values" to the list of data collected at the Screening.	To provide clarification.
Section 8.2.1, Efficacy Assessments.	Moving the subheading to new subheading 8.6.2 under Pharmacodynamics. Accordingly, Section 8.2 is now changed to "Not applicable".	To correct a template misalignment.

Section Number and Name	Description of Change	Brief Rationale
Section 8.3.4, Clinical Safety Laboratory Tests.	Revision of Table 7 title to "Laboratory variables" Amendment of Table 7, footnote "a" to indicate that eGFR will be calculated every time creatinine is collected. Amendment of Table 7, footnote "b" to indicate Creatinine, K^+, and Na^+ will be measured between "Screening (Visit 1)" and End of Treatment (EoT) (Visit 6). Amendment of Table 7 footnote "d" to include "serum pregnancy test will be performed centrally".	To provide clarification and prevent misinterpretation during sampling and analysis.
Section 9.4.3.1, Adverse Events.	Removal of mention of "other significant AEs".	To align with the SAP.
Appendix E6, Laboratory Tests.	Removal of the current IgM anti-HSV test and replacement with the HSV-1 and HSV-2 IgM testing OR HSV-1 and HSV-2 PCR testing depending on regional requirements	This operational update is meant to improve diagnostic accuracy without impacting the study's primary or secondary objectives, patient safety, or the overall management of the study.
Appendix F, Protocol Version History.	Addition of protocol version history to the CSP appendices.	To align with the protocol template requirement.

ACTH = Adrenocorticotropic hormone; AE = Adverse event; CCI [redacted] CSP = Clinical Study Protocol; eGFR = Estimated Glomerular Filtration Rate; EoT = End of treatment; FDA = Food and Drug Administration; HSV-1 = Herpes Simplex Virus type 1; HSV-2 = Herpes Simplex Virus type 2 IgM = Immunoglobulin M; PCR = Polymerase chain reaction; K^+ = Potassium; N^+ = Sodium; PK = Pharmacokinetic(s); SAP = Statistical Analysis Plan.

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis; Section 3.0, Objectives, Endpoints, and Estimands.	Amendment of secondary endpoint to read "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 stimulated cortisol is defined as < CCI µg/dL at CCI minutes AND < CCI µg/dL at CCI minutes. Participants with abnormal stimulated cortisol (< CCI µg/dL at CCI min) at baseline will not be considered".	To provide clarification on the abnormal cortisol values and exclusion of participants with abnormal results at Randomisation.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis; Section 3.0, Objectives, Endpoints, and Estimands; Section 9.3, Populations for Analysis; Section 9.4.2, Pharmacodynamic Analysis; Section 9.4.3, Safety.	Amendment of "Pharmacodynamic Analysis Set" to "Full Analysis Set".	Correction of analysis set.
Section 1.1, Synopsis; Section 4.1, Overall Design.	Addition of a test timepoint as "CCI minutes after ACTH stimulation test (with CCI µg/dL cut-off)" to unscheduled repeat ACTH stimulation test when retesting in case of abnormal stimulated cortisol value at EoT Visit (Visit 6).	CCI
Section 1.1, Synopsis; Section 9.4.2.1, Primary and Secondary Endpoints.	Amendment of the statistical methods to align with the updated secondary objectives and endpoints and to include details about the repeat ACTH stimulation testing, as well as indicating that participants with abnormal cortisol levels at baseline will be excluded from the analysis.	To provide clarification for the analyses.
Section 5.1, Inclusion Criteria.	Correction of inclusion criterion 7 to read "Participants must have a morning cortisol (measured at 08:00 AM ± 2 hours) ≥CCI µg/dL".	Correction of acceptable morning cortisol level.

ACTH = Adrenocorticotropic hormone; EoT = End of Treatment; FDA = Food and Drug Administration.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
ACEI	Angiotensin-converting Enzyme Inhibitor
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
AESI	Adverse Event of Special Interest
AI	Adrenal insufficiency
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase/Transaminase
AOBPM	Automated Office Blood Pressure Measurement
ARB	Angiotensin-receptor Blocker
AST	Aspartate Aminotransferase/Transaminase
AxMP	Auxiliary Medicinal Product
β-hCG	Beta-human Chorionic Gonadotropin
BP	Blood Pressure
CIRB	Central Institutional Review Board
CKD	Chronic Kidney Disease
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTT	Clinical Trial Transparency
CYP	Cytochrome P450
DAE	Discontinuation due to Adverse Event(s)
DBP	Diastolic Blood Pressure
DES	Data Entry Site
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic Acid
DUS	Disease Under Study
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EoT	End of Treatment
FDA	Food and Drug Administration

Abbreviation or special term	Explanation
FOCBP	Female(s) of Child-bearing Potential
FSH	Follicle Stimulating Hormone
FU	Follow-up
GCP	Good Clinical Practice
HbA1c	Glycated Haemoglobin
HBS	Human Biological Sample(s)
HF	Heart Failure
HSV-1	Herpes Simplex Virus Type 1
HSV-2	Herpes Simplex Virus Type 2
HTN	Hypertension
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
K^+	Potassium
MedDRA	Medical Dictionary for Regulatory Activities
MRA	Mineralocorticoid Receptor Antagonist
N/A	Not Applicable
Na^+	Sodium
NIMP	Non-investigational Medicinal Product
NSAID	Non-steroidal Anti-inflammatory Drug
NYHA	New York Heart Association
OD	Once Daily
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
QT	QT Interval
QTcF	Fridericia's Corrected QT
R	Randomisation

Abbreviation or special term	Explanation
RAAS	Renin-angiotensin-aldosterone System
RBC	Red Blood Cells
RTSM	Randomisation and Trial Supply Management
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SFU	Safety Follow-up Visit
SoA	Schedule of Activities
SOC	System Organ Class
TBL	Total Bilirubin
uHTN	Uncontrolled Hypertension
ULN	Upper Limit of Normal

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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

Brief Title:

A Study to Evaluate Cortisol Reserve in Response to Adrenocorticotropic Hormone Stimulation Test Following Baxdrostat Treatment Compared to Placebo in Participants with Uncontrolled Hypertension

Regulatory Agency Identifier Number(s): IND 146112

Rationale:

This Phase II study is intended to evaluate the cortisol reserve in response to adrenocorticotropic hormone (ACTH) stimulation test following treatment with baxdrostat administered at 2 mg once daily (OD) orally versus placebo, in participants aged ≥ 18 years with uncontrolled hypertension (uHTN) despite a stable regimen of ≥ 1 antihypertensive agent (including a diuretic).

Baxdrostat (previously referred as RO6836191 and CIN-107) is a highly potent, selective, and competitive inhibitor of human aldosterone synthase (encoded by CYP11B2 gene), being developed specifically to address the unmet need in participants whose blood pressure (BP) is refractory to 2 or more therapies in order to lower their BP.

The synthesis pathway of cortisol is catalysed by 11β-hydroxylase (CYP11B1), which shares high sequence homology with aldosterone synthase (CYP11B2). Undesired inhibition of 11β-hydroxylase leads to suppression of cortisol levels leading to subclinical or clinical adrenal insufficiency. Therefore, the selectivity of baxdrostat to aldosterone synthetase has been evaluated in vitro, in nonclinical and in Phase I clinical studies.

Prior data do not show baxdrostat to cause reduced cortisol response to ACTH stimulation. Although baxdrostat is a highly selective competitive aldosterone synthase inhibitor with no evidence from prior studies of inhibition of 11β-hydroxylase nor ACTH stimulated cortisol secretion, this double-blind, placebo-controlled study is proposed to further evaluate cortisol reserve in response to ACTH stimulation test after prolonged exposure of 8 weeks to baxdrostat treatment in participants with uHTN. This study, along with results from other studies, will allow a comprehensive evaluation of cortisol reserve following baxdrostat treatment.

Objectives, Endpoints, and Estimands:

Objectives	Estimands/Endpoints
Primary	
• To characterise the total serum cortisol before and after ACTH stimulation test at baseline and Week 8.	• Individual cortisol level before and after ACTH stimulation test at baseline and Week 8.
Secondary	
• To evaluate the total serum cortisol response after ACTH stimulation test at Week 8.	• 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 min), an abnormal result for repeat stimulated cortisol is defined as < CCI µg/dL at CCI minutes AND < CCI µg/dL at CCI minutes. Participants with abnormal stimulated cortisol (< CCI µg/dL at CCI minutes) at baseline will not be considered.
Exploratory	
• To evaluate CCI	• CCI
• To assess the pharmacokinetics of baxdrostat.	• Plasma concentrations of baxdrostat.
• To explore how CCI [a]	• Exploratory endpoints CCI
• To explore how CCI [a]	• Exploratory endpoints CCI
Safety	
• To assess the safety and tolerability of baxdrostat as compared to placebo.	• Outcome variables: safety and tolerability will be evaluated in terms of: • AEs, SAEs, and DAEs. • Vital signs (BP, pulse rate, body weight). • Safety investigations and laboratory tests (ECG, clinical chemistry, haematology). • AESIs (hyperkalaemia, hyponatraemia, and hypotension CCI based on Investigator reported AEs).

[a] CCI . Results will not be reported in the CSR.

ACTH = Adrenocorticotropic hormone; AE = Adverse event; AESI = Adverse event of special interest; CCI BP = Blood pressure; CSR = Clinical study report; DAE = Discontinuation due to adverse event(s); CCI ECG = Electrocardiogram; SAE = Serious adverse event.

For estimands description, please see Section 3 of the protocol.

Overall Design Synopsis:

This is a Phase II, randomised, double-blind, placebo-controlled study to evaluate cortisol reserve after ACTH stimulation test following treatment with 2 mg baxdrostat versus placebo, administered OD orally on top of standard-of-care, in approximately 45 participants ≥ 18 years of age with uHTN (seated systolic BP [SBP] ≥ 130 mmHg at screening, ≥ 130 mmHg at Randomisation) despite a stable regimen of ≥ 1 antihypertensive agent (including a diuretic).

The study is planned to be conducted in the United States in approximately 12 study sites.

Brief Summary:

The purpose of this study is to evaluate cortisol reserve after ACTH stimulation test following treatment with 2 mg baxdrostat compared to placebo in participants with uHTN.

The study duration will be up to 16 weeks, including:

- A 4-week screening period.
- An 8-week double-blind treatment period. The end-of-study assessment will be at Visit 6 (Week 8), at which data will be collected and an ACTH stimulation test will be performed. Participants can be on treatment for up to 10 weeks*, while waiting for the ACTH stimulation test result to be available.
  *10 weeks is not the targeted duration of the treatment period, but only intends to provide flexibility in case of unforeseen event. The last date of treatment can be later than the End of Treatment (EoT) Visit date.
- A safety follow-up 2 weeks after last dose.

Disclosure Statement: This is a randomised, double-blind, placebo-controlled, parallel group study with 2 arms that is participant, Investigator and Sponsor blind.

Number of Participants:

Approximately 45 participants will be randomised and assigned to study intervention such that, with an estimated 10% drop-out rate, approximately 40 evaluable participants complete the study.

Note: 'Screened' means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study,

but are not randomised/assigned in the study, are considered 'screen failures', unless otherwise specified by the protocol.

Study Arms and Duration:

After an up to 4-week screening period, eligible participants will be randomised in a 2:1 ratio to one of 2 treatment arms:

- 2 mg baxdrostat (target number of participants: 30).
- Placebo (target number of participants: 15).

During the 8-week double-blind treatment period, participants should remain on their background antihypertensive treatment regimen. Doses of background medications should not be changed during this period unless participants experience SBP < CCI mmHg with symptoms of hypotension. Rescue therapy is permitted if the SBP exceeds 170 mmHg or diastolic BP (DBP) exceeds 105 mmHg. The choice of rescue therapy is based on the Investigator's best clinical judgement; however, the use of K^+-sparing diuretics and mineralocorticoid receptor antagonists (MRAs) is prohibited.

An ACTH stimulation test using 250 µg ACTH will be performed at Visit 2 (Randomisation) prior to the first dose of study intervention and Visit 6 (Week 8) with cortisol measured before and after the stimulation test (CCI minutes after injection). The ACTH stimulation testing procedure will be done locally at the site, but the serum cortisol measurement pre- and post-ACTH stimulation testing will be processed centrally. Participants need to be on treatment until the ACTH stimulation test result is available, ie, treatment may last up to 10 weeks depending on the availability of the ACTH stimulation test result or in case the test needs to be repeated. If applicable, the repeat tests shall be rescheduled as soon as possible to keep the duration of the treatment within 10 weeks. The Investigational Medicinal Product (IMP) will be discontinued immediately following the completion of the repeated ACTH stimulation test.

Cortisol analysis will be performed using the CCI measured at a central laboratory. Cortisol level at CCI minutes after ACTH stimulation that is < CCI µg/dL at baseline (Visit 2) and EoT (Visit 6, Week 8) will be considered abnormal, indicating impaired cortisol reserve. An abnormal cortisol level after ACTH stimulation test at baseline (Visit 2), will result in the participant's discontinuation of the study intervention. At EoT (Visit 6, Week 8), in the rare incidence of an abnormal ACTH stimulated cortisol level, the participant will be asked to remain on treatment and to undergo repeat ACTH stimulated cortisol measurements during an unscheduled visit which includes cortisol measurements CCI minutes 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 will be considered normal. The results from the repeat test will supersede the original Week 8 results.

The following is a summary of different types of cortisol measurements at different timepoints:

- **AM serum cortisol without ACTH stimulation (8 AM ± 2 hours)**
  - Cortisol level ≥ CCI µg/dL is considered normal.
- **Routine serum cortisol collected before and CCI minutes after ACTH stimulation**
  - Cortisol level ≥ CCI µg/dL at CCI minutes after ACTH is considered normal.
- **Retest serum cortisol collected before, CCI minutes AND CCI minutes after ACTH stimulation**
  - Cortisol level ≥ CCI µg/dL at CCI minutes after ACTH stimulation is considered normal. Cortisol level ≥ CCI µg/dL at CCI minutes after ACTH stimulation is considered normal.
    Note: If only one of the two results is abnormal, the overall test will still be considered normal.

Further evaluation and management of the participant should be at the discretion of the Investigator, and if needed, in consultation with an endocrinologist.

Laboratory and safety visits are outlined in the schedule of assessments.

After completing the 8-week double-blind treatment period (this period can be extended up to 10 weeks if waiting for ACTH results, or in the situation that a repeat test is needed) or if participants permanently discontinue treatment earlier than 8 weeks, participants will return for a safety follow-up, 14 days after the last dose.

Data Monitoring/Other Committee:

No data monitoring committee has been appointed for this study. However, all cases of abnormal ACTH stimulation test will be reviewed by an independent blinded adrenal expert.

Statistical Methods:

Statistical analyses will be descriptive in nature, without formal statistical hypothesis testing.

This study is planning to randomise approximately 45 participants using a 2:1 ratio to either receive 2 mg baxdrostat OD or placebo OD, in addition to a stable regimen of ≥ 1 antihypertensive agent (including a diuretic) in the double-blind treatment period of 8 weeks. The sample size is considered to be adequate for supporting descriptive analysis of

the cortisol response to ACTH, based on previous experience with baxdrostat.

Cortisol response to ACTH stimulation test will be assessed on individual level via line plot of total serum cortisol values prior to ACTH stimulation testing and after CCI minutes, both at baseline and at Week 8. In the event of abnormal ACTH stimulated cortisol results at Week 8, an unscheduled visit with repeat pre-ACTH stimulated and CCI minutes and CCI minutes post-ACTH cortisol measurements will be performed for each treatment group. 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 performed, the results of the repeat ACTH stimulation test at the unscheduled visit will be used for the analysis.

Participants with abnormal cortisol levels at baseline will not be considered. Those discontinued participants will be listed and plotted separately.

The baseline values are the last non-missing values prior to the administration of the first dose of IMP. CCI [redacted] The data collected after the other intercurrent events will be included in the data analyses (Treatment Policy Strategy).

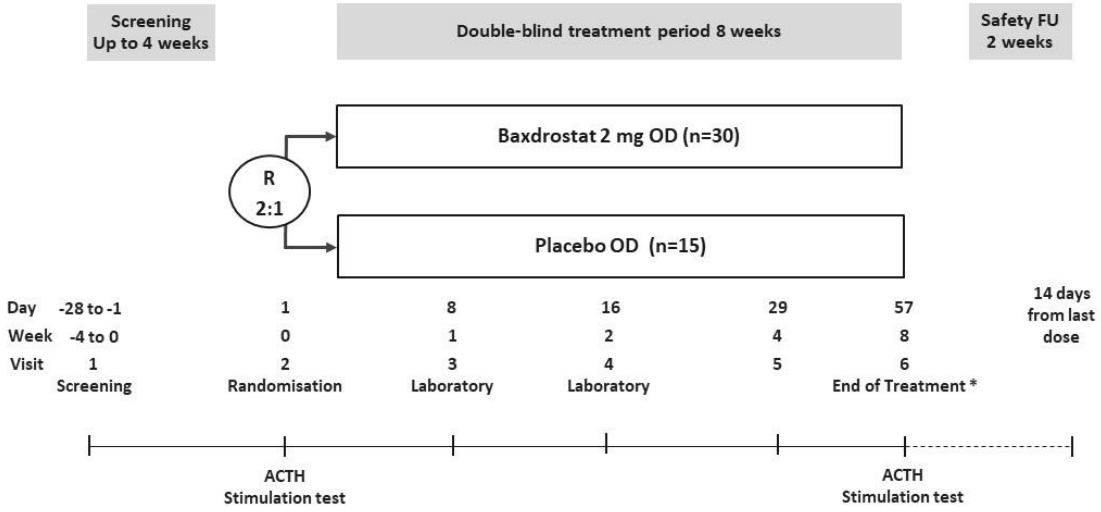
Incidence of abnormal stimulated cortisol (ie, total serum cortisol above below the pre-specified threshold after CCI minutes) at baseline and Week 8 by treatment group will be assessed via frequency table, in participants with normal stimulated cortisol at baseline. Of note, participants with abnormal stimulated cortisol at baseline will be reported separately. If performed, the results of the repeat ACTH stimulation test at the unscheduled visit will be used for the analysis.

The primary and secondary endpoints will be analysed in the Full Analysis Set, defined as all randomised participants who received at least one dose of study intervention (treatment classification will be based on the study intervention that participants were randomly assigned to).

The safety endpoint aims to assess the safety and tolerability of baxdrostat as compared to placebo; the safety data will be presented using descriptive statistics unless otherwise specified. Safety analyses will be performed in the Full Analysis Set.

1.2 Schema

Figure 1 Study Design



* Participants can be on treatment for up to 10 weeks, while waiting for the ACTH stimulation test results to be available.
ACTH = Adrenocorticotropic hormone; FU = Follow-up; OD = Once daily; R = Randomisation.

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure	Screening	Randomisation	Double-blind period			EoT [a,b]	Safety FU	Details in protocol section or appendix
Visit	**1**	**2**	**3 (Laboratory Visit)**	**4 (Laboratory Visit)**	**5**	**6**	**SFU [c]**	
Week	**(-4 to 0)**	**0**	**1**	**2**	**4**	**8 [b]**		
Day	**(-28 to -1)**	**1**	**8 (+ 4)**	**16 (± 3)**	**29 (± 3)**	**57 (± 4) [b]**	**14 days from last dose (± 4)**	
Signed informed consent	X							Section 5.1
Inclusion and exclusion criteria	X	X						Section 5.1 Section 5.2 Section 5.4.1
Enrolment in IRT/RTSM	X							Section 6.3
Demography	X							Section 8.1.1
Randomisation		X						Section 6.3
Complete physical examination [d]	X	X				X		Section 8.3.1
Targeted physical examination [e]							X	Section 8.3.1
Medical/surgical history	X							Section 8.1.2
Concomitant medications	X	X			X	X	X	Section 6.1 Section 6.9
ACTH stimulation test [b,f]		X				X		Table 3 and Section 8.6.2
Serum cortisol measurement [f,]	X[h]	X[g]				X[g]		Table 3 and Section 8.6.2
Collect sample for clinical safety analysis	X	X	X	X	X	X	X	Table 2 and Section 8.3.4

Procedure	Screening	Randomisation	Double-blind period			EoT [a,b]	Safety FU	Details in protocol section or appendix
Visit	**1**	**2**	**3 (Laboratory Visit)**	**4 (Laboratory Visit)**	**5**	**6**	**SFU [c]**	
Week	**(-4 to 0)**	**0**	**1**	**2**	**4**	**8 [b]**		
Day	**(-28 to -1)**	**1**	**8 (+ 4)**	**16 (± 3)**	**29 (± 3)**	**57 (± 4) [b]**	**14 days from last dose (± 4)**	
12-lead ECG	X					X	X	Section 8.3.3
Vital signs [i]	X	X			X	X	X	Section 8.3.2
IMP dispensation		X [j]			X [j]			Section 6.1
IMP accountability					X	X	X	Section 6.2 Section 6.5
Adverse events [k]	X (SAE only)	X			X	X	X	Section 8.4

[a] Participants who prematurely withdraw study intervention will undergo an EoT Visit, ideally scheduled as soon as possible at the time of premature withdrawal from study intervention. Following the EoT Visit, the participant will then proceed to complete the final SFU Visit as per SoA. If the EoT Visit is conducted > 10 days after the last administered dose, all assessments (except the PK sampling) required at EoT and SFU Visits are to be conducted within the same visit (inclusive of the ACTH stimulation testing, serum cortisol measurement, and K+ only testing) and a complete physical examination will be performed.

[b] Participants need to stay on treatment until ACTH stimulation test results are available ie, up to 10 weeks. In rare incidence that participant has abnormal ACTH stimulated cortisol level, the participant will be asked to remain on treatment and to undergo repeat ACTH stimulated cortisol measurements during an unscheduled visit. See Footnote "g". If applicable, the repeat tests shall be rescheduled as soon as possible to keep the duration of the treatment within 10 weeks. The IMP will be discontinued immediately following the completion of the repeated ACTH stimulation test. The participant will be informed by a telephone call to stop treatment after ACTH stimulation test results are available.

[c] The SFU Visit will be performed 14 days after the participant receives the last IMP dose.

[d] A complete physical examination will be performed by the Investigator or a suitably qualified medical designee and include assessments of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, and neurological systems. Additionally, height will be measured during screening.

[e] A targeted physical examination should include, at a minimum, cardiovascular and lung evaluations, and examination of any peripheral oedema.

[f] ACTH stimulation testing procedure will be done locally at the site (at 8.00 AM [± 2 hours]), but the serum cortisol measurement pre- and post-ACTH stimulation testing will be processed centrally. See Table 3 for more details.

[g] Blood samples will be collected to measure serum total cortisol prior to the ACTH stimulation test and CCI minutes after. If the cortisol level is abnormal at EoT (Visit 6, Week 8), the test will be repeated during an unscheduled visit (prior to ACTH stimulation test, CCI minutes after ACTH stimulation test, and CCI minutes after ACTH stimulation test). See Table 3 for more details.

[h] Morning serum total cortisol to ensure inclusion criteria are met. Blood sample should be collected at site (at 8.00 AM [± 2 hours]) but it will be processed centrally. Participants must have a morning cortisol (measured at 08:00 AM ± 2 hours) ≥ [redacted] µg/dL, determined as per central laboratory to be eligible for the study.

[i] Including seated attended office automated BP, pulse rate and body weight measurements.

[j] One IMP-containing blister pack will be dispensed at Visit 2 (Randomisation) and 2 IMP-containing blister packs, at Visit 5.

[k] Adverse events will be collected from randomisation throughout the study intervention period, including at the SFU Visit but excluding at Visits 3 and 4. Serious adverse events will be collected from the time of signing informed consent and onward.

ACTH = Adrenocorticotropic hormone; BP = Blood pressure; ECG = Electrocardiogram; EoT = End of treatment; FU = Follow-up; IMP = Investigational medicinal product; IRT = Interactive response technology; RTSM = Randomisation and trial supply management; SAE = Serious adverse event; SFU = Safety follow-up; SoA = Schedule of activities.

Table 2 Schedule of Laboratory Samples

Procedure	Screening	Randomisation	Double-blind period			EoT	Safety FU	Details in protocol section or appendix
Visit	**1**	**2**	**3 (Laboratory Visit)**	**4 (Laboratory Visit)**	**5**	**6**	**SFU[g]**	
Week	**(-4 to 0)**	**0**	**1**	**2**	**4**	**8**		
Day	**(-28 to -1)**	**1**	**8 (+ 4)**	**16 (± 3)**	**29 (± 3)**	**57 (± 4)**	**14 days from last dose (± 4)**	
Whole safety panel (central laboratory) [a]	X	X			X	X	X	Section 8.3.4
Dipstick urinalysis		X						Section 8.3.4
Safety laboratory: Only creatinine, eGFR, K^+, and Na^+ (central laboratory) [b]			X	X				Section 8.3.4
K^+ only (local laboratory)		X	X	X	X	X		Section 8.3.4.1
PK sampling (pre-dose) [c]					X	(X) [c]		Section 8.5.1
CCI [redacted] CCI [redacted] [redacted]		X						Section 8.7 Appendix D
HbA1c test [d]	X							Section 8.3.4
FSH test (for female participants only) [e]	X							Section 8.3.4
Urine pregnancy test (FOCBP only) [f]	X	X			X	X	X	Section 8.3.4

[a] The whole safety panel includes haematology and clinical chemistry analyses (see Table 7 in Section 8.3.4 for further details). This assessment will include creatinine analysis (for eGFR calculation) and the measurement of Na^+ and K^+ levels in blood.

[b] At Visits 3 and 4, only creatinine (for eGFR calculation), K^+ and Na^+ are tested by the central laboratory. Additionally, these analytes are also included in the whole safety panel during the respective visits. eGFR calculation is required at all visits.

[c] Pharmacokinetic samples will be collected pre-dose from all participants at Visit 5. For participants who are discontinued from study intervention due to hyperkalaemia, a PK sample should be collected at the EoT Visit.

[d] The HbA1c test will be performed to exclude poorly controlled diabetes at screening.
[e] For confirmation of postmenopausal status of women aged < 50 years only. Females aged < 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more, following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
[f] Urine pregnancy test can be replaced by a serum pregnancy test. Additional ad-hoc test to be used at the discretion of the Investigator during the treatment period if there is a suspected pregnancy.
[g] If the EoT Visit is conducted > 10 days after the last administered dose, all assessments required at EoT and SFU Visits are to be conducted within the same visit (inclusive of K+ only testing) (see Table 1 for a complete list of tests).

eGFR = Estimated glomerular filtration rate; EoT = End of treatment; FOCBP = Female(s) of child-bearing potential; FSH = Follicle stimulating hormone; FU = Follow-up; HbA1c = Glycated haemoglobin; K^+ = Potassium; Na^+ = Sodium; PK = Pharmacokinetic(s); SFU = Safety follow-up.

Table 3 Schedule of Cortisol Measurements

Timing of Assessment	Cortisol Measurement	ACTH Stimulation	Time for ACTH Stimulation	Time for Cortisol Collection	Normal Value	Purpose of Test
Screening (Visit 1)	AM Serum Cortisol	No	N/A	8 AM ± 2 hours	≥ CCI µg/dL	Part of screening procedure with results as part of Inclusion/Exclusion criteria
Visit 2	Routine Serum Cortisol Collection **before** and **after** ACTH	Yes	8 AM ± 2 hours	CCI min after ACTH stimulation	≥ CCI µg/dL	Assess cortisol response prior to starting intervention
Visit 6	Routine Serum Cortisol Collection **before** and **after** ACTH	Yes	8 AM ± 2 hours	CCI min after ACTH stimulation	≥ CCI µg/dL	Assess cortisol response after completing intervention
Unscheduled (Retests ONLY when Visit 6 results are abnormal)	Retest Serum Cortisol Collection before and after ACTH	Yes	8 AM ± 2 hours	CCI min **And** CCI min after ACTH stimulation	≥ CCI µg/dL at CCI min after ACTH ≥ CCI µg/dL at CCI min after ACTH	Retesting procedure if routine cortisol collection before and after ACTH stimulation is abnormal at Visit 6.

ACTH = Adrenocorticotropic Hormone; Min = Minute.

2 INTRODUCTION

2.1 Study Rationale

This Phase II study is intended to evaluate the cortisol reserve in response to ACTH stimulation test following treatment with baxdrostat administered at 2 mg OD orally versus placebo, in participants aged ≥ 18 years with uHTN despite a stable regimen of ≥ 1 antihypertensive agent (including a diuretic).

Baxdrostat (previously referred as RO6836191 and CIN-107) is a highly potent, selective, and competitive inhibitor of human aldosterone synthase (encoded by CYP11B2 gene), being developed specifically to address the unmet need in participants whose BP is refractory to 2 or more therapies in order to lower their BP.

The synthesis pathway of cortisol is catalysed by 11β-hydroxylase (CYP11B1), which shares high sequence homology with aldosterone synthase (CYP11B2). Undesired inhibition of 11β-hydroxylase leads to suppression of cortisol levels leading to subclinical or clinical adrenal insufficiency (Oelkers, 1996, Wagner and White, 1984, Wagner et al, 1984).

Adrenal insufficiency has an incidence of 1:10,000 in the global population. The evaluation of AI is based on clinical context i.e. an initial assessment of clinical signs and symptoms (e.g., weight loss, anorexia, hyperpigmentation, hypotension and constitutional symptoms). If identified, a morning serum cortisol is measured, which can be followed up by dynamic evaluation such as an ACTH stimulation or insulin tolerance test with cortisol measurement. Importantly, all the available cutoffs of abnormal cortisol response to ACTH have been established in populations with moderate-high pre-test probability of AI (Javorsky et al, 2021). The selectivity of baxdrostat to aldosterone synthetase has been evaluated in vitro, in nonclinical and in Phase I clinical studies.

In humans, the maximum suppression of plasma and urine aldosterone levels is achieved at a dose of 10 mg baxdrostat and the ability of baxdrostat to lower aldosterone without affecting cortisol levels was previously confirmed following administration of baxdrostat at well above the anticipated therapeutic dose range. In healthy subjects, single doses of baxdrostat up to 360 mg (180-fold the maximum dose in Phase III HTN studies), ACTH stimulated cortisol levels remained unchanged at all doses tested, up to and inclusive of 360 mg. Furthermore, no increase in the precursors 11-deoxycorticosterone and 11-deoxycortisol were present at doses ≤ 90 mg, roughly a 44-fold higher exposure than achieved with 2 mg dose (Bogman et al, 2017).

In a multiple ascending dose study in participants treated with baxdrostat, while there was expected dose-dependent reduction of aldosterone, there was no significant suppression of ACTH stimulated plasma cortisol (Freeman et al, 2023a). In vitro, baxdrostat exhibited a high selectivity ratio for aldosterone synthase compared to 11β-hydroxylase (cortisol synthesis). In

cynomolgus monkey, baxdrostat decreased aldosterone production but had no effect on cortisol levels (Bogman et al, 2017). Taken together, prior data do not show baxdrostat to cause reduced cortisol response to ACTH stimulation. Although baxdrostat is a highly selective competitive aldosterone synthase inhibitor with no evidence from prior studies of inhibition of 11β-hydroxylase nor ACTH stimulated cortisol secretion, this double-blind, placebo-controlled study is proposed to further evaluate cortisol reserve in response to ACTH stimulation test after prolonged exposure of 8 weeks to baxdrostat treatment in participants with uHTN. This study, along with results from other studies, will allow a comprehensive evaluation of cortisol reserve following baxdrostat treatment.

2.2 Background

Aldosterone is a steroid hormone that contributes to the regulation of Na^+ reabsorption, volume retention and BP control. Aldosterone is the principal mineralocorticoid in humans, synthesised in the adrenal cortex by the enzyme aldosterone synthase and acts as a critical regulator of fluid and electrolyte homeostasis through its agonism of the mineralocorticoid receptor.

Baxdrostat (also known as CIN-107) is a highly potent, selective, and competitive inhibitor of human aldosterone synthase (encoded by CYP11B2 gene), being developed specifically to address the unmet need in participants whose BP is refractory to other therapies in order to lower their BP. Aldosterone synthase converts 11-deoxycorticosterone to aldosterone via a multistep biosynthetic pathway. Baxdrostat is 100-fold more active against aldosterone synthase (CYP11B2) than the closely related enzyme that produces cortisol, 11β-hydroxylase (CYP11B1).

In Phase I and II studies, baxdrostat has demonstrated high selectivity for aldosterone synthase (selectivity ratio 100:1) as compared to the enzyme required for cortisol synthesis (Bogman et al, 2017, Freeman et al, 2023a, Freeman et al, 2023b), resulting in significantly lowered aldosterone levels without affecting cortisol levels over a wide dose range. In a Phase II study of baxdrostat versus placebo in participants with rHTN, baxdrostat elicited statistically and clinically significant SBP reductions compared to placebo (Freeman et al, 2023b). In addition, in the Phase II HALO Study (CIN-107-124), baxdrostat substantially reduced aldosterone levels and increased plasma renin activity in a dose-dependent manner in the adherent patient population. Based on these findings, baxdrostat may be a novel treatment for uHTN.

For a detailed description of the chemistry, pharmacology, efficacy, and safety of baxdrostat, please refer to the IB.

2.3 Benefit/Risk Assessment

The primary benefit for participants with uHTN, randomised to baxdrostat, is expected to be

the reduction of BP. Baxdrostat safety and efficacy have been demonstrated in previous completed studies conducted in participants with rHTN. It is expected to be better tolerated than spironolactone, the guidelines recommended therapy for rHTN.

For detailed information about previous clinical studies, the known and expected benefits and risks and reasonably expected AEs of baxdrostat, please see latest baxdrostat IB.

2.3.1 Risk Assessment

A summary of the potential risks with baxdrostat is presented in Table 4.

Table 4 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention (baxdrostat)-related risks		
Important identified risk of hyperkalaemia	Baxdrostat is an aldosterone synthase inhibitor, leading to decreased renal K^+ excretion and increased serum K^+ levels due to lowered circulating aldosterone. In clinical studies with baxdrostat, increases from baseline in mean serum K^+ were observed. In the BrigHTN Study (CIN-107-121), mean increases from baseline to EoT at 12 weeks were 0.36 and 0.29 mEq/L in the 1- and 2-mg groups, respectively. In the HALO Study (CIN-107-124), mean increases from baseline to EoT at 8 weeks were 0.26 and 0.12 mEq/L in the 1- and 2-mg groups, respectively. In the CCI [redacted]	• Hyperkalaemia is considered an AESI CCI [redacted] • Serum K^+ level and minimum baseline renal function are included as inclusion criterion (see inclusion criterion 6 [serum K^+ level ≥ 3.5 and < 5.0 mmol/L at screening] and inclusion criterion 5 [eGFR ≥ 45 mL/min/1.73 m² at screening]; Section 5.1). • Certain drugs known to increase serum K^+ are prohibited in the study (see Section 6.9). • Serum K^+ will be monitored at all visits (see Section 8.3.4.1). • CCI [redacted] (see Section 7.1.3).
Important potential risk of hyponatraemia	Baxdrostat leads to increased natriuresis due to lowered circulating aldosterone, resulting in a minor decrease in serum Na^+ level.	• Hyponatraemia is considered an AESI CCI [redacted]

Table 4 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	Additionally, hyponatraemia is a known complication to diuretics, a common background medication in this study population. In clinical studies with baxdrostat, clinically insignificant decreases from baseline in mean serum Na^+ were observed. In the BrigHTN Study (CIN-107-121), mean decreases from baseline to EoT at 12 weeks were 1.1 and 2.4 mEq/L in the 1- and 2-mg groups, respectively. In the CCI [redacted] In the baxdrostat BrigHTN Study, 10 (3.6%) participants developed moderate hyponatraemia (serum Na^+ < 130 mEq/L), whereof one in the placebo group.	• Serum Na^+ level is an exclusion criterion (see exclusion criterion 4; Section 5.2). • Serum Na^+ will be monitored at Visits 3 and 4, in addition to when these analytes are measured as part of the whole safety panel (see Section 8.3.4). • CCI [redacted] (see Section 7.1.3).
Important potential risk of hypotension	Hypotension is reported as a risk with all classes of antihypertensives. As a consequence of the urinary Na^+ loss, osmotic water loss can lead to hypovolemia and, consequently, to orthostatic hypotension with a corresponding increase in heart rate. In the baxdrostat Phase II BrigHTN and HALO Studies (CIN-107-121 and CIN-107-124), CCI [redacted] were considered related to baxdrostat. Pooled data from these 2 studies also revealed a higher frequency of headache, dizziness, and nausea on baxdrostat than on placebo (all	• Hypotension is considered an AESI CCI [redacted] • Seated BPs will be monitored throughout the study (see Section 8.3.2). • Discontinuation/restarting criteria are provided (see Section 7).

Table 4 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	possible symptoms of hypotension). There was a small decrease from seated BP to standing BP in the 2-mg group in the BrigHTN Study of approximately 2 mmHg at EoT at 12 weeks. One non-serious AE of orthostatic hypotension was reported in the 2-mg group.	
Study procedure (ACTH stimulation test)-related risks		
Potential risks of adverse reactions on cosytropin	Cosyntropin injection hypersensitivity reactions including anaphylaxis have been reported.	• Participants must be asked about allergies hypersensitivity to cosyntropin injection, synthetic ACTH, or to any of the excipients before use (see exclusion criterion 19; Section 5.2) • Monitoring of participants for hypersensitivity reactions and treatment as needed will performed following ACTH stimulation testing procedure prior to blood sampling for cortisol measurements (see Section 8.6.2)

ACTH = Adrenocorticotropic hormone; AE = Adverse event; AESI = Adverse event of special interest; BP = Blood pressure; eGFR = Estimated glomerular filtration rate; EoT = End of treatment; K^+ = Potassium; Na^+ = Sodium.

2.3.2 Benefit Assessment

Participants enrolled in this study could benefit from the BP lowering effect of baxdrostat, which acts as an aldosterone synthase inhibitor.

Aldosterone synthase inhibition is a new therapeutic option. The aldosterone synthase inhibition lowering effect on BP is expected to be greater than the non-steroidal MRAs and not associated with the endocrine adverse side effects seen with steroidal MRAs usage, which include gynaecomastia and menstrual irregularities (Lainscak et al, 2015). Aldosterone regulates blood volume and pressure by regulating salt and water retention. Serum aldosterone levels are often elevated in response to chronic ACEIs/ARBs, which can diminish BP control and have an associated progression of end organ damage (Bomback and Klemmer, 2007). This is a physiological response from the RAAS and thus, it is expected that direct aldosterone

synthase inhibition, lowering serum aldosterone levels, may provide additional benefit on top of the established standard-of-care.

Taken together, the preclinical data and existing clinical data support the efficacy and safety of baxdrostat and its continued clinical evaluation.

2.3.3 Overall Benefit/Risk Conclusion

Considering the measures taken to minimise risk to participants in this study, the potential risks identified in association with baxdrostat are justified by the anticipated benefits that may be afforded to participants with HTN.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Study objectives and endpoints are presented in Table 5.

Table 5 Objectives and Estimands/Endpoints

Objectives	Estimands/Endpoints
Primary	
• To characterise the total serum cortisol before and after ACTH stimulation test at baseline and Week 8.	• Individual cortisol level before and after ACTH stimulation test at baseline and Week 8.
Secondary	
• To evaluate the total serum cortisol response after ACTH stimulation test at Week 8.	• 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 stimulated cortisol is defined as < CCI µg/dL at CCI min AND < CCI µg/dL at CCI minutes. Participants with abnormal stimulated cortisol (< CCI µg/dL at CCI min) at baseline will not be considered.
Exploratory	
• CCI	• CCI
• To assess the pharmacokinetics of baxdrostat.	• Plasma concentrations of baxdrostat.
• To explore how CCI [a] • To explore how CCI [a]	• Exploratory endpoints CCI • Exploratory endpoints CCI
Safety	
• To assess the safety and tolerability of baxdrostat as compared to placebo.	• Outcome variables: safety and tolerability will be evaluated in terms of: • AEs, SAEs and DAEs. • Vital signs (BP, pulse rate, body weight). • Safety investigations and laboratory tests (ECG, clinical chemistry, haematology). • AESIs (hyperkalaemia, hyponatraemia, and hypotension CCI ; based on Investigator reported AEs).

[a] CCI Results will not be reported in the CSR.

ACTH = Adrenocorticotropic hormone; AE = Adverse event; AESI = Adverse event of special interest; CCI BP = Blood pressure; CSR = Clinical study report; DAE = Discontinuation due to adverse event(s); CCI ECG = Electrocardiogram; SAE = Serious adverse event.

Primary Estimand

The primary clinical question of interest is to evaluate the serum total cortisol response after ACTH stimulation test after 8 weeks.

The estimand is described by the following attributes:

- Population: Participants with uHTN, as defined by the inclusion/exclusion criteria. Implemented in the Full Analysis Set, excluding participants with abnormal ACTH stimulated cortisol at baseline.
- Endpoint: Individual cortisol level before and after ACTH stimulation test at baseline and Week 8. If applicable, the unscheduled visit results will be included.
- Treatment condition:
  - 2 mg baxdrostat
  - Placebo
- Intercurrent events: The intercurrent events and the handling strategies are described below:

Intercurrent Event	Strategy
Initiation of CCI (See Section 6.9.1 for list of medication).	CCI The data collected after this intercurrent event CCI
Treatment discontinuation; use of antihypertensive rescue therapy; other intercurrent events that do not interfere with cortisol production.	Treatment Policy Strategy: The data collected after this intercurrent event will be included in the data analyses.

- Population-level summary: Descriptive statistics on individual cortisol level before and after ACTH stimulation.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase II, randomised, double-blind, placebo-controlled study to evaluate cortisol reserve after ACTH stimulation test following treatment with 2 mg baxdrostat versus placebo, administered OD orally on top of standard-of-care, in approximately 45 participants ≥ 18 years of age with uHTN (seated SBP ≥ 130 mmHg at screening, ≥ 130 mmHg at Randomisation) despite a stable regimen of ≥ 1 antihypertensive agent (including a diuretic).

The study duration will be up to 16 weeks, including:

- A 4-week screening period.
- An 8-week double-blind treatment period. The end-of-study assessment will be at Visit 6 (Week 8), at which data will be collected and an ACTH stimulation test will be performed. Participants can be on treatment for up to 10 weeks*, while waiting for the ACTH stimulation test result to be available.
  *10 weeks is not the targeted duration of the treatment period, but only intends to provide flexibility in case of an unforeseen event. The last date of treatment can be later than the EoT Visit date.
- A safety follow-up 2 weeks after last dose.

Consenting participants will be screened up to 4 weeks and then randomised in a 2:1 ratio to one of 2 treatment arms:

- 2 mg baxdrostat (target number of participants: 30).
- Placebo (target number of participants: 15).

During the 8-week double-blind treatment period, participants should remain on their background antihypertensive treatment regimen. Doses of background medications should not be changed during this period unless participants experience SBP < CCI mmHg with symptoms of hypotension. Rescue therapy is permitted if the SBP or DBP exceeds 170 mmHg or 105 mmHg, respectively. The choice of rescue therapy is based on the Investigator's best clinical judgement, however the use of K^+-sparing diuretics and MRAs is prohibited.

An ACTH stimulation test using 250 µg ACTH will be performed at Visit 2 (Randomisation) prior to the first dose of study intervention and Visit 6 (Week 8) with cortisol measured before and after the stimulation test (CCI minutes after injection) (Fragoso Perozo et al, 2023). The ACTH stimulation testing procedure will be done locally at the site, but the serum cortisol measurement pre- and post-ACTH stimulation testing will be processed centrally. Participants need to be on treatment until ACTH stimulation test result is available, ie, treatment may last

up to 10 weeks depending on the availability of the ACTH stimulation test result or in case the test needs to be repeated. If applicable, the repeat tests shall be rescheduled as soon as possible to keep the duration of the treatment within 10 weeks. The IMP will be discontinued immediately following the completion of the repeated ACTH stimulation test.

Cortisol analysis will be performed using the CCI measured at a central laboratory. Cortisol level at CCI minutes after ACTH stimulation that is < CCI µg/dL at baseline (Visit 2) and EoT (Visit 6, Week 8) will be considered abnormal, indicating impaired cortisol reserve (Fragoso Perozo et al, 2023). An abnormal cortisol level after ACTH stimulation test at baseline (Visit 2), will result in the participant's discontinuation of the study intervention (See Section 7 for discontinuation details). At EoT (Visit 6, Week 8), in the rare incidence of an abnormal ACTH stimulated cortisol level, the participant will be asked to remain on treatment and to undergo repeat ACTH stimulated cortisol measurements during an unscheduled visit which will include cortisol measurements CCI minutes 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 will be considered normal. The results from the repeat test supersedes the original Week 8 results.

The following is a summary of different types of cortisol measurements at different timepoints:

- **AM serum cortisol without ACTH stimulation (8 AM ± 2 hours)**
  - Cortisol level ≥ CCI µg/dL is considered normal.
- **Routine serum cortisol collected before and CCI minutes after ACTH stimulation**
  - Cortisol level ≥ CCI µg/dL at CCI minutes after ACTH is considered normal.
- **Retest serum cortisol collected before, CCI minutes AND CCI minutes after ACTH stimulation**
  - Cortisol level ≥ CCI µg/dL at CCI minutes after ACTH stimulation is considered normal. Cortisol level ≥ CCI µg/dL at CCI minutes after ACTH stimulation is considered normal.
    Note: If only one of the two results is abnormal, the overall test will still be considered normal.

Further evaluation and management of the participant should be at the discretion of the Investigator, and if needed, in consultation with an endocrinologist.

Laboratory and safety visit timepoints are provided in the SoA Table 1.

After completing the 8-week double-blind treatment period (this period can be extended up to 10 weeks if waiting for ACTH results) or if participants permanently discontinue treatment earlier than 8 weeks, participants will return for an SFU, 14 days after the last dose.

A study diagram is presented in Figure 1 and study randomisation details are presented in Section 6.3.

The study is planned to be conducted in the United States in approximately 12 study sites.

4.2 Scientific Rationale for Study Design

The study design is developed to evaluate cortisol reserve in response to ACTH stimulation test in participants treated with baxdrostat.

4.2.1 Justification for Placebo Control

In this study, placebo is chosen as control to objectively assess the response after ACTH stimulation while on baxdrostat and to maintain the blind in this study design. In addition, inclusion of placebo control will ensure that any potential variations in cortisol reserve is accounted for. This will allow the evaluation of cortisol reserve in response to ACTH stimulation test in participants with uHTN.

4.2.2 Justification for Study Length

Baxdrostat maximal inhibition of CYP11B2 occurs by steady state over roughly 7 days (Freeman et al, 2023b). Thus, if cortisol suppression was to occur through inhibition of the enzyme, it should have occurred by steady state. Additionally, according to ICH guidance on technical requirements for clinical evaluation of new antihypertensive drugs (ICH E12, 2000), in studies involving a placebo group, participants cannot be without antihypertensive medications for more than 12 weeks. In this study, because it is a double-blind, placebo-controlled study with a 4-week screening period, this guideline is being adhered to by selecting an 8-week treatment period.

Thus, considering the baxdrostat mechanism of action, its PK/PD as well as efficacy/safety profiles, and the regulatory limitation on the duration of a placebo-controlled group needed to characterise cortisol reserve, AstraZeneca has designed the study with an 8-week treatment exposure.

4.3 Justification for Dose

Baxdrostat doses up to 2 mg OD were well-tolerated in participants in Phase II studies (CIN-107-121 and CIN-107-124), with a mild to moderate increase in serum K^+, mild hyponatraemia (decrease in Na^+) and a slight decrease in eGFR observed. More significant laboratory changes such as mild to moderate hyperkalaemia (K^+ level above normal range) or hyponatraemia were infrequent and well managed in the majority of instances. In less frequent

cases, brief dosing interruption was required and resulted in a return of electrolytes to normal levels. These laboratory parameter changes were not associated with significant clinical AEs. Sporadic hypotension and associated dizziness appeared to be mild.

The highest dose of baxdrostat being tested in the Phase III studies (D6970C00002 and D6970C00009 studies) is 2 mg. Therefore, the 2-mg dose was selected to evaluate the effects of baxdrostat on the cortisol reserve in the current study.

4.4 End-of-study Definition

For the purpose of CTT, the FDA regulatory requirements define 2 completion dates for the end of the study:

- Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.
- Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA (see Section 1.3).

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Male or female participant must be ≥ 18 years old, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Participants with mean seated SBP on AOBPM ≥ 130 mmHg and < 170 mmHg at screening (participants who do not meet this criterion may be rescreened at the Investigator's discretion, see Section 5.4.1).

3 Participants with mean seated SBP on AOBPM of ≥ 130 mmHg and < 170 mmHg at Randomisation (participants who do not meet this criterion may be rescreened at the Investigator's discretion, see Section 5.4.1).

4 Participants must have a stable regimen of ≥ 1 antihypertensive medication (at least one should be a diuretic), for at least 4 weeks prior to screening (participants who do not meet this criterion may be rescreened at the Investigator's discretion, see Section 5.4.1). Beta-blockers used to treat other conditions (ie, migraine, HF, coronary artery disease) should not be counted as an antihypertensive medication for the purpose of qualifying for this study.

5 Participants must have an eGFR ≥ 45 mL/min/1.73 m² at screening (participants who have an eGFR < 45 mL/min/1.73 m² may be rescreened at the Investigator's discretion, see Section 5.4.1).

6 Participants must have a serum K^+ level ≥ 3.5 and < 5.0 mmol/L at screening, determined as per central laboratory (participants who have serum K^+ levels < 3.5 mmol/L or ≥ 5.0 mmol/L may be rescreened at the Investigator's discretion, see Section 5.4.1).

7 Participants must have a morning cortisol (measured at 08:00 AM ± 2 hours) ≥ [redacted] µg/dL, determined as per central laboratory.

Sex and Contraceptive/Barrier Requirements

8 Specific to only female participants

Contraceptive used by female participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

(a) Females not of child-bearing potential are defined as females who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age specific requirements apply:

(i) Females < 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.

(ii) Females ≥ 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

(b) Female participants of child-bearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of child-bearing potential who are sexually active with a non-sterilised male partner must agree to use one highly effective method of birth control, as defined below, from 30 days before enrolment and throughout the study, and until at least 30 days after last dose of study intervention.

(i) The following are not acceptable methods of contraception: periodic abstinence (calendar, symptom-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only and lactational amenorrhoea. Female condom and male condom should not be used together.

(ii) All FOCBP must have a negative urine pregnancy test result at screening and not be at stage of breastfeeding. Urine pregnancy test may be replaced by a serum pregnancy test if required by local authorities.

(iii) Highly effective birth control methods include: total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study interventions); a vasectomised partner; bilateral tubal occlusion; intrauterine device/levonorgestrel intrauterine system; Implanon®; Depo-Provera™ injections. CCI [redacted] as it may affect the accuracy of the ACTH stimulation test. Therefore, progesterone only contraceptive methods are acceptable; however, oestrogen-containing contraceptive methods are not acceptable for the study.

Informed Consent

9 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

10 Provision of signed and dated written CCI [redacted] Information and Consent Form prior to collection of samples for CCI [redacted] that supports the CCI [redacted] (see Appendix D 2).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 As judged by the Investigator, any evidence which in the Investigator's opinion makes it undesirable for the participant to participate in the study.

2 Mean seated DBP on AOBPM ≥ 110 mmHg at Randomisation (participants who meet this criterion may be rescreened at the Investigator's discretion, see Section 5.4.1).

3 Prior treatment (within the 4 weeks before screening) with ARBs and ACEIs (both taken simultaneously).

4 Serum Na^+ level < 135 mmol/L at screening, determined as per central laboratory (participants who meet this criterion may be rescreened at the Investigator's discretion, see Section 5.4.1).

5 Participant with the following known secondary causes of HTN: renal artery stenosis, uncontrolled or untreated hyperthyroidism, uncontrolled or untreated hypothyroidism, pheochromocytoma, Cushing's syndrome, aortic coarctation.

6 NYHA functional HF Class IV at screening.

7 Medical history of stroke, acute coronary syndrome, hypertensive encephalopathy, or hospitalisation for HF within 6 months prior to randomisation or within the screening period.

8 Planned percutaneous coronary intervention/coronary artery bypass grafting or percutaneous coronary intervention/coronary artery bypass grafting done within 6 months prior to screening.

9 Known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease.

10 Left bundle branch block and any cardiac arrhythmia requiring treatment.

11 Known severe hepatic impairment, defined as Child-Pugh Class C, based on records that confirm documented medical history.

12 Uncontrolled diabetes with HbA1c > 10.0% (86 mmol/mol) at screening.

13 QTcF value > 470 ms at screening, unless having a pacemaker.

14 Family history of long QT syndrome.

15 Heart rate < 45 or > 110 beats/minute in a resting position, as per vital signs assessment.

16 Participants suspected to have severe cardiac hypertrophy.

17 Participants who are pregnant or breastfeeding.

18 Participants with a diagnosis of adrenal insufficiency or other disease affecting the adrenal gland.

19 Hypersensitivity reaction to cosyntropin injection, synthetic ACTH, or to any of the excipients.

20 Any of the following related to COVID-19 infection (participants who meet this criterion may be rescreened at the Investigator's discretion, see Section 5.4.1):

(a) Suspected (as judged by the Investigator) or confirmed COVID-19 infection within the last 4 weeks prior to screening or at Randomisation.

(b) Hospitalisation for COVID-19 within the last 12 weeks prior to screening.

Prior/Concomitant Therapy

21 Prior medical treatment with any MRAs, antiarrhythmic medications, or K^+-sparing diuretic used within 4 weeks prior to screening.

22 Treatment with K^+ binders within 8 weeks prior to screening.

23 Participant expected to receive or receiving any of the exclusionary drugs such as strong inducers of CCI , chronic use of NSAIDs (taken more than 3 times a week for more than 3 months).

24 Treatment with CCI prior to screening.

25 Treatment with CCI prior to Screening. See Section 6.9.1 for the list of medications.

26 Drugs that prolong QT should be avoided, if possible, and if there are other alternatives without the QT liability, these should be preferred. If such QT prolonging drugs are still needed, the Investigator must ensure appropriate monitoring of ECGs and electrolytes are performed, as per clinical judgement.

27 Current or prior treatment within 6 months prior to screening with cytotoxic therapy.

28 Treatment with K^+ supplements are not prohibited but should be continuously assessed and monitored throughout the study.

Prior/Concurrent Clinical Study Experience

1. Participation in another clinical study with an investigational product administered in the 3 months prior to randomisation in this study.
2. Participants with a known hypersensitivity to baxdrostat or drugs of the same class or any of its excipients.

Other Exclusions

3. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
4. Judgement by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.
5. Previous enrolment or randomisation in the present study.
6. Participants working shifts (ie, shifts that comprise working hours at different times on different days).

5.3 Lifestyle Considerations

No lifestyle restrictions such as diet, smoking habits, alcohol restrictions, etc are required to participate in this study.

Restrictions relating to concomitant medications are described in Section 6.9.

5.3.1 Meals and Dietary Restrictions

Generally, no dietary restrictions are required. Participants can take the study intervention with or without food. If participants have abnormal K^+ and/or Na^+, dietary counselling may be provided. Hyperkalaemia should be managed as per local standard-of-care (see Section 7.1).

Participants should be instructed to maintain their usual fluid intake as best as possible, unless additional oral hydration is needed. If the participant is suspected to be dehydrated, closer supervision, including K^+ monitoring is warranted (see Section 8.3.4.1 for K^+ monitoring). Investigators should also consider encouraging participants to limit K^+ rich foods intake and to follow other main guidelines, such as:

- Avoid drinking liquid from canned fruits or vegetables.
- Eat a variety of foods but in moderation.
- Moderate serving size for each meal.
- Always read the labels of any prepared foods.
- Leach one's favourite high K^+ vegetable to remove some of the K^+.

5.3.2 Caffeine, Alcohol, and Tobacco

Participants should not smoke or consume caffeinated beverages or food 30 minutes prior to assessment of AOBPM (see Section 8.3.2.1).

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from Regulatory Authorities. Minimal information includes demography, screen failure details, eligibility criteria, any SAE(s) and any concomitant medication(s) related to the SAE(s).

Data collected at screening are detailed in Section 8.1.

5.4.1 Rescreening

Individuals who do not meet the following criteria for participation in this study (screen

failures) may be rescreened, at the Investigator's discretion and only if the other criteria are met:

- Inclusion criteria 2, 3, 4, 5 and 6: Have a mean seated SBP on AOBPM ≥ 130 mmHg and < 170 mmHg at screening and at Randomisation; have a stable regimen of ≥ 1 antihypertensive medication (at least one should be a diuretic) for at least 4 weeks prior to screening; have an eGFR ≥ 45 mL/min/1.73 m² and a serum K^+ level ≥ 3.5 and < 5.0 mmol/L at screening, determined as per central laboratory.
- Exclusion criteria 2, 4 and 20: Have a mean seated DBP on AOBPM ≥ 110 mmHg at Randomisation; have a serum Na^+ level < 135 mmol/L at screening, determined as per central laboratory and any of the following related to COVID-19 infection:
  - Suspected (as judged by the Investigator) or confirmed COVID-19 infection within the last 4 weeks prior to screening or at Randomisation.
  - Hospitalisation for COVID-19 within the last 12 weeks prior to screening.

Rescreening is only allowed twice in the study. Rescreened participants should be assigned the same participant number as for the initial screening. A new informed consent is required to be signed for each rescreening.

Individuals who do not meet the eGFR, Na^+ and/or K^+ inclusion/exclusion criteria at screening for participation in the study, may have these laboratory parameters retested once at the Investigator's discretion.

5.5 Criteria for Temporarily Delaying Enrolment/Randomisation/ Administration of Study Intervention

Not applicable.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified IMPs and NIMPs intended to be administered to the study participants during the study conduct.

6.1 Study Interventions Administered

Study interventions and procedures to be administered and investigated in this study are described in Table 6.

Table 6 Study Intervention and Procedure

Arm name	**2 mg baxdrostat**	**Placebo**
Intervention name	Baxdrostat	Placebo

Table 6 Study Intervention and Procedure

Arm name	**2 mg baxdrostat**	**Placebo**
Type	Drug	Drug
Dose formulation	Tablet	Tablet
Unit dose strengths	2 mg per tablet	N/A
Dosage levels	2 mg baxdrostat OD	Placebo OD
Route of administration	Oral	Oral
Regimen	One tablet per day, preferably in the morning	One tablet per day, preferably in the morning
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca
Packaging and labelling	Study intervention will be provided in blister packs containing IMP tablets. Each blister pack will be labelled as required per country requirement.	Study intervention will be provided in blister packs containing IMP tablets. Each blister pack will be labelled as required per country requirement.

The external label and appearance of all tablets, for all study interventions, will be the same in order to keep the blind.
AxMP = Auxiliary medicinal product; IMP = Investigational medicinal product; N/A = Not applicable; NIMP = Non-investigational medicinal product; OD = Once daily.

Study intervention will be given to participants at the study visits summarised in the SoA (see Section 1.3) and participants will self-administer doses of 2 mg baxdrostat or placebo orally OD at home during the non-study visits.

The following medicinal products are defined as NIMP/AxMP in this study and will be obtained by the study participants.

- Background antihypertensive medications: The stable regimen of background antihypertensive medication that participants receive when they are enrolled in this study (see Section 4.1 for more details) and which they will continue receiving after they are randomised to study intervention. Doses of background medications should not be changed during this period unless participants experience SBP < CCI mmHg with symptoms of hypotension.
- Rescue antihypertensive medications: Rescue therapy is permitted if the SBP or DBP exceeds 170 mmHg or 105 mmHg, respectively. The choice of rescue therapy is based on

the Investigator's best clinical judgement; however, the use of K^+-sparing diuretics and MRAs is prohibited.

The ACTH stimulation test performed to assess the cortisol reserve is also defined as NIMP/AxMP and will be either sourced locally (by the site) or provided centrally by the CRO (as needed). This test will be performed with a single intravenous injection of 250 µg ACTH (cosyntropin injectable solution) at Visit 2 (Randomisation) and Visit 6 (EoT).

All NIMPs/AxMPs used in this clinical study are authorised and are to be used in accordance with the terms of their marketing authorisations.

6.2 Preparation, Handling, Storage, and Accountability

The IMP should be stored in accordance with the product labelling. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range.

The Investigator or designee (eg, unblinded pharmacist) must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received at the site and throughout the entire study until authorisation is provided for on-site destruction or removal of the IMP, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying AstraZeneca (or designated party); release of IMP for clinical use can only occur once the event has been reviewed and approval is provided by AstraZeneca (or designated party).

Only participants enrolled in the study may receive study intervention, and only authorised site staff may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

The Investigator or authorised site staff are responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual. Additionally, concomitant medication compliance will be verified as per local standards/guidelines.

6.3 Assignment to Study Intervention

All participants who meet all the eligibility criteria (see Section 5.1) and none of the exclusion criteria (see Section 5.2) will be centrally assigned to randomised study intervention using an

automated IRT/RTSM system that will allocate participants into 2:1 ratio to one of the 2 treatment arms:

- 2 mg baxdrostat (target number of participants: 30).
- Placebo (target number of participants: 15).

Randomisation will be performed in balanced blocks of fixed size. The randomisation codes will be computer generated and loaded into the IRT/RTSM database.

All randomisations will be performed by the Investigator directly using the IRT/RTSM system. No randomisation codes are to be reused.

Randomisation information will be concealed from the Investigators, the participants, and the study team until all participants have completed the study, except for an emergency situation involving a participant that requires unblinding of the treatment assignment (see Section 6.4).

Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site.

6.3.1 Incorrectly Enrolled/Randomised Participants

In the event that a participant is incorrectly enrolled/randomised, the Study Medical Monitor will discuss with the Sponsor the risk/benefit for the participant of continuing in the study (please refer to Section 7.1.3 and Section 7.1.4 for temporary interruption and permanent interruption of study intervention).

6.4 Blinding

This is a randomised, double-blind study where neither the participants nor the Sponsor or Investigator will know which intervention participants are receiving until study completion.

During the 8-week double-blind treatment period, the IRT/RTSM will provide to the Investigators, the kit identification number to be allocated to each participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each site.

The IRT/RTSM will be programmed with blind-breaking instructions. The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. Participant safety must always be the first consideration in making such a determination. The Investigator will document and report any blind break to AstraZeneca, without revealing the treatment given to the participant to other clinical site or blinded study personnel. If a participant's intervention assignment is unblinded, AstraZeneca must be notified within 24 hours after breaking the blind.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study intervention and that potentially require expedited reporting to Regulatory Authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

Pharmacokinetic samples will be analysed by the bioanalytical laboratory performing the bioanalyses only for participants on active treatment, as referenced in Section 8.5.2. To allow for the appropriate selection of samples, the bioanalytical laboratory will, therefore, have access to the treatment codes but will not share the codes with the Sponsor or others involved in the study until the blinding is broken for the study.

Pharmacokinetic and PD results from the central laboratory will be blinded.

6.5 Study Intervention Compliance

When participants are dosed at the site, during on-site visits specified in the SoA (see Section 1.3), they will receive study interventions directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study interventions at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the quantity of IMPs dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates will also be recorded in the eCRF.

Compliance with study intervention will be documented in the source documents and eCRF as follows:

- Study intervention exposure measured by treatment interruptions and/or treatment discontinuation will be recorded in the eCRF using the exposure form. Intervention start and stop dates will also be recorded in the eCRF.

6.6 Dose Modification

Dose modification of baxdrostat is not permitted in this study. For stopping study intervention due to safety or other reasons, please see Section 7.

6.7 Continued Access to Study Intervention After the End of the Study

Participants will have no access to study intervention beyond completion of the study. The recommendation will be to treat the participant according to guidelines.

6.8 Treatment of Overdose

Overdose refers to the administration of a quantity of the study intervention given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol.

For this study, any dose of baxdrostat greater than 2 mg per day will be considered an overdose.

The most likely manifestations of an overdose based on the mechanism of baxdrostat action would be hypotension, hypovolaemia, and hyperkalaemia, which would require supportive measures to maintain hydration, electrolyte balance and vital functions.

In the event of an overdose, the Investigator should:

- Evaluate the participant to determine, in consultation with the Study Clinical Lead, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled Follow-up Visit. Refer to Section 8.4.11 for details of AE/SAE reporting related to overdose.
- Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study intervention if requested by the Study Clinical Lead (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.
- Treat overdose symptoms using clinical judgement.

6.9 Prior and Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant (except for screen failures) is receiving at the time of enrolment or receives during the study must be recorded in the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.

- Dosage information including dose, frequency, and route.

The Study Clinical Lead should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Prohibited Concomitant Medications

The medications and supplements listed below are prohibited during this study:

- Potassium-sparing diuretics (eg, amiloride, triamterene) and direct renin inhibitor (eg, aliskiren).
- Mineralocorticoid receptor antagonists or aldosterone antagonists (eg, eplerenone, finerenone, spironolactone).
- CCI
- CCI
- Once enrolled, treatment with any form of CCI or on over the counter CCI while enrolled in the study, and treatment with CCI at any dose.

6.9.2 Restricted Concomitant Medications

The medications and supplements listed below are restricted during this study:

- CCI
- Simultaneous use of ARBs and ACEIs (participants should be on stable dose of either drug class; any changes to drug dose or class must be closely monitored).
- Potassium binders (prohibited at screening but can be started as a corrective action during the study).
- Tacrolimus, calcineurin inhibitors and cyclosporin (topical/inhaled immunosuppressants are permitted).
- Chronic NSAID use (taken more than 3 times a week for more than 3 months. Occasional NSAID usage is permitted; however, closer monitoring is warranted at these times).
- Strong CCI
- Treatment with K^+ supplements is not prohibited but should be continuously assessed and monitored throughout the study (see Section 8.3.4.1 for K^+ laboratory measurements).

6.9.3 Rescue Medicine

The study sites will be responsible for prescribing rescue antihypertensive medications, which are categorised as NIMP/AxMP in this study (see Section 6.1).

Rescue therapy is permitted if the SBP or DBP exceeds 170 mmHg or 105 mmHg, respectively. The choice of rescue therapy is based on the Investigator's best clinical judgement; however, the use of K^+-sparing diuretics and MRAs is prohibited.

The start date of rescue antihypertensive medication administration as well as the name and dosage regimen of the rescue antihypertensive medication must be recorded.

During this study, participants should remain blinded to the study intervention while receiving rescue therapy.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole is handled as described in Appendix A.

7.1 Discontinuation of Study Intervention

Note that discontinuation from study intervention is not the same thing as a discontinuation or withdrawal from the study (see Section 7.2).

In case of abnormal ACTH stimulated cortisol values at baseline, participant discontinues the study intervention and follows steps as described below.

If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study in order to complete the EoT Visit and the SFU Visit, for details see Section 7.1.4. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in the algorithm (see Appendix E) or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, or if the Investigator believes that it is in best interest of the participant.

7.1.2 QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline [which is the Screening Visit value] in QT interval corrected using QTcF) after enrolment, the Investigator or qualified designee will determine if the participant can continue

on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Any QTcF value ≥ CCI ms should be evaluated thoroughly for accuracy of the ECG measurement and the electrolytes should be corrected, if needed. If the QTcF value decreases and there is another explanation for the QT prolongation, eg, another drug with QT prolongation effect, the restart of the study intervention may be considered, and study intervention will not be permanently stopped (see Section 7.1.3). On the contrary, if there are no other factors that could explain the QTcF value being CCI ms or higher, study intervention will have to be permanently discontinued (see Section 7.1.4).

7.1.3 Temporary Interruption of Study Intervention

Study intervention will be temporarily interrupted in the following situations:

- If a participant has a QTcF ≥ CCI ms, study intervention will be temporarily interrupted at first and may be permanently discontinued afterwards. See details in Section 7.1.2.
- Hypotension: If the participant's SBP is ≤ CCI mmHg, the study intervention should be temporarily interrupted and may be restarted only if an alternative aetiology for symptomatic hypotension has been identified and the event has fully resolved. If study intervention is resumed, SBP should be re-checked at an unscheduled visit within 7-10 days (± 4 days) from restart of study intervention but can be re-checked at the next study visit if it falls within the suggested window.
- Hyponatraemia: If the participant's Na^+ level is < CCI mmol/L, the participant may remain on study intervention; however, the Na^+ should be re-checked within 72 hours by the central laboratory and the participant should be instructed to reduce free water consumption prior to retesting. If the laboratory retest confirms Na^+ < CCI mmol/L, the study intervention should be temporarily interrupted. The study intervention may be restarted when the Na^+ has increased to > CCI mmol/L. Sodium should then be re-checked by the central laboratory within 7-10 days (± 4 days) from restart of study intervention.
- Hyperkalaemia should be managed as per local standard-of-care. Participants may be treated acutely or chronically with K^+ binding agents, at the discretion of the Investigator and treating physicians.

  Study-specific discontinuation criteria and management regarding K^+ are described below. Inappropriate sample handling/storage or lengthy transport time to local/central laboratory may result in falsely elevated K^+ levels in analysed blood samples. It is expected that local laboratory results (from either serum/plasma samples) will be available prior to central laboratory results and expected to take priority for decision-making/monitoring:

  - If K^+ is ≥ CCI to < CCI mmol/L, the participant may remain on study intervention; however, the K^+ should be re-checked within 72 hours by the local and/or central laboratory and if confirmed ≥ CCI mmol/L, the study intervention should be temporarily interrupted.
  - If K^+ is ≥ CCI mmol/L, immediately temporarily interrupt study intervention, manage as per local standard-of-care and re-check K^+ within 72 hours by the local and/or central laboratory. If the repeated K^+ measurement is also ≥ CCI mmol/L, refer to Section 7.1.4 for permanent study intervention discontinuation details.
  - The study intervention may be restarted when K^+ level is ≤ CCI mmol/L. Potassium should then be re-checked by the local and/or central laboratory within 2-7 days from restart of study intervention.

    For further details on K^+ laboratory measurements see Section 8.3.4.1.

- Participants with signs and symptoms of AI should remain on treatment (either baxdrostat or placebo), unless severe signs and symptoms of adrenal insufficiency are present, in which case the treatment should be temporarily discontinued. In any case of AI signs and symptoms, an ACTH stimulation test should be performed (see Section 8.4.5.1). If the ACTH stimulation test:
  - has an abnormal result, and the participant is diagnosed with AI, the participant is recommended to be referred to an endocrinologist for management and treatment should be permanently discontinued, see Section 7.1.4.
  - has a normal result, the participant will not undergo additional workup for AI and he/she will continue the study as planned.

7.1.4 Permanent Discontinuation of Study Intervention

Participants may be permanently discontinued from the study intervention in the following situations:

- Participant decision: The participant is at any time free to discontinue treatment, without prejudice to further treatment.
- An AE that, in the opinion of the Investigator or AstraZeneca, warrants discontinuation from further dosing.
- Severe non-compliance with the CSP. Safety reasons as judged by the Investigator where continued treatment may put participant at undue risk.
- If the participant becomes pregnant during the study (see Section 8.4.9).
- The participant has a mean seated SBP and seated DBP that exceeds 170 mmHg and 105 mmHg, respectively, in 2 separate occasions, despite rescue therapy being given after each of these 2 occasions (see Section 6.9.3). See Section 8.3.2.1 for BP measurement procedures.

- Hypotension: If the participant's SBP is ≤ CCI mmHg and the participant has symptoms that do not have an alternative aetiology for symptomatic hypotension other than the study intervention, the study intervention must be permanently discontinued.
- Hyponatraemia: Permanently discontinue study intervention if a participant experiences a recurrent hyponatraemia event (post-randomisation Na^+ level is < CCI mmol/L) after a previous event (see Section 7.1.3), if there was no explanation for the recurring event other than restarting study intervention.
- Hyperkalaemia: Permanently discontinue study intervention if a participant experiences a recurrent hyperkalaemia event ($K^+ \geq$ CCI mmol/L) after a previous event (see Section 7.1.3), if there was no explanation for the recurring event other than restarting study intervention. See Section 8.3.4.1 for further details on K^+ laboratory measurements.
- Participants who develop adrenal insufficiency during the study, confirmed as per the ACTH stimulation test (see Section 7.1.3), should discontinue the study intervention, and remain in the study for continued safety surveillance. In this situation an attempt should be made to establish whether the participant has primary, secondary or tertiary adrenal insufficiency. Refer to Section 8.3.4 for additional details.
- Participants who are under temporary interruption of the study intervention when they reach Visit 5, and for which the Investigator deems not possible to restart the study intervention during that specific visit, need to be permanently discontinued from the study intervention. Details for this permanent discontinuation should be recorded in the eCRF.

If the study intervention is permanently discontinued, the participant will undergo an EoT Visit (including ACTH stimulation cortisol testing), ideally scheduled as soon as possible at the time of discontinuation or premature withdrawal from the study intervention. Following the EoT Visit, the participant will then proceed to complete the final SFU Visit as per SoA (see Section 1.3). If the EoT Visit is conducted > 10 days after the last administered dose, the assessments outlined in the SFU Visit will be performed during the EoT Visit.

7.1.5 Rechallenge

7.1.5.1 Study Intervention Restart or Rechallenge After Liver Stopping Criteria Are Met

Study intervention restart, after liver chemistry stopping criteria are met, is allowed in this study. If the participant meets liver chemistry stopping criteria, do not restart the participant with study intervention unless:

- Sponsor approval **is granted.**
- IEC and/or IRB approval is obtained, if required.

NOTE: If study intervention was interrupted for suspected intervention-induced liver injury, the participant should be informed of the risk of death, liver transplantation, hospitalisation, and jaundice.

Refer to Appendix E for details on the study intervention restart process.

If the Sponsor approval to restart the participant with study intervention is **not granted**, then the participant must permanently discontinue study intervention and may continue in the study for protocol-specified follow-up assessments.

7.2 Participant Discontinuation/Withdrawal from the Study

Discontinuation from the study describes specific situations where the Investigator ends the individual's participation in the study. Withdrawal from the study describes a participant's voluntary decision to end their participation in the study.

Discontinuation of the participant from the study by the Investigator:

- A participant may be discontinued from the study at any time at the discretion of the Investigator for behavioural or compliance reasons.
- At the time of discontinuing from the study, if the participant has not been discontinued from the study intervention, see Section 7.1.

Voluntary withdrawal from the study by the participant may occur in the following situations:

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason). A participant who prematurely withdraws consent from the study will have an early EoT Visit performed at the time of the withdrawal or as soon as possible, preferable with 2 weeks.
- A participant who wishes to withdraw from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records). If a participant agrees to a modified follow-up until the end of the study, he/she will not be considered withdrawn from the study.
- If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If the participant withdraws from the study, AstraZeneca may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the Investigator and the

Investigator must inform the Local and Global Study Team. Destruction of any samples taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation.

Participants who develop signs and symptoms, which may indicate adrenal insufficiency during the study should remain on treatment unless severe signs and symptoms develop, should undergo ACTH stimulation testing, and stay in the study for continued safety surveillance. Refer to Section 8.4.5.1 for additional details.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant should be counselled on the importance of maintaining the assigned visit schedule. At this time ascertain whether the participant should or wishes to or continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, texts, emails, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have been lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (see Section 1.3). Protocol waivers or exemptions are not allowed. Descriptions of the scheduled evaluations are outlined in the subsections below. Before study entry, throughout the study and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and efficacy assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. Such unscheduled assessments will be captured in the protocol-specific database as appropriate.

- The Investigator ensures the accuracy and completeness of eCRFs, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will electronically sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.
- Urgent safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Instructions for the collection and handling of HBS will be provided in the study-specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on handling of HBS see Appendix C.

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by AstraZeneca or the Investigator, as per local health authority/ethics requirements.

Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

8.1 Administrative and General/Baseline Procedures

Screening and randomisation procedures will be performed as specified in the SoA (see Section 1.3).

For all participants, the following data will be collected:

- At screening:
  - Obtain informed consent
  - Eligibility criteria (see Section 5)

- Demography details
- Participant's medical/surgical history
- Collection of concomitant medications (see Section 6.1 and Section 6.9)
- Safety assessment data (complete physical examination, 12-lead ECG, and vital signs; see Section 8.3)
- Safety laboratory collection (whole safety panel including creatinine analysis for eGFR calculation and measurement of Na^+ and K^+ blood levels), cortisol values,HbA1c, FSH, and urine pregnancy test (see Section 8.3.4)
- Any SAEs occurring from the time of signing the ICF (see Section 8.4.8)

- At randomisation:
  - Confirmation of eligibility criteria (see Section 5)
  - Reporting of concomitant medications (see Section 6.1 and Section 6.9)
  - Safety assessment data (complete physical examination and vital signs; see Section 8.3)
  - Safety laboratory collection (whole safety panel including creatinine analysis for eGFR calculation and measurement of Na^+ and K^+ blood levels), K^+ measurements, urine pregnancy and dipstick tests (see Section 8.3.4)
  - Optional CCI samples for CCI research (see Section 8.7)
  - Any AEs occurring from randomisation throughout the study intervention period including the SFU period (see Section 8.4)

The following data for screen failures will be collected at screening: demography details, eligibility criteria (reason for screen failure), any SAE(s), and any concomitant medication(s) related to the SAE(s).

8.1.1 Demographics

The Investigator, or designee, will record the participant's sex, age, race, and ethnicity at screening.

8.1.2 Medical/Surgical History

The Investigator, or designee, will record, at screening, any significant medical or surgical history of the participant along with the year in which such medical issue began (if known) or when the medical surgery was performed.

8.2 Efficacy Assessments

Not applicable.

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (see Section 1.3).

8.3.1 Physical Examinations

Physical examination will be performed at timepoints as specified in the SoA (see Section 1.3).

A complete physical examination will be performed by the Investigator or a suitably qualified medical designee and include assessments of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems. Additionally, height will be measured during the Screening Visit.

A targeted physical examination will be conducted at the SFU Visit and will include, at a minimum, assessments of the lung and cardiovascular evaluations, and examination of any peripheral oedema.

8.3.2 Vital Signs

Vital signs will be performed at timepoints as specified in the SoA (see Section 1.3).

Vital signs will include seated attended office automated BP, pulse rate and body weight measurements. Blood pressure will be measured using the standardised procedures described in Section 8.3.2.1.

Deterioration of vital signs compared to screening/randomisation values, should only be reported as AEs if these values meet the criteria listed in Section 8.4.4 and/or Section 8.4.6.

8.3.2.1 Seated Blood Pressure Measurements

Seated BP measurements will be recorded using standardised automated BP machines and using the following standardised procedures:

- Participants should not exercise, smoke, or consume caffeinated beverages or food 30 minutes prior to assessment of AOBPM.
- Participants should be seated for at least 5 minutes in the examination room with the back supported, feet flat on the floor.
- Mean seated BP is defined as the average of 2 seated BP measurements.

Extreme reduction of BP measurements between screening and randomisation values should only be reported as AEs if these meet the criteria listed in Section 8.4.4.

8.3.3 Electrocardiograms

Twelve-lead ECGs will be performed at timepoints as specified in the SoA (see Section 1.3).

Electrocardiograms will be performed after the participant has been resting in supine position for at least 5 minutes. Twelve-lead ECGs will be printed and will be evaluated as soon as possible for the presence of abnormalities by a qualified physician.

Standard 12-ECG parameters will be measured, and the following 12-ECG parameters will be recorded:

- Heart rate and heart rhythm.
- QRS, PR, RR, QT and QTc (QTcF) intervals (see Section 7.1.2 for QTc stopping criteria details).

An ECG machine that automatically calculates the heart rate and rhythm, and measures PR, QRS, QT, and QTc intervals, will be used. Interpretation of the clinical safety ECG findings will be reviewed and confirmed by the Investigator.

Investigators should contact AstraZeneca or designee if any clinically meaningful changes from baseline (Screening Visit value) are noted on review (see Section 8.4.4 for ECG-related abnormalities that should be reported as AEs).

8.3.4 Clinical Safety Laboratory Tests

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the visits indicated in the SoA (see Table 2 in Section 1.3).

The clinical chemistry and haematology analyses will be performed at a central laboratory. The date of sample collection will be recorded on the appropriate eCRF. Sample tubes and sample sizes will be described in the Laboratory Manual. Please see Section 8.3.4.1 for details on K^+ measurements.

The following laboratory variables will be measured (Table 7).

Table 7 Laboratory Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum)
Haemoglobin	Creatinine [a,b]
Leukocyte count	TBL
Leukocyte differential count (absolute count)	ALP
Platelet count	AST
HbA1c [c]	ALT

Table 7 Laboratory Variables

RBC count	Albumin
Urinalysis (dipstick; urine) [e]	K^+ [b]
Haemoglobin/Erythrocytes/Blood	Calcium, total
Protein/Albumin	Na^+ [b]
Glucose	Magnesium
Leucocytes	Bicarbonate
Nitrites	Phosphate
Pregnancy test [d]	**Hormonal Analysis (serum)**
	FSH [c]
	β-hCG [d]

[a] eGFR will be calculated every time the creatine is collected (at all visits) using the creatinine results obtained from blood samples.
[b] Creatinine, K^+ and Na^+ will be measured centrally at every study visit that is scheduled between Screening (Visit 1), and EoT(Visit 6).
[c] Only measured at Screening (Visit 1).
[d] Urine pregnancy tests will be performed at Screening (Visit 1), Randomisation (Visit 2), Double-blind Period (Visit 5), EoT (Visit 6), and Safety Follow-up (SFU Visit) for FOCBP. However, these can be replaced by serum pregnancy tests (serum pregnancy test will be performed centrally).
[e] Dipstick urinalysis is only performed locally at Randomisation (Visit 2).
ALP = Alkaline phosphatase; ALT = Alanine aminotransferase/transaminase; AST = Aspartate aminotransferase/transaminase; β-hCG = Beta-human chorionic gonadotropin; eGFR = Estimated glomerular filtration rate; EoT = End of treatment; FOCBP = Female(s) of child-bearing potential; FSH = Follicle stimulating hormone; HbA1c = Glycated haemoglobin; K^+ =Potassium; Na^+ = Sodium; RBC = Red blood cells; TBL = Total bilirubin.

In case a participant shows an AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, please refer to Appendix E, for further instructions and see Section 8.4.4 for AEs based on examination tests. If TBL value is elevated, the laboratory should also report the direct and indirect bilirubin values. Further details are described in the Laboratory Manual.

Potassium values measured in the local laboratories will prevail over the results obtained in the central laboratory to assess for hyperkalaemia. Potassium values will be collected in the eCRF if they meet the criteria for hyperkalaemia AE (see Section 8.4.6.1).

The eGFR will be monitored systemically throughout the study by the central laboratory. The eGFR will be calculated using the creatinine results obtained from blood sample analysis and using the CKD-EPI 2021 equation, which is as follows:

$$eGFR = 142 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.9938^{age} \times 1.012 \text{ [if female]}$$

Where, Scr is standardised serum creatinine (mg/dL); κ is 0.7 for females and 0.9 for males; α is -0.241 for females and -0.302 for males; min indicates the minimum of Scr/κ or 1 and max indicates the maximum of Scr/κ or 1. Age is expressed in years (Inker et al, 2021).

8.3.4.1 Potassium Laboratory Measurements

Serum K^+ levels will be monitored systemically throughout the study. Potassium will be measured in both, the central and local laboratories, and will be measured at the times specified in SoA (see Section 1.3). Both serum and plasma K^+ tests will be acceptable, as per local practice. Local laboratory sample values will be used for safety decision-making at site level and central laboratory samples will be used for analysis purposes. Potassium results from the local laboratories will be recorded on the eCRF only if they meet AE criteria.

Unscheduled assessments of K^+ levels should be planned at the Investigator's discretion (eg, for a follow-up of elevated K^+ levels, after changing concomitant medications which may affect serum K^+ levels and/or renal function [eg, NSAIDs/ACEIs/ARBs/nephrotoxic agents], following acute changes in the clinical condition or when there is suspected dehydration, vomiting/diarrhoea, etc). Patients taking K^+ supplements must have closer supervision.

Repeated and unscheduled testing for K^+ should be measured at both, the local and central laboratories (see Section 7.1.3 and Section 7.1.4 for temporary interruption and permanent discontinuation criteria of the study intervention, respectively, based on K^+ levels).

Potassium levels will be reported in the eCRF in case of hyperkalaemia (see Section 8.4.6.1).

8.4 AEs, SAEs, and Other Safety Reporting

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorised representative) will notify the Investigator or designees of symptoms. These must then be assessed by the Investigator and if considered an AE it will be reported by the Investigator.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

AE Variables

The following variables will be collected for each AE:

- AE (verbatim)

- The date when the AE started and stopped
- Maximum intensity (mild, moderate, severe)
- Whether the AE is serious or not
- Investigator causality rating against the IMPs (yes or no)
- Action taken with regard to IMPs
- AE caused participant's withdrawal from the study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE description
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from Randomisation (Visit 2) throughout the treatment period and including the SFU period but excluding at Visits 3 and 4.

Serious adverse events will be recorded from the time of signing the ICF.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a treated participant, the Investigator shall, without undue delay, report the SAE to AstraZeneca (see Section 8.4.8 for details on reporting of SAEs).

8.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or visit in the study are followed up by the Investigator for as long as medically indicated, but without further

recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.4.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.4.4 AEs Based on Examinations and Tests

Deterioration as compared to baseline/randomisation in protocol-mandated laboratory values and/or vital signs should only be reported as AEs if they meet any of the following:

- Fulfil any of the SAE criteria.
- Are the reason for discontinuation of the study intervention.
- Are clinically relevant as judged by the Investigator (which may include but is not limited to consideration as to whether intervention or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline/randomisation assessment will be reported as an AE unless unequivocally related to the DUS.

The results from the protocol-mandated laboratory tests and vital signs will be summarised in the CSR.

8.4.5 AEs Based on Signs and Symptoms

All signs or symptoms spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous

visit', or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.5.1 CCI

CCI

8.4.6 Adverse Events of Special Interest

The Investigator will monitor each participant for clinical and laboratory evidence for pre-defined AESIs throughout his or her participation in this clinical study.

The Investigator will assess and record any additional information on the AESI in detail on an AE form which must be submitted as per standard timelines for AEs. The Investigator should assess possible contributing factors to the AESI and record these in the eCRF.

For this clinical study, AESIs include the following: hyperkalaemia, hyponatraemia and hypotension events CCI. These events consist of high K^+ in blood, abnormally low Na^+ concentration in blood and abnormally low BP, respectively. These AESIs will be confirmed by a clinician.

Potassium and Na^+ levels will be measured in the clinical laboratory analysis (see Section 8.3.4), using the blood samples extracted at the timepoints specified in the SoA (see Table 2 in Section 1.3). Blood pressure will be measured as detailed in Section 8.3.2.1. During the course of the study, additional AESIs may be identified by AstraZeneca. All AESIs must be recorded in the eCRF.

8.4.6.1 Hyperkalaemia

An AESI of hyperkalaemia is an event of high K^+ levels CCI mmol/L) in serum CCI

Local laboratory K^+ values for all events of hyperkalaemia that fulfil the AE reporting criteria should be recorded in the specific eCRF form (see Section 8.3.4.1 for K^+ laboratory measurement details).

8.4.6.2 Hyponatraemia

An AESI of hyponatraemia is an event of low Na^+ levels [redacted] mmol/L) in serum [redacted]

8.4.6.3 Hypotension

An AESI of hypotension is an event of low SBP (eg, [redacted] mmHg) [redacted]

8.4.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.4.8 Reporting of SAEs

All SAEs must be reported whether or not considered causally related to the study intervention. All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety DES **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports the SAE via secure method to the appropriate AstraZeneca representative.

When the EDC is temporarily not accessible, the AstraZeneca Study Representative should confirm that the Investigator/site staff enters the SAE in the AstraZeneca EDC when access resumes.

For further guidance on the definition of an SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca IMP.

8.4.9 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention.
- Pregnancies in the partner of male participants.

Participants will give consent on enrolment that the Investigator will report any pregnancy to AstraZeneca and that further information will be collected until delivery.

8.4.9.1 Maternal Exposure

If a participant becomes pregnant during the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives immediately but no later than **24 hours** after he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety DES **within one or 5 calendar days** for pregnancies associated with SAEs (see Section 8.4.8) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

Pregnancies will be reported in the eCRF. The PREGREP module in the eCRF is used to report the pregnancy and the paper based PREGOUT module is used to report the outcome of the pregnancy.

8.4.9.2 Paternal Exposure

Male study participants do not require to use contraception. There is no restriction on male participants fathering children or donating sperm during the study.

8.4.10 Medication Error, Drug Abuse, and Drug Misuse

8.4.10.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.4.8) and **within 30 days** for all other events.

8.4.10.2 Medication Error

For the purposes of this clinical study, a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix B 4.

8.4.10.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.4.10.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.4.11 Reporting of Overdose

Refer to Section 6.8 for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnoses/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP or AstraZeneca NIMP occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety DES **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.4.8) and **within 30 days** for all other overdoses.

8.5 Pharmacokinetics

Pre-dose plasma samples will be collected for measurement of plasma concentrations of study intervention at the central laboratory as specified in the SoA (see Section 1.3).

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the Investigator and AstraZeneca, eg, for urgent safety reasons, and this may be reflected as a protocol deviation.

The timing of sampling may be altered during the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Plasma samples will be used to analyse the exposure of baxdrostat. Samples collected for analyses of baxdrostat concentration in plasma may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

For storage, re-use, and destruction of samples for PK, see Appendix C.

Pharmacokinetics samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier).

Additional analyses may be conducted on the anonymised, pooled, or individual PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.1 Collection of Samples for Pharmacokinetics

All PK samples will be collected pre-dose; thus, participants should be reminded not to take their study intervention at home on the day of Visit 5 (Week 4) as they will receive study intervention in clinic on that day.

8.5.2 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by Labcorp, on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Drug concentration information that could unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

Pharmacokinetic samples will be analysed only for participants on active treatment. Placebo samples will not be analysed unless there is a need to confirm that correct treatment has been given to study participants (please see Section 6.4).

8.6 Pharmacodynamics

Blood sample collection for cortisol and ACTH stimulation test procedures are described in Section 8.6.1 and Section 8.6.2, respectively.

8.6.1 Collection of Samples for Pharmacodynamics

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Blood samples will be collected for measurement of cortisol at timepoints planned in the SoA (see Section 1.3).

For storage, re-use, and destruction of samples for PD, see Appendix C.

8.6.2 ACTH Stimulation Test and Cortisol Level Measurement

An ACTH stimulation test using 250 µg ACTH will be performed at Visit 2 (randomisation) and Visit 6 (EoT; Week 8), with serum cortisol level measured before and CCI minutes after ACTH stimulation test, based on Butt et al, 2020. Please refer to Section 6.1 for further details on the ACTH stimulation injection kit.

The cortisol analysis will be performed by a central laboratory using the CCI CCI (Javorsky et al, 2021, Fragoso Perozo et al, 2023). A cortisol level

CCI minutes after ACTH stimulation test that is < CCI µg/dL will be considered abnormal, indicating impaired cortisol reserve. The procedure steps are as follows:

1 Start ACTH (also called cosyntropin) stimulation testing at 8.00 AM (± 2 hours).
2 Perform blood draw to measure serum cortisol level prior to ACTH stimulation testing.
3 Dilute 250 µg cosyntropin in 2 to 5 mL of normal saline and inject intravenously over 2 minutes.
4 Perform blood draw to measure serum cortisol level CCI minutes after ACTH stimulation testing.
5 Ship all blood samples (pre- and the two post-ACTH stimulation) to the central laboratory as per Laboratory Manual.

If the participant has abnormal cortisol levels at Week 8, the participant should remain on treatment until a repeat ACTH testing has been performed, ie, treatment may last for up to 10 weeks. It is recommended that participants with abnormal ACTH stimulation test results be referred to an endocrinologist for evaluation. The procedure steps are as follows for repeat ACTH stimulation and cortisol collection:

1 Start ACTH (also called cosyntropin) stimulation testing at 8.00 AM (± 2 hours).
2 Perform blood draw to measure serum cortisol level prior to ACTH stimulation testing.
3 Dilute 250 µg cosyntropin in 2 to 5 mL of normal saline and inject intravenously over 2 minutes.
4 Perform blood draw to measure serum cortisol level CCI minutes after ACTH stimulation testing.
5 Perform blood draw to measure serum cortisol level CCI minutes after ACTH stimulation testing.
6 Ship both blood samples (pre- and post-ACTH stimulation) to the central laboratory as per Laboratory Manual.

8.7 CCI

Collection of optional samples for CCI is also part of this study as specified in the SoA (see Section 1.3) and is subject to participant agreement in the optional CCI information ICF.

CCI sample for CCI isolation will be collected from participants who have consented to participate in the CCI analysis component of the study. Participation is optional. Participants who do not wish to participate in CCI research may still participate in the study.

See Appendix D for information regarding the [redacted] samples. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices of this protocol or in the Laboratory Manual.

8.8 Biomarkers

Not applicable, biomarkers are not evaluated this study.

8.9 Immunogenicity Assessments

Not applicable, immunogenicity is not assessed in this study.

8.10 Medical Resource Utilisation and Health Economics

Not applicable, health economics/medical resource utilisation and health economics parameters are not evaluated in this study.

8.11 Study Participant Feedback Questionnaire

Participants feedback questionnaires will not be utilised in this study.

9 STATISTICAL CONSIDERATIONS

Any changes to the methods described in the SAP will be described and justified as needed in the CSR.

9.1 Statistical Hypotheses

Statistical analyses will be descriptive in nature, without formal statistical hypothesis testing.

9.2 Sample Size Determination

This study is planning to randomise approximately 45 participants using a 2:1 ratio to either receive 2 mg baxdrostat OD or placebo OD, in addition to a stable regimen of ≥ 1 antihypertensive agent (including a diuretic) in the double-blind treatment period of 8 weeks. The sample size is considered to be adequate for supporting descriptive analysis of the cortisol response to ACTH, based on previous experience with baxdrostat, as described in Section 2.

Approximately 45 participants will be randomised and assigned to study intervention such that, with an estimated 10% drop-out rate, approximately 40 evaluable participants complete the study.

Note: 'Screened' means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomised/assigned in the study, are considered 'screen failures', unless

otherwise specified by the protocol.

9.3 Populations for Analyses

The following populations are defined:

Table 8 Populations for Analysis

Population/analysis set	Description
Screened	All participants who sign the ICF.
Randomised/assigned to study intervention	All randomised participants. This population will be used for the purpose of participant disposition.
Full Analysis Set	All randomised participants who received at least one dose of study intervention. This population will be the primary population for all endpoints.
PK Analysis Set	All randomised participants who had at least one evaluable pre-dose plasma concentration data for PK analysis and who received active treatment.

ICF = Informed consent form; PK = Pharmacokinetic(s).

9.4 Statistical Analyses

9.4.1 General Considerations

The SAP will detail how baseline data will be described, which refers to all data collected at the beginning of the clinical study for all participants. These data will include demographics, such as age, sex, race and ethnicity and study-specific measures.

Study-collected data will be summarised by treatment using descriptive statistics, graphs and/or data listings. Descriptive statistics for continuous variables will include number of participants (n), mean, SD, median, minimum, and maximum values. Analysis of categorical variables will include frequency and percentage.

In this study, baseline is defined as the last assessment taken on or before first dose of study intervention.

9.4.2 Pharmacodynamic Analysis

Statistical analyses will be descriptive in nature, and no formal statistical testing will be performed. The primary and secondary endpoints will be analysed in the Full Analysis Set.

9.4.2.1 Primary and Secondary Endpoints

Cortisol response to ACTH stimulation test will be 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. In the event of abnormal stimulate cortisol results at Week 8,

cortisol response to ACTH stimulation testing will be assessed CCI minutes and CCI minutes after ACTH stimulation at an unscheduled visit, for each treatment group. 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 performed, the results of the repeat ACTH stimulation test at the unscheduled visit will be used for the analysis.

Participants with abnormal cortisol levels at baseline will not be considered. Those discontinued participants will be listed and plotted separately.

The baseline values are the last non-missing values prior to the administration of the first dose of IMP. CCI The data collected after the other intercurrent events will be included in the data analyses (Treatment Policy Strategy).

Incidence of abnormal stimulated cortisol (ie, total serum cortisol below the pre-specified threshold after CCI minutes) at baseline and Week 8 by treatment group will be assessed via frequency table, in participants with normal stimulated cortisol at baseline. Of note, participants with abnormal stimulated cortisol at baseline will be reported separately. If performed, the results of the repeat ACTH stimulation test at the unscheduled visit will be used for the analysis.

9.4.3 Safety

Safety analyses will be performed in the Full Analysis Set. Safety data will be presented using descriptive statistics unless otherwise specified.

The safety endpoint aims to assess the safety and tolerability of baxdrostat as compared to placebo. This will be evaluated in terms of:

- AEs, SAEs, and DAEs.
- Vital signs (BP, pulse rate, body weight).
- Safety investigations and laboratory tests (ECG, clinical chemistry, haematology).
- AESIs (hyperkalaemia, hyponatraemia, and hypotension CCI CCI; based on Investigator reported AEs).

9.4.3.1 Adverse Events

Adverse events will be coded using MedDRA. The most recent version of the dictionary will be used at study start and up-versioning will be performed during study conduct as applicable.

Adverse events will be presented for each treatment, by SOC and/or PT covering number and percentage of participants reporting at least one event and number of events where appropriate.

An overview of AEs will be presented for each treatment group, by SOC and PT, along with the number and percentage of participants with any AE, AEs with outcome of death, SAEs and AEs leading to discontinuation of study intervention. Separate tables will be provided for AESIs.

Separate AE tables will be provided, taking into consideration AE relationship to study intervention, as assessed by the Investigator, maximum intensity, seriousness, death, and DAEs.

An additional table will present the number and percentage of participants with the most common AEs. Most common (eg, frequency of > x%, ≥ x%) will be defined in the SAP.

Key participant information will be presented for participants with AEs with an outcome of death, SAEs and DAEs.

Separate summaries will be presented for the on-treatment and on-study periods, where the on-treatment period is defined as up to the time of last study intervention administration and on-study period is defined as up to the SFU Visit.

An AE listing for the Full Analysis Set will cover details for each individual AE.

Full details of AE analyses will be provided in the SAP.

9.4.3.2 Vital Signs

Vital sign parameters will be presented for each treatment group using summary statistics. Frequency tables and shift tables cover number and percentage of participants in respective categories will also be presented.

For each scheduled post-Randomisation Visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline. For multiple results taken at the same timepoint the multiple results will be averaged before analysis.

Details of vital sign analysis, including categories to be included in shift tables will be provided in the SAP.

9.4.3.3 Clinical Safety Laboratory Tests

Laboratory parameters will be presented for each treatment group using summary statistics.

For each scheduled post-Randomisation Visit, descriptive statistics for all clinical chemistry

and haematology parameters will be presented for observed values and change from baseline.

A shift table presents laboratory status (eg, low, normal, high) from baseline to maximum and minimum post-randomisation value.

Elevation in liver parameters for assessment of Hy's Law will be done and reported appropriately if potential cases have been identified during the course of the study.

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

Details of laboratory analyses will be provided in the SAP.

9.4.3.4 Electrocardiogram

Electrocardiogram parameters will be presented for each treatment group using summary statistics.

For each scheduled post-screening assessment, descriptive statistics for all ECG parameters will be presented for observed values and change from baseline.

A table presents the interpretation of the ECG reading (normal, abnormal – clinically not significant, abnormal – clinically significant) at baseline and each post-screening timepoint.

Details of ECG analyses will be provided in the SAP.

9.4.4 Other Exploratory Analyses

Plasma concentrations of baxdrostat will be descriptively summarised based on the PK Analysis Set. Any additional PK analyses will be described in a separate data analysis plan and the results will be provided in a separate report.

9.5 Interim Analyses

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

9.6 Data Monitoring/Other Committee

No data monitoring committee has been appointed for this study. However, all cases of abnormal ACTH stimulation test will be reviewed by an independent blinded adrenal expert.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local Regulatory Authority and other Regulatory Agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, IRB/IEC, and Investigators.

- For all studies except those utilising medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal obligations and ethical obligations are met.

- A "serious breach" means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the Regulatory Authority, IRB/IEC, and Investigators.

If any (potential) serious breach occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately.

In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local Regulatory Authority and other Regulatory Agencies about such breaches.

The Investigator should have a process in place to ensure that:

- The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach.
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-Investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca to submit complete and accurate financial certification or disclosure statements to the appropriate Regulatory Authorities. Investigators are responsible for providing information on financial interests during the study and for one year after completion of the study.

A 3 Informed Consent Process

- The Investigator or their representative will explain the nature of the study to the participant or their legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative, defined as an individual or judicial or other body authorised under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures involved in the study, will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study site.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- If new information requires changes to the ICF, consider if participants must be reconsented and if so, this must be to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant’s legally authorised representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional HBS. The Investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from Regulatory Authorities.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymised. The General Data Protection Regulation (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- While AstraZeneca has processes in place to deal with personal data breaches it is important that Investigators that work with AstraZeneca have controls in place to protect patient data privacy.

[1] The **data controller** determines the **purposes** for which and the **means** by which personal data are processed, as defined by the European Commission.

The Investigator should have a process in place to ensure that:

- Allow site staff or service providers delegated by the Investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- Have taken all necessary steps to avoid personal data breaches and
- Have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining, and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- Where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- Where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal data breach to participants:

- Notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator,

acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.

- If a personal data breach involving an AstraZeneca's representative device (ie, Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Committees Structure

No data monitoring committee, event adjudication committee or any other entities will be engaged in this study.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on www.astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and Regulatory Agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined in the Risk Assessment Categorisation Tool (RACT) to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the

study, and important deviations from the QTLs and remedial actions taken will be summarised in the CSR.

- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan and Data Surveillance Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Medical Monitoring Plan.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data, and its origin can be found in the monitoring guidelines.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by AstraZeneca or the Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, AstraZeneca's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the Investigators, the IRBs/IECs, the Regulatory Authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B AEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of AEs

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not it is considered related to the medicinal (investigational) product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of SAEs

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the medicinal product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability, or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated).
- Moderate (discomfort sufficient to cause interference with normal activities).
- Severe (incapacitating, with inability to perform normal activities).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When assessing causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the medicinal product.

- Time Course. Exposure to suspect drug. Has the participant received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host, or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the DUS has deteriorated due to lack of effect should be classified as 'no reasonable possibility'.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- **Was identified and** intercepted before the participant received the drug.
- Did not occur, but circumstances were recognised that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion.
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant.
- Drug not administered as indicated, eg, wrong route or wrong site of administration.
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature.
- Wrong participant received the medication (excluding IRT/RTSM errors).
- Wrong drug administered to participant (excluding IRT/RTSM errors).

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error.
- Participant accidentally missed drug dose(s), eg, forgot to take medication.
- Accidental overdose (will be captured as an overdose).
- Participant failed to return unused medication or empty packaging.

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study).
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high.

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person.
- The drug is sold to other people for recreational purposes.
- The drug is used to facilitate assault in another person.
- The drug is deliberately administered by the wrong route.
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole.
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose.
- Someone who is not enrolled in the study intentionally takes the drug.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each site keeps full traceability of collected biological samples from the participants while in storage at the site until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at the site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca team for the remainder of the sample life cycle.

All appropriately consented samples will be retained for maximum 15 years from last subject last visit.

Pharmacokinetic samples will be disposed after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures the participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and study site is notified.

C 3 International Air Transport Association Guidance Document 62nd Edition

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

The International Air Transport Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B, or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN 3373 and IATA 650

Exempt Substances are substances which do not contain infectious substances, or substances which are unlikely to cause disease in humans or animals, are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/contentassets/b08040a138dc4442a4f066e6fb99fe2a/dgr-62-en-pi650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.

Appendix D CCI

D 1 Use/Analysis of CCI

- AstraZeneca intends to collect and store CCI (such as CCI and CCI for CCI and comprehensive CCI research (such as CCI CCI and CCI which may include CCI CCI analysis, to explore how CCI and timepoint CCI variations may affect clinical parameters, risk and prognosis of diseases, and the response to medicinal product.
- This CCI research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care, and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a CCI sample will be collected for CCI analysis from consenting participants.
- This optional CCI research may consist of the analysis of the structure of the participant's CCI, ie, the CCI
- The results of these CCI analyses may be reported in a separate study summary.
- AstraZeneca will store the CCI samples in a secure storage space with adequate measures to protect confidentiality.

D 2 CCI Research Plan and Procedures

Selection of CCI Research Population

All participants will be asked to participate in this CCI research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this CCI research, participants must fulfil all of the inclusion criteria described in the main body of the protocol and: Provide informed consent for the CCI sampling and analyses.

Exclusion Criteria

Exclusion from this CCI research may be for any of the exclusion criteria specified in the main study or any of the following:

- CCI
- CCI sample collection.

- Healthy volunteers and paediatric participant samples will not be collected for the CCI

Withdrawal of Consent for CCI Research

- Participants may withdraw from this CCI research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main protocol.

Collection of Samples for CCI Research

- The CCI sample for this CCI research will be obtained from the participants at CCI Although CCI is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at CCI it may be taken at any visit until the last study visit. Only one sample should be collected per participant for CCI research during the study.

Coding and Storage of CCI Samples

The processes adopted for the coding and storage of samples for CCI analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years from the date of last subject last visit, after which they will be destroyed. CCI are a finite resource that will be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

- An additional second code will be assigned to the samples either before or at the time of sample processing, replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca analysis laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the CCI CCI
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant samples for analysis, facilitate correlation of CCI results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this CCI research component, are outlined in Appendix A.

Informed Consent

- The CCI components of this study are optional, and the participant may participate in other components of the main study without participating in this CCI component. To participate in the CCI component of the study the participant must sign and date both the consent form for the main study and the CCI Information and Consent Form. Copies of both signed and dated consent forms must be given to the participant and the originals filed at the study site. The Principal Investigator(s) is responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdraw from the CCI aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide CCI results to participants, any insurance company, any employer, their family members, or general physician unless required to do so by law. Extra precautions are taken to preserve confidentiality and prevent CCI data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the CCI data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a participant's identity and also have access to his or her CCI data. Regulatory Authorities may require access to the relevant files, though the participant's medical information and the CCI files would remain physically separate.

Data Management

- Any CCI data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as CCI differences from groups of individuals with a disease) from this CCI CCI research with other researchers, such as hospitals, academic organisations, or drug- or health-related companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.

- Some or all of the clinical datasets from the main study may be merged with the CCI data in a suitable secure environment separate from the clinical database.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law cases and Hy's Law cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential Hy's Law criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of potential Hy's Law and Hy's Law events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, potential Hy's Law criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible potential Hy's Law events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to potential Hy's Law/Hy's Law cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law
Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study intervention irrespective of an increase in ALP.

Hy's Law
Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For potential Hy's Law and Hy's Law the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of potential Hy's Law it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Central Laboratories Being Used:

When a participant meets any of the potential Hy's Law identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the potential Hy's Law identification criteria are met, where this is the case, the Investigator will:

- Notify the AstraZeneca representative.
- Request a repeat of the test (new blood draw) by the central laboratory without delay.
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result.

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the participant meets potential Hy's Law criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

Local Laboratories Being Used:

The Investigator will without delay review each new laboratory report and, if the identification criteria are met, will:

- Notify the AstraZeneca representative.

- Determine whether the participant meets potential Hy's Law criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the participant does not meet potential Hy's Law criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the protocol.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet potential Hy's Law criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within one day of potential Hy's Law criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important Medical Event' and causality assessment 'yes/related' according to the protocol process for SAE reporting.
- For participants who met potential Hy's Law criteria prior to starting IMP, the Investigator is not required to submit a potential Hy's Law SAE unless there is a significant change[#] in the participant's condition.
- The Study Clinical Lead will contact the Investigator, to provide guidance, discuss, and agree an approach for the study participant's follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact, the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Clinical Lead. For central laboratories, this includes deciding which of the tests available in the Hy's Law laboratory kit should be used.
  - Complete the 3 Liver eCRF Modules as information becomes available.

A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Clinical Lead if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this appendix should be followed for all cases where potential Hy's Law criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the Study Clinical Lead will contact the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date potential Hy's Law criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: Update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term, causality, and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the Hy's Law case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to protocol process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are still met. Update the previously submitted potential Hy's Law SAE report following protocol process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory Tests

Please see table for Hy's Law Laboratory Kit for Central Laboratories below.

Hy's Law Laboratory Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM and IgG anti-CMV IgG anti-HSV, and HSV-1 and HSV-2 IgM testing, OR HSV-1 and HSV-2 PCR testing [d] IgM and IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
[c] CD-transferrin and transferrin are not available in China. Study teams should amend this list accordingly.
[d] HSV-1 and HSV-2 IgM testing or HSV-1 and HSV-2 PCR testing depending on the region.

Appendix F Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

CSP Version 2.0 (Amendment 1.0), 05 June 2024

Overall Rationale for the Modification:

The primary rationale for this amendment is CCI [redacted] and to correct and/or clarify details related to some procedures, tests, and participant-related evaluation and management aspects of the study. Additionally, this amendment incorporated corrections and clarifications not impacting the study design, as listed below.

Summary of Changes:

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis; Section 1.3, Schedule of Activities; Section 8.2.1, ACTH Stimulation Test and Cortisol Level Measurement; Section 9.4.2.1, Primary and Secondary Endpoints	Addition of a "±CCI minute" window to the "CCI minutes" post-ACTH stimulation timepoint for the collection of ACTH stimulation blood samples within Table 1 footnote "g", and throughout the document.	To provide flexibility in study conduct without affecting study integrity.
Section 1.3, Schedule of Activities	Updating Table 1 footnote "a" to read "If the EoT Visit is conducted > 10 days after the last administered dose, all assessments (except the PK sampling) required at EoT and SFU Visits are to be conducted within the same visit (inclusive of the ACTH stimulation testing, serum cortisol measurement and K^+ only testing) and a complete physical examination will be performed", also adding footnote "g" to Table 2 to align with this change.	To provide clarification on how to handle the assessments at the EoT when it comes close to the timing of the SFU.
Section 1.3, Schedule of Activities; Section 8.3.4, Clinical Safety Laboratory Tests	Removal of "urinalysis" from whole safety panel assessments within Table 2 footnote "a" and adding urinalysis is only performed "locally" in Table 6 footnote "e".	To clarify that dipstick urinalysis is done locally and not centrally and only at Visit 2.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities; Section 8.3.4, Clinical Safety Laboratory Tests	Addition of pregnancy testing at Double-blind Period (Visit 5), EoT (Visit 6, Week 8), and Safety Follow-up (SFU Visit) within Table 2 and mentioning pregnancy timepoints in Table 6 footnote "d".	To clarify pregnancy assessment timepoints during the study in line with CIRB request.
Section 7.1.3, Temporary Interruption of Study Intervention; Section 7.2, Participant Discontinuation/Withdrawal from the Study; Section 8.4.5.1, CCI [redacted]	Addition of the subsection "Differential Diagnosis for CCI [redacted]" and text that "CCI [redacted], and insertion of the cross-references made to this topic.	To provide clarification regarding diagnostic assessment required for participants with unexplained signs and symptoms that may indicate CCI [redacted]

ACTH = Adrenocorticotropic hormone; CIRB = Central institutional review board; EoT = End of treatment; K^+ = Potassium; PK = Pharmacokinetic(s); SFU = Safety follow-up.

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