
Clinical Study Protocol

Study Intervention	Baxdrostat (CIN-107)
Study Code	D6970C00009
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EU CT Number 2023-507640-36

A Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Effect of Baxdrostat on Ambulatory Blood Pressure in Participants with Resistant Hypertension

Sponsor Name: AstraZeneca

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden.

Regulatory Agency Identifier Numbers: IND 146112; EU CT Number 2023-507640-36

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 Phase III study to Investigate the Effect of Baxdrostat on Ambulatory Blood Pressure in Participants with Resistant Hypertension.

Study Phase: Phase III

Acronym: Bax24Study 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).

International Coordinating Investigator:



SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date
CSP Version 2.0	29 May 2024
CSP Version 1.0	17 October 2023

CSP = clinical study protocol

CSP Version 2.0 [29 May 2024]

This modification is considered non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Modification:

This Clinical Study Protocol (CSP) amendment serves to implement measures to make the recruitment process more efficient and possibly ease participation in the study through the incorporation of broader participant rescreening and retesting options.

Additionally, for consistency in the clinical program, the intercurrent event of rescue therapy will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of initiation of rescue therapy.

This CSP amendment also contains minor corrections and clarifications not impacting the study design, as listed below.

Formatting improvements, such as updates to abbreviations, typos, and punctuation corrections, are not presented in this summary.

Summary of Changes

Section Number and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Assessments	Deletion of footnote 'd' which stated, 'The safety Follow-up Visit will be performed 14 days after the participant receives the last IMP dose'.	Information already provided in the SoA.
	Additional information added in footnotes that clarifies that the EoT Visit does not apply to participants who are not randomised.	Clarification

Section Number and Name	Description of Change	Brief Rationale
	Footnote for IMP administration was updated to clarify when participants are taking study intervention.	Clarification
	Additional 'X' was added for collection of blood samples pre-dose at Visit 4 and deleted from collection of blood samples at Visit 4, in Table 1.	For consistency with Table 2.
	New footnote added for DOT to clarify that participants will take study intervention and their morning and midday background antihypertensive medication as part of DOT during Visits 3 and 8.	Clarification
	Row added for IMP administration at site with an explanatory footnote.	To clarify that study intervention will be administered to participants at site during study visits, after BP measurements are performed.
	Footnote 'h' updated in Table 2 to clarify that at Visit 9, PK samples will be collected after ABPM measurements are completed.	Clarification
Section 3 Objectives, Endpoints and Estimands	The intercurrent event of rescue therapy will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of initiation of rescue therapy.	For consistency in the program.
Section 4.1.2 Placebo Single-Blind Run-in Period	Flexibility added to the Run-in period window.	To allow greater flexibility for participants to complete the Run-in Period.
	Details provided as to when participants will be taking the placebo tablets.	Clarification
Section 4.1.4 Safety Follow-up Period	Sentence "The Safety Follow-up Visit will be performed 14 days after the participant receives the last study intervention dose" replaced with "Participants will enter this period after finalising the 12-week double-blind period".	For consistency with SoA changes.
Section 5.2 Exclusion Criteria	Wording for exclusion criteria 2 and 3 was updated.	Clarification of time window.

Section Number and Name	Description of Change	Brief Rationale
	Criterion 22 modified to allow for the use of beta-blockers and calcium channel blockers classified as Class II/IV antiarrhythmic medications, and digoxin.	Clarification
	Criterion number 24 updated to allow for low-dose aspirin as per medical judgement and to limit the exclusion of chronic use of systemic steroids to a period of 8 weeks prior to screening.	Clarification
Section 5.4 Screen Failures	Additional subsection inserted at the start of this section (as Section 5.4.1), introducing retesting options for participants not meeting certain parameters.	To account for variability in laboratory parameters and blood pressure measurements.
	Rescreening text has been modified to include criteria that forbid participants to undergo rescreening, instead of specifying conditions which allow for it.	To facilitate rescreening.
Section 5.4.2 Rescreening	Additional bullet point added to the list of failed criteria that won't allow rescreening.	Correction
Section 6.1 Study Intervention Administered	Text added to indicate that if another ABPM attempt is needed, the last dose of study intervention will be part of the repeated DOT.	Clarification
	New text inserted to clarify in which study visit days participants will self-administer study intervention at home.	Clarification
	Additional information added to indicate when participants should take placebo during the Run-in period, as part of DOT.	Clarification
Section 6.5 Study Intervention Compliance	Sentence modified to clarify that the date and time of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF only for DOT visits.	Correction

Section Number and Name	Description of Change	Brief Rationale
Section 6.9.1 Prohibited Concomitant Medications	Text for occasional NSAID usage was updated.	Clarification
Section 7.1.1 Temporary Interruption of Study Intervention	A bullet point has been added to specify that “If a participant has a QTcF increase from baseline ≥ 60 ms study treatment will be temporarily interrupted at first and may be permanently discontinued afterwards”. More details are inserted in Section 7.1.4.	Additional criterion for study drug interruption added for consistency in the program.
	If sodium is re-checked due to hyponatraemia, this test will be done by the central laboratory (not local).	Correction
Section 7.1.2 Permanent Discontinuation of Study Intervention	Deletion of the following bullet point: “safety reasons as judged by the Investigator where continued treatment may put participant at undue risk”.	Correction
	Modified text to clarify how to handle participants with symptoms associated with adrenal insufficiency.	Clarification.
Section 7.1.4 QTc Stopping Criteria	Additional information has been inserted to specify that ECGs will be thoroughly evaluated if QTcF value increases from baseline by ≥ 60 ms, and discontinuation of treatment will be based on this evaluation.	Additional criterion for study drug interruption added for consistency in the program.
Section 7.2 Participant Discontinuation / Withdrawal from the Study	Addition of the following sentence “The EoT Visit does not apply to participants who are not randomised”.	Clarification
Section 8.2.1 Blood Pressure Measurements	Sentence inserted to clarify that if an error occurred when measuring BP, during the procedures specified in Section 8.2.1.1 or Section 8.2.1.2, study personnel should refer to the dedicated manual for the centrally provided AOBPM device.	Clarification
Section 8.2.1.2 Seated Blood Pressure Measurements	Triple SBP measurement removed as the mandatory mean for selecting the arm with	To facilitate arm selection for subsequent BP measurements.

Section Number and Name	Description of Change	Brief Rationale
	the higher blood pressure at Screening, and to be used as optional mean.	
	Information added to clarify that both, the dedicated centrally provided AOBPM device or the local blood pressure monitor, can be used to determine laterality.	To make the arm selection process more flexible.
Section 8.3.3 Electrocardiograms	The following sentence was deleted: “electrocardiogram assessments will be performed after obtaining BP measurements.”	Correction
Section 8.3.4 Clinical Safety Laboratory Tests	CKD-EPI 2021 equation for eGFR was updated.	Correction
Section 8.4.5.1 Differential Diagnosis for Adrenal Insufficiency	Modified text to clarify how to handle participants with symptoms associated with adrenal insufficiency.	Clarification
Section 8.4.6 Adverse Events of Special Interest	Sentence added to specify that investigators should assess factors possibly contributing to the AESIs and record these in the eCRF.	Clarification
Section 8.5.1 Collection of Samples for Pharmacokinetics	Sentence added to clarify that at Visit 9, PK samples will be collected after ABPM measurements are completed (except for early EoT Visit).	Clarification
Section 8.6.1 Collection of Samples for Pharmacodynamics	Information updated as to when blood samples should be collected.	Correction
Section 8.8 Biomarkers	Text has been reworded to exclude ‘serum analytes’ or ‘specific candidate genes’ as PD biomarkers.	No transcriptomics samples for evaluating genes will be collected.
Section 9.4.2.1 Primary Endpoints	More detailed information added for what will the primary analysis include and how data following treatment discontinuation or initiation of rescue therapy will be handled.	Information inserted for consistency in the program.
Section 9.4.2.2 Secondary Endpoints	Analysis of binary secondary endpoints updated.	For consistency in the program.

Section Number and Name	Description of Change	Brief Rationale
Appendix C1 Chain of Custody	Language updated for storage of all samples retained for future use.	Correction of text.
Appendix G Anatomical Therapeutic Chemical Codes for NIMPs/AxMPs	Addition of new ATC codes: C02C ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING C02L ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION C09A ACE INHIBITORS, PLAIN, and C09C ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), PLAIN.	Correction

AE = adverse event; AESI = AE of special interest; ATC = Anatomical Therapeutic Chemical; AOBPM = Automated office blood pressure measurement; BP = blood pressure; CKD EPI = Creatinine Equation for Glomerular Filtration Rate; DOT = direct observed therapy; eCRF = electronic case report form; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EC = Executive Committee; EoT = end of treatment; EU = European Union; IMP = investigational medicinal product; QTcF = QT corrected by Fridericia; NSAID = non-steroid anti-inflammatory drug; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious AE; SBP = systolic blood pressure; SoA = schedule of assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
ABPM	Ambulatory blood pressure monitoring
ACEI	Angiotensin converting enzyme inhibitors
AE	Adverse Event
AESI	Adverse Event of special interest
ALP	Alkaline Phosphatase
ANCOVA	Analysis of covariance
ALT	Alanine Aminotransferase/Transaminase
AOBPM	Automated office blood pressure measurement
AST	Aspartate Aminotransferase/Transaminase
ATC	Anatomical Therapeutic Chemical
AxMP	Auxiliary Medicinal Product
β-hCG	Human chorionic gonadotropin
BP	Blood pressure
CFR	Code of Federal Regulations
CKD EPI	Creatinine Equation for Glomerular Filtration Rate
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTIS	Clinical Trials Information System
CYP	Cytochrome P450
DAE	Discontinuation of IP due to AE
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
Dipper	Subject with $\geq 10\%$ reduction in night-time BP compared to daytime BP.
DMC	Data Monitoring Committee
DOT	Direct observed therapy
eCRF	electronic Case Report Form
EC	Executive Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate

Abbreviation or special term	Explanation
EoT	End of treatment
EU	European Union
EU CT	EU Clinical Trial
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	Glycosylated haemoglobin
HBS	Human Biological Sample(s)
HF	Heart failure
IATA	International Air Transport Association
IB	Investigator's Brochure
ICE	Intercurrent event
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
K ⁺	Potassium
LS	Least square
MRA	Mineralocorticoid receptor antagonists
Na ⁺	Sodium
NIMP	Non-investigational Medicinal Product
Non-dipper	Subject with less than a 10% reduction in night-time BP compared to daytime BP.
NSAID	Nonsteroidal anti-inflammatory drug
PD	Pharmacodynamic(s)
PI	Principal Investigator
PK	Pharmacokinetic(s)
PRA	Plasma renin activity
QD	<i>Quaque die</i> (one per day)
QTcF	QT interval corrected using Fridericia's formula
QTL	Quality tolerance limit
rHTN	Resistant hypertension
RTSM	Randomisation and Trial Supply Management
SAE	Serious Adverse Event

Abbreviation or special term	Explanation
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SoA	Schedule of Activities
TBL	Total Bilirubin
ULN	Upper Limit of Normal

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Effect of Baxdrostat on Ambulatory Blood Pressure in Participants with Resistant Hypertension.

Brief Title: A Phase III study to Investigate the Effect of Baxdrostat on Ambulatory Blood Pressure in Participants with Resistant Hypertension.

Regulatory Agency Identifier Numbers: IND 146112; EU CT Number 2023-507640-36

Rationale:

Elevated blood pressure (BP) is a leading global risk factor for cardiovascular disease, stroke, disability and death and affects an estimated 1.4 billion persons worldwide. Hypertension control can be challenging to achieve, with barriers to hypertension control attributed to patients, health-care providers, health-care systems and the silent nature of the disease.

Resistant hypertension (rHTN) is defined as BP targets not achieved despite the use of at least 3 anti-hypertensive drugs of different classes (at maximum tolerated dose), including a diuretic. It is estimated that in the US, at least 10% of hypertensive patients (10 to 12 million persons) have rHTN. Worldwide, the prevalence of rHTN is estimated to range from 9% to 15% of adult patients with hypertension, as determined from BP readings in the clinic.

Individuals with rHTN have a substantially increased risk of suffering cardiovascular and renal diseases, as failure to achieve BP targets leaves them exposed to the injurious effects of chronically elevated BP on their heart, brain and kidneys. While physicians and patients have many therapeutic drug classes to choose from for the treatment of hypertension, there is a substantial unmet need for effective and well-tolerated medications to treat rHTN.

Additionally, with lower BP targets being currently recommended by hypertension guidelines, the accuracy in BP measurement has become even more important in order to achieve optimal BP control and to prevent adverse effects of over-treatment. Current guidelines recommend the broad use of ambulatory BP measurement (ABPM) to both enhance the accuracy of

measurement and better identify “white coat” hypertension.

Aldosterone is a steroid hormone that contributes to the regulation of sodium 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 the cytochrome P450 11B2 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. Aldosterone synthase converts 11-deoxycorticosterone to aldosterone via a multistep biosynthetic pathway.

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, 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 patients with resistant hypertension, baxdrostat elicited statistically and clinically significant systolic BP (SBP) reductions compared to placebo. Based on these findings, baxdrostat may be a novel treatment for rHTN. The primary objective of this study is to assess the effect of treatment with baxdrostat 2 mg vs placebo on ambulatory 24-hour SBP at Week 12 and to evaluate the effect of baxdrostat on night-time BP levels, as these are associated with an increased CV disease risk.

Objectives, Endpoints:

Objectives	Endpoints
Primary	
To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory 24-hour average SBP at Week 12.	Change from baseline in ambulatory 24-hour average SBP at Week 12.
Secondary	
To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory night-time average SBP at Week 12.	Change from baseline in ambulatory night-time average SBP at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory daytime average SBP at Week 12.	Change from baseline in ambulatory daytime average SBP at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on seated SBP at Week 12.	Change from baseline in seated SBP at Week 12.

Objectives	Endpoints
To assess the effect of treatment with baxdrostat 2 mg versus placebo on achieving ambulatory 24-hour average SBP < 130 mmHg at Week 12.	Participants achieving ambulatory 24-hour average SBP of < 130 mmHg at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory 24-hour average DBP at Week 12.	Change from baseline in ambulatory 24-hour average DBP at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory night-time average DBP at Week 12.	Change from baseline in ambulatory night-time average DBP at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory daytime average DBP at Week 12.	Change from baseline in ambulatory daytime average DBP at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on seated DBP at Week 12.	Change from baseline on seated DBP at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo in the nocturnal dipping pattern at Week 12.	Participants achieving a nocturnal SBP dipping of > 10% at Week 12.
Exploratory	
To evaluate the pharmacokinetics of baxdrostat.	Plasma concentrations of baxdrostat.
To evaluate the biomarkers related to the pharmacodynamic action of baxdrostat vs placebo on the RAAS pathway.	To be reported in a separate report.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on seated SBP.	- Change from baseline in seated SBP at Week 4. - Change from baseline in seated SBP at Week 8.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on seated DBP.	- Change from baseline in seated DBP at Week 4. - Change from baseline in seated DBP at Week 8.
To collect and store optional genetic samples for future exploratory genetic research.	To be reported in a separate report.
Safety	
To assess the safety and tolerability of baxdrostat as compared to placebo.	Safety and tolerability will be evaluated in terms of: - AEs, SAEs and DAEs. - Vital signs (BP, pulse rate and body weight). - Safety investigations and laboratory tests (ECG, clinical chemistry, haematology). - AESIs (hyperkalaemia, hyponatremia and hypotension; based on Investigator reported AEs).

AE = adverse event; AESI = adverse event of special interest; BP = blood pressure; DAE = discontinuation of IMP due to AE; DBP = diastolic blood pressure; ECG = electrocardiogram; nocturnal dip = difference between ambulatory daytime average SBP and ambulatory night-time average SBP, expressed as a percentage of the daytime average SBP.; RAAS = renin-angiotensin-aldosterone system; SAE = serious adverse event; SBP = systolic blood pressure.

For the descriptions of estimands, see Section 3 of the protocol.

Overall Design Synopsis:

This is a Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel group study to evaluate the safety, tolerability and the effect of 2 mg baxdrostat versus placebo, administered once a day (QD) orally, on the reduction of ambulatory SBP in participants with rHTN, defined as BP targets not being achieved in an individual despite the use of at least 3 antihypertensive agents of different classes (at maximum tolerated dose in the judgement of the Investigator), one of which is a diuretic.

Consenting participants must meet the following key criteria at screening to be enrolled in the study: be ≥ 18 years of age, have average seated automated office BP measurement of ≥ 140 mmHg and < 170 mmHg, measured after > 5 minute in a seated position; have a stable regimen of ≥ 3 antihypertensive medications from different therapeutic classes (at least one must be a diuretic), at maximum tolerated dose in the judgement of the Investigator and for at least 4 weeks prior to screening; have estimated glomerular filtration rate ≥ 45 mL/min/1.73 m²; serum potassium level ≥ 3.5 and < 5.0 mmol/L determined as per central laboratory.

Participants must also meet the following criteria at randomisation: mean ambulatory SBP ≥ 130 mmHg; have no change in background therapy regimen and dose consisting of ≥ 3 antihypertensive medications (at least one is a diuretic) for at least 4 weeks prior to randomisation; have an 80% to 120% adherence to placebo during the run-in period to be enrolled into the study; and have demonstrated good adherence to the prescribed antihypertensive medications by performing DOT at randomisation.

Eligible participants will be assigned to treatment (baxdrostat or placebo) by randomisation, in a 1:1 ratio, after completing a single-blind (placebo) run-in period of 2 weeks. Participants will continue taking their prescribed background antihypertensive medications during the study.

The study is planned to be conducted globally in approximately 100 study centres and approximately 22 countries.

Brief Summary:

The purpose of this study is to assess the effect of treatment with baxdrostat 2 mg, compared with placebo, on ambulatory 24-hour average SBP in participants with rHTN, as well as baxdrostat safety and tolerability.

Study details include:

- The study duration will be up to 20 weeks.

- The treatment duration will be of 12 weeks.
- The visit frequency will vary, with visits happening at least once every 1 to 4 weeks during the treatment period, and with 2 visits being performed at Week 0 and Week 12.

Disclosure Statement: This is a parallel group study with 2 treatment arms, that is Sponsor, participant and Investigator blinded. This study is comprised of a single-blind run-in period and a double-blind treatment period.

Number of Participants:

Approximately 212 participants will be randomised to study intervention.

Note: ‘Screened’ means a participant’s agreement, 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’, regardless of their eligibility in reference to the inclusion/exclusion criteria, unless otherwise specified by the protocol. This includes subjects who met all eligibility criteria but were not randomised (eg, due to death or withdrawal by the participant during the screening period).

Study Arms and Duration:

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

- 2 mg baxdrostat
- Placebo

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

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

After completing the 12 weeks double-blind treatment period participants will complete a 2-week safety follow-up period.

Data Monitoring/Other Committee: Yes

A Data Monitoring Committee has been appointed for this study. The Data Monitoring Committee is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention and to make recommendations to AstraZeneca regarding the stopping of a study for harms. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

An Executive Committee will be formed to provide scientific oversight and approval of the overall study design, of the CSP and any protocol amendments.

Statistical Methods

This study is planning to randomise approximately 212 participants using a 1:1 ratio to either receive 2 mg baxdrostat QD or placebo QD, in addition to the participants' stable regimen of background antihypertensive medication. The sample size takes into account the statistical power for the primary endpoints and secondary endpoints.

The primary efficacy analysis will compare the change in ambulatory 24-hour average SBP from baseline at Week 12, measured by ABPM between baxdrostat 2 mg and placebo treatment groups. The primary endpoints will be analysed using an ANCOVA model with fixed effects for treatment and baseline ambulatory 24-hour average SBP as a covariate, based on the full analysis set, including participants with completed ABPM assessments at both baseline and Week 12. The least squares mean, standard error and 2-sided 95% confidence interval for the group of participants receiving baxdrostat, together with the comparison with the placebo group, will be provided.

The primary analysis will be conducted in accordance with the primary estimand and the strategies for specific types of intercurrent events outlined in the Statistical Analysis Plan.

The continuous secondary endpoints, ie, change from baseline in ambulatory night-time average SBP at Week 12, change from baseline in ambulatory daytime average SBP at Week 12, change from baseline in seated SBP at Week 12, change from baseline in ambulatory 24 hour average DBP at Week 12, change from baseline in ambulatory night time average DBP at Week 12, change from baseline in ambulatory daytime average DBP at Week 12 and change from baseline in seated DBP at Week 12, will be analysed analogous to the primary analyses of the primary endpoint.

The binary secondary endpoints will be analysed as follows:

- Participants achieving ambulatory 24-hour average SBP < 130 mmHg at Week 12 will be analysed via a logistic regression model, including baseline ambulatory 24-hour average SBP measurement as a covariate and treatment as a factor.

- Participants achieving a nocturnal SBP dipping of $\geq 10\%$ at Week 12 will be analysed similarly, via a logistic regression model, including a baseline dipping status as covariate and treatment as a factor.

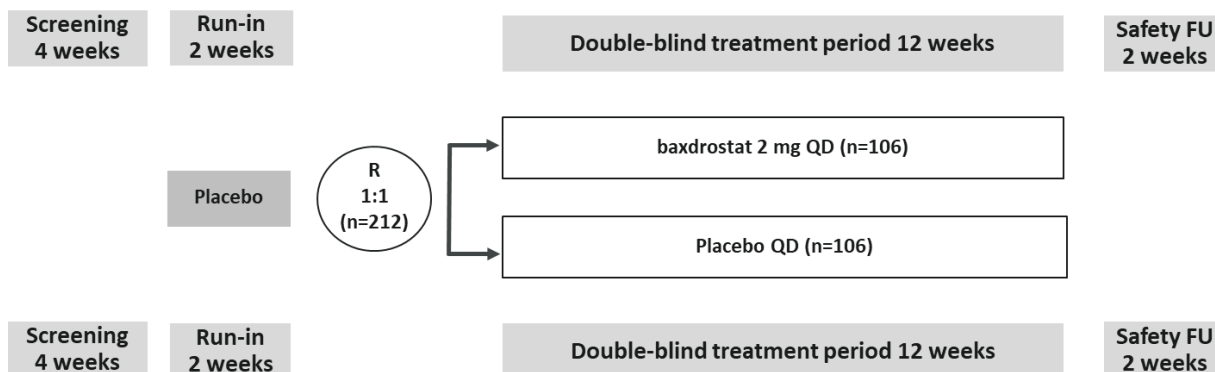
A multiplicity testing procedure will be used to strongly control the familywise Type I error rate 0.05 (two-sided), between the primary and secondary endpoints. In the first step of the confirmatory testing, the primary endpoint change from baseline in ambulatory 24 hour average SBP at Week 12 will be tested at two-sided alpha of 0.05. Thereafter, the secondary endpoints will be tested in sequence until a test fails to reject the null hypothesis or until all the listed null hypotheses are rejected.

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

1.2 Schema

A schema of the study design is presented [Figure 1](#).

Figure 1 Study Design



FU = follow-up; QD = once daily; R = randomisation; n = number of participants in that category

Note: participants should remain on their background antihypertensive medication throughout the entire study duration.

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure	Screening	Run-in		Randomisation	Intervention Period					EoT ^a	Safety F/U	Details in protocol section or appendix
Visit	1	2	3	4 ^b	5.1 ^c	5.2 ^c	6	7	8	9 ^b	Safety F/U	
Week	(-6 to -2) ^d	-2	0	0	1	2	4	8	12	12	14	
Day			-1	1	8	16	29	57	84	85	99	
Visit window (days)					+ 4	± 3	± 4	± 4	± 4		± 4	
Sign Informed consent	X											Appendix A 3
Inclusion and exclusion criteria	X			X								Section 0
Direct observed therapy ^e			X						X			Section 8.2.1.4
Enrolment in IRT/RTSM	X											Section 6.3
Demography	X											Section 8.1.1
Randomisation				X								Section 6.3
Full physical examination	X			X						X		Section 8.3.1
Targeted physical examination											X	Section 8.3.1
Medical/surgical history	X			X								Section 8.1.2
Concomitant medications	X	X	X	X			X	X	X	X	X	Section 6.9
Collect blood sample pre-dose (see Table 2)				X			X			X		Section 8.5.1 Section 8.6.1
Collect blood sample (see Table 2)	X				X	X		X			X	Section 8.3.4
12-lead ECG	X			X			X			X		Section 8.3.3
Vital signs ^f	X	X		X			X	X		X	X	Section 8.3.2
Height	X											Section 8.3.1

Procedure	Screening	Run-in		Randomisation	Intervention Period					EoT ^a	Safety F/U	Details in protocol section or appendix
Visit	1	2	3	4 ^b	5.1 ^c	5.2 ^c	6	7	8	9 ^b	Safety F/U	
Week	(-6 to -2) ^d	-2	0	0	1	2	4	8	12	12	14	
Day			-1	1	8	16	29	57	84	85	99	
Visit window (days)					+ 4	± 3	± 4	± 4	± 4		± 4	
ABPM measurement start ^g			X						X			Section 0
ABPM measurement end				X						X		Section 0
Seated BP	X	X		X			X	X		X	X	Section 8.2.1.2
Orthostatic BP				X						X		Section 8.2.1.3
Adverse events	X SAE only	X SAE only	X SAE only	X			X	X	X	X	X	Section 8.4 Section 8.4.1
IMP accountability				X			X	X		X		Section 6.5
IMP dispensation ^h		X		X			X	X				Section 6.1
IMP administration at site ⁱ		X	X	X			X	X	X			Section 6.1

^a Participants who prematurely withdraw study treatment will have an early EoT Visit performed at the time of the withdrawal. If study intervention is permanently discontinued, an EoT Visit should be performed as soon as possible, preferably within 2 weeks. During this early EoT Visit, all assessments indicated for Visit 9 will be performed (except for ABPM). After performing the EoT visit, the participant will complete the rest of the study visits as per SoA (including EoT Visit). The EoT Visit does not apply to participants who are not randomised.

^b Visits 4 and 9 will be scheduled at a timing that allows investigators to obtain a minimum of 25-hour ABPM readings (ie, visits should be scheduled minimum 25 hours after starting the ABPM measurements on Visit 3 or Visit 8, respectively).

^c Please note that Study Visits 5.1 and 5.2 are for safety laboratory measurements only.

^d The Screening Visit should occur at least 4 days before the Run-in Visit to allow for central laboratory results to be available. Participants should enter run-in period as soon as possible after the Screening Visit.

^e At Visits 3 and 8, participants will take study intervention and their morning and midday background antihypertensive medication as part of DOT.

^f Data regarding smoker status will be collected during Visit 4 alongside vital signs data.

^g If the last 25-hour ABPM measurements need to be repeated, the assessments scheduled for Visit 4 and Visit 9 will be delayed and will only be performed after the 25-hour ABPM repeated measurements have been obtained.

^h If a participant attends an early unscheduled visit and he/she will be returning to his/her next visit > 32 days later, an extra pack of study treatment tablets will be dispensed.

ⁱ Study intervention will be administered to participants at site, during study visits, after BP measurements are performed. During Visits 5.1 and 5.2 participants will self-administer study intervention at home.

Procedure	Screening	Run-in		Randomisation	Intervention Period					EoT ^a	Safety F/U	Details in protocol section or appendix
Visit	1	2	3	4 ^b	5.1 ^c	5.2 ^c	6	7	8	9 ^b	Safety F/U	
Week	(-6 to -2) ^d	-2	0	0	1	2	4	8	12	12	14	
Day			-1	1	8	16	29	57	84	85	99	
Visit window (days)					+ 4	± 3	± 4	± 4	± 4		± 4	

ABPM = ambulatory blood pressure measurement; BP = blood pressure; DOT = direct observed therapy; ECG = electrocardiogram; EoT = end of treatment; EP = endpoint; F/U = follow-up; IMP = investigational medicinal product; IRT/RTSM = Interactive Response Technology/Randomisation and Trial Supply Management; SAE = serious adverse event; SoA = schedule of activities.

Table 2 **Schedule of Laboratory Samples**

Procedure	Screening	Run-in		Randomisation	Intervention Period					EoT ^a	Safety F/U	Details in protocol section or appendix
Visit	1	2	3	4	5.1 ^b	5.2 ^b	6	7	8	9	Safety F/U	
Week	(-6 to -2) ^c	-2	0	0	1	2	4	8	12	12	14	
Day			-1	1	8	16	29	57	84	85	99	
Visit window (days)					+ 4	± 3	± 4	± 4	± 4		± 4	
Safety Laboratory. Whole safety panel (Central Laboratory) ^d	X			X				X		X	X	Section 8.3.4
Safety Lab. Creatinine, K ⁺ and Na ⁺ only (Central Laboratory) ^e					X	X	X					Section 8.3.4
K ⁺ only (Local Laboratory) ^f				X	X	X	X	X		X		Section 8.3.4.1
PD sampling (Central Laboratory) ^g				X			X			X		Section 8.6.1
PK sampling (pre-dose) ^h							X			X		Section 8.5.1
Optional genomics initiative, exploratory genomics sample ⁱ				X								Section 8.7 Appendix D
Urine dipstick test				X								Section 8.3.4
HbA1c test ^j	X											Section 8.3.4
FSH test ^k	X											Section 8.3.4
Urine pregnancy test (β-hCG) in WOCBP only ^l	X			X								Section 8.3.4

^a Participants who prematurely withdraw study treatment will have an EoT Visit performed at the time of withdrawal. If study intervention is permanently discontinued, an EoT Visit should be performed as soon as possible, preferably within 2 weeks. During this EoT Visit, the assessments indicated in Visit 9 will be performed. The EoT Visit does not apply to participants who are not randomised.

^b Please note that Study Visits 5.1 and 5.2 are for safety laboratory measurements only.

^c The Screening Visit should occur at least 4 days before Run-in Visit to allow for central laboratory results to be available. Participants should enter run-in period as soon as possible after Screening Visit.

^d The whole safety panel includes creatinine analysis (for eGFR calculation) and the measurement of Na⁺ and K⁺ levels in blood.

^e Creatinine, Na⁺ and K⁺ are also measured by the central laboratory at Visits 5.1; 5.2 and 6, in addition to when these analytes are measured as part of the whole safety panel.

Procedure	Screening	Run-in		Randomisation	Intervention Period					EoT ^a	Safety F/U	Details in protocol section or appendix
Visit	1	2	3	4	5.1 ^b	5.2 ^b	6	7	8	9	Safety F/U	
Week	(-6 to -2) ^c	-2	0	0	1	2	4	8	12	12	14	
Day			-1	1	8	16	29	57	84	85	99	
Visit window (days)					+ 4	± 3	± 4	± 4	± 4		± 4	

^f Potassium will be measured/assessed by the local laboratories at Visits 4 to 7, and at Visit 9, in addition to the K⁺ analysis performed by the central laboratory during these visits, which are part of the whole safety panel.

^g Collection of blood samples for PD markers should be performed in the morning at the clinical site, after the participant has been out of bed for approximately 2 hours and has been seated for 5 to 15 minutes, and will be performed pre-dose. Pharmacodynamic markers include PRA, corticosterone, 11-deoxycorticosterone, 18-OH corticosterone, aldosterone and aldosterone / PRA ratio.

^h At Visit 6, PK samples will be collected pre-dose. At Visit 9, PK samples will be collected after ABPM measurements are completed. For participants who are discontinued from study intervention due to hyperkalaemia, a PK sample should also be collected at the EoT Visit.

ⁱ If for any reason the sample is not drawn at Visit 4, it may be taken at any visit until the last study visit (see [Appendix D](#)).

^j The HbA1c test will be performed to exclude poorly controlled diabetes at screening.

^k For confirmation of post-menopausal status of women aged < 50 years only.

^l Urine pregnancy test can be replaced by a serum pregnancy test if required by local authorities. Also, if required by local authorities, additional pregnancy tests can be performed during the study. Ad hoc test to be used at the discretion of the Investigator during the treatment period if there is a suspected pregnancy.

BP = blood pressure; β-hCG = human chorionic gonadotropin; eGFR = estimated glomerular filtration rate; EoT = end of treatment; F/U = follow-up; FSH = Follicle-stimulating hormone; HbA1c = glycosylated haemoglobin; IMP = investigational medicinal product; K⁺ = potassium; Na⁺ = sodium; PD = pharmacodynamic; PK = pharmacokinetic; PRA = plasma renin activity; WOCBP = women of child-bearing potential.

2 INTRODUCTION

2.1 Study Rationale

This study is intended to evaluate the safety and tolerability of baxdrostat and the effect of 2 mg baxdrostat versus placebo, administered QD orally, on the reduction of ambulatory SBP in participants aged ≥ 18 years with rHTN, which is defined as a condition where BP targets are not achieved despite the use of at least 3 antihypertensive drugs of different classes (at maximum tolerated dose in the judgement of the Investigator), one of which is a diuretic.

2.2 Background

Elevated BP is a leading global risk factor for cardiovascular disease, stroke, disability and death, and affects an estimated 1.4 billion persons worldwide ([Mills et al 2016](#)). Hypertension control can be challenging to achieve, with barriers to hypertension control attributed to patients, health-care providers and health-care systems, and the silent nature of the disease ([Wofford and Smith 2008](#)).

In recent years, a number of studies have been performed to determine the prevalence of rHTN ([Brambilla et al 2013](#)). It is estimated that in the US, at least 10% of hypertensive patients (10 to 12 million persons) have rHTN ([Mills et al 2016](#)). A nationally representative cross-sectional study showed that 5.3% of the adults treated for hypertension in Canada are identified to have apparent treatment-rHTN ([Leung et al 2022](#)). Population studies on the prevalence of hypertension provide indirect estimates of the prevalence of rHTN. A multicentre study carried out in Central and East European countries (Albania, Belarus, Bosnia, Czech Republic, Lithuania, Romania, Serbia, Slovakia and Ukraine), reported an incidence between 12.8% and 19.4% ([Brambilla et al 2013](#)). Worldwide, the prevalence of rHTN is estimated to range from 9% to 15% in the population of adult patients with hypertension, as determined from BP readings in the clinic ([Pimenta and Calhoun 2012](#), [Sarafidis et al 2013](#)).

Individuals with rHTN have a substantially increased risk of cardiovascular and renal diseases, as failure to achieve BP targets leaves them exposed to the injurious effects of chronically elevated BP on heart, brain and kidneys ([Bourque and Hiremath 2022](#), [Sim et al 2015](#), [Trimarco et al 2023](#)). While physicians and patients have many therapeutic drug classes to choose from for the treatment of hypertension, there is a substantial unmet need for effective and well-tolerated medications to treat rHTN.

Aldosterone is a steroid hormone that contributes to the regulation of sodium 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 the CYP11B2 gene), being developed specifically to address the unmet need in patients 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.

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 patients with rHTN, baxdrostat elicited statistically and clinically significant SBP reductions compared to placebo ([Freeman et al 2023b](#)). Based on these findings, baxdrostat may be a novel treatment for rHTN. The primary objective of this study is to assess the effect of treatment with baxdrostat 2 mg vs placebo on ambulatory 24-hour SBP at Week 12 and to evaluate the effect of baxdrostat on night-time BP levels, as these are associated with an increased CV disease risk.

2.3 Benefit/Risk Assessment

The primary benefit for participants with rHTN, randomised to baxdrostat, is expected to be the reduction of BP and risk of long-term cardiovascular and renal damage. Baxdrostat is expected to be as safe and effective as in previous completed clinical studies and better tolerated than spironolactone, the guidelines recommended therapy for rHTN.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of baxdrostat may be found in the IB.

2.3.1 Risk Assessment

A summary of the potential risks of baxdrostat is presented in [Table 3](#).

Table 3 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 BrigHTN study (CIN-107-121), mean increases from baseline to end of treatment at 12 weeks were 0.36 and 0.29 mEq/L in the 1 and 2 mg groups, respectively. In HALO study (CIN-107-124), mean increases from baseline to end of treatment at 8 weeks were 0.26 and 0.12 mEq/L in the 1 and 2 mg groups, respectively. In the baxdrostat Phase II studies, moderate hyperkalaemia (K⁺ ≥ 6.0 mEq/L), was observed in 2.2% and 2.5% of subjects in the 1 and 2 mg treatment groups, respectively, with 0.8% in the placebo groups.	- Hyperkalaemia is considered an AESI in the study only in situations when participants need medical intervention. - Serum K⁺ level and minimum baseline renal function are included as inclusion criterion (inclusion criterion 5 [serum K⁺ level ≥ 3.5 and < 5.0 mmol/L at screening] and inclusion criterion 4 [eGFR ≥ 45 mL/min/1.73 m² at screening]; Section 5.1). - Certain drugs known to increase serum K⁺ are prohibited in the study. - Serum K⁺ will be monitored at screening, at most visits from baseline to the EoT and at the Safety Follow-up Visit. - Specific discontinuation criteria for hyperkalaemia are provided as well as monitoring guidance (see Section 7.1).
Important potential risk of hyponatraemia	Baxdrostat leads to increased natriuresis due to lowered circulating aldosterone, resulting in a minor decrease in serum sodium level. 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 sodium were observed. In BrigHTN (CIN-107-121) study, mean decreases from baseline to end of treatment at 12 weeks were 1.1 and 2.4 mEq/L in the 1 and 2 mg groups, respectively. In HALO study (CIN-107-124), mean decreases from baseline to end of treatment at 8 weeks were 1.8 and 1.4 mEq/L in the 1 and 2 mg groups, respectively.	- Hyponatraemia is considered an AESI in the study only in situations when participants need medical intervention. - Serum sodium level is an exclusion criterion (see exclusion criterion 5; Section 5.2). - Serum sodium will be monitored at screening, at most visits from baseline to the EoT and at the Safety Follow-up Visit. - Specific discontinuation criteria for hyponatraemia are provided (see Section 7.1).

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	In the baxdrostat BrigHTN study, 10 (3.6%) participants developed moderate hyponatraemia (serum sodium < 130 mEq/L), whereof 1 in the placebo group.	
Important potential risk of hypotension	Hypotension is reported as a risk with all classes of antihypertensives. As a consequence of the urinary sodium 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 studies BrigHTN and HALO (CIN-107-121/CIN-107-124), 3 non-serious AEs of hypotension 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 possible symptoms of hypotension). There was a small decrease from seated BP to standing BP in the 2 mg group in BrigHTN of approximately 2 mmHg at end of treatment at 12 weeks. One nonserious AE of orthostatic hypotension was reported in the 2 mg group.	- Hypotension is considered an AESI in the study only in situations when participants need medical intervention. - Seated and standing BP will be monitored throughout the study. - Discontinuation/restarting criteria are provided (see Section 7.1).

AE = adverse event; AESI = adverse event of special interest; BP = blood pressure; eGFR = estimated glomerular filtration; EoT = end of treatment; K⁺ = potassium.

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 gynecomastia 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 angiotensin-converting-enzyme/angiotensin-receptor blockers, which can diminish blood pressure control and lead to the progression of organ damage ([Bomback and Klemmer 2007](#)). This is a physiological response from the renin-angiotensin-aldosterone system 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 hypertension.

3 OBJECTIVES, ENDPOINTS AND ESTIMANDS

Study objectives and endpoints are presented in [Table 4](#).

Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory 24-hour average SBP at Week 12.	Change from baseline in ambulatory 24-hour average SBP at Week 12.
Secondary	
To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory night-time average SBP at Week 12.	Change from baseline in ambulatory night-time average SBP at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory daytime average SBP at Week 12.	Change from baseline in ambulatory daytime average SBP at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on seated SBP at Week 12.	Change from baseline in seated SBP at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on achieving ambulatory 24-hour average SBP < 130 mmHg at Week 12.	Participants achieving ambulatory 24-hour average SBP of < 130 mmHg at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory 24-hour average DBP at Week 12.	Change from baseline in ambulatory 24-hour average DBP at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory night-time average DBP at Week 12.	Change from baseline in ambulatory night-time average DBP at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on ambulatory daytime average DBP at Week 12.	Change from baseline in ambulatory daytime average DBP at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on seated DBP at Week 12.	Change from baseline on seated DBP at Week 12.
To assess the effect of treatment with baxdrostat 2 mg versus placebo in the nocturnal dipping pattern at Week 12.	Participants achieving a nocturnal SBP dipping of $\geq 10\%$ at Week 12.
Exploratory	
To evaluate the pharmacokinetics of baxdrostat.	Plasma concentrations of baxdrostat.

Objectives	Endpoints
To evaluate the biomarkers related to the pharmacodynamic action of baxdrostat vs placebo on the RAAS pathway.	To be reported in a separate report.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on seated SBP.	- Change from baseline in seated SBP at Week 4. - Change from baseline in seated SBP at Week 8.
To assess the effect of treatment with baxdrostat 2 mg versus placebo on seated DBP.	- Change from baseline in seated DBP at Week 4. - Change from baseline in seated DBP at Week 8.
To collect and store optional genetic samples for future exploratory genetic research, as detailed in Appendix D .	To be reported in a separate report.
Safety	
To assess the safety and tolerability of baxdrostat as compared to placebo.	Safety and tolerability will be evaluated in terms of: - AEs, SAEs and DAEs. - Vital signs (BP, pulse rate and body weight). - Safety investigations and laboratory tests (ECG, clinical chemistry, haematology). - AESIs (hyperkalaemia, hyponatremia and hypotension; based on Investigator reported AEs).

AE = adverse event; AESI = adverse event of special interest; BP = blood pressure; DAE = discontinuation of IMP due to AE; DBP = diastolic blood pressure; ECG = electrocardiogram; IMP = investigational medicinal product; nocturnal dip = difference between ambulatory daytime average SBP and ambulatory night-time average SBP, expressed as a percentage of the daytime average SBP; RAAS = renin-angiotensin-aldosterone system; SAE = serious adverse event; SBP = systolic blood pressure.

Primary estimand

The primary estimand is described by the following attributes:

- Population: participants with rHTN, as defined by the inclusion and exclusion criteria.
- Endpoint: change from baseline in ambulatory 24-hour average SBP at Week 12.
- Treatment condition: 2 mg baxdrostat QD and stable regimen of background antihypertensive medication, alternative treatment condition is placebo QD and stable regimen of background antihypertensive medication
- Intercurrent events: the intercurrent event of treatment discontinuation will be handled via a treatment policy strategy, ie, to ascertain the treatment effect regardless of treatment discontinuation. The intercurrent event of rescue therapy will be handled via a hypothetical strategy, ie, to ascertain the treatment effect regardless of initiation of rescue therapy.
- Population-level summary: difference in average change from baseline between baxdrostat (2 mg) versus placebo.

4 STUDY DESIGN

4.1 Overall Design

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

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

- 2 mg baxdrostat
- Placebo

The randomisation will be stratified by mean ambulatory SBP at baseline ($<$ 140 mmHg, $\geq$ 140 mmHg).

During the 12-week double-blind treatment period, participants should remain on their background antihypertensive medication. Doses of background antihypertensive medications should not be changed during this period unless participants experience SBP $<$ 100 mmHg with symptoms of hypotension. Rescue therapy is permitted if the SBP or DBP exceeds 170 or 105 mmHg, respectively (see Section 6.9.2). The choice of rescue therapy is based on the Investigator's best clinical judgement; however, the use of potassium-sparing diuretics and MRAs are prohibited (see Section 6.9.1).

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

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 globally at approximately 100 study centres and in approximately 22 countries.

A Data Monitoring Committee will be appointed for this study to monitor the safety and scientific integrity of a human research intervention and to make recommendations to AstraZeneca regarding the stopping of the study due to any harms (see Section 9.6).

An Executive Committee will be formed to provide scientific oversight and approval of the overall study design, of the clinical study protocol (CSP) and any protocol amendments.

4.1.1 Screening

All participants that consent to be involved in the study will be screened within 4 weeks, prior to starting the run-in period, to determine whether they are eligible for the study.

A 7-day extension of the screening period is allowed for transient unforeseen personal events that result in a missed visit.

4.1.2 Placebo Single-Blind Run-in Period

Eligible participants who complete the Screening Visit procedures, will enter a 2-week single-blind run-in period and will receive placebo in addition to any existing background antihypertensive medication.

Participants will take the placebo tablets with their existing background antihypertensive medication during this period (see Section 6.1 for further information).

The objective of this period is to decrease the placebo effect after baseline and to ensure that participants have a stable background antihypertensive medication (see inclusion criterion 3; Section 5.1).

A 7-day extension of the run-in period is allowed for transient unforeseen personal events that result in a missed visit. The Run-in period can also be shortened by up to 4 days (a minimum length of 10 days instead of 2 weeks) if deemed necessary, due to unforeseen events.

4.1.3 Double-Blind Placebo-Controlled Treatment Period

Approximately 212 participants, who meet the study Inclusion Criteria (see Section 5.1), will be randomised in a 1:1 ratio to receive either 2 mg baxdrostat QD or placebo QD, and stratified by mean ambulatory SBP at baseline (< 140 mmHg, ≥ 140 mmHg). Participants will receive treatment for 12 weeks (from Week 0 to Week 12).

During this period, participants should remain on their background antihypertensive medication regimen and dose (see SoA [Section 1.3] and Section 6.1). Doses of background antihypertensive medication should not be changed during this treatment period unless participants experience SBP < 100 mmHg with symptoms of hypotension.

For participants who meet the criteria for receiving rescue antihypertensive medication (SBP or DBP exceeds 170 or 105 mmHg, respectively), see Section 6.9.2.

4.1.4 Safety Follow-up

All study participants will complete a 2-week safety follow-up period prior to finalising the

overall study. Participants will enter this period after finalising the 12-week double-blind period.

Participants who withdraw from the study or who are discontinued as per the Investigator's discretion (see Section 7.2), should be asked to complete an early Safety Follow-up Visit, which will be scheduled 14 days (± 4 days) after they receive the last study intervention dose.

4.2 Scientific Rationale for Study Design

The study design is developed to investigate the safety, tolerability and the effect of 2 mg baxdrostat vs placebo in individuals with rHTN when added to the participant's antihypertensive medication regimen of ≥ 3 antihypertensive agents, including one diuretic.

In order to assess the study's objectives, the following are included in the study design:

- Resistant hypertension is difficult to firmly diagnose due to the variability in patient adherence to their prescribed antihypertensive medication. An initial run-in period is included to this study to decrease the placebo effect and to ensure there is a stable background therapy once participants start receiving study treatment.
- A placebo-controlled arm is incorporated to demonstrate the study treatment efficacy of baxdrostat. Placebo is chosen as control to objectively assess the effects of study treatment.
- Ambulatory BP measurements are used to minimise the observed placebo effect due to a white coat phenomenon - which causes BP to spike when it is measured at clinical sites or around doctors in comparison with BP results obtained at home - and to provide additional data about the effect of baxdrostat on the reduction of blood pressure within 24 hours.
- Direct observed therapy is used before and after the 12-week treatment period to determine the participants' adherence to his/her prescribed background antihypertensive medications and to the study intervention intake.
- To ensure the integrity of study results, the ABPM/AOBPM will be recorded digitally; BP measurements for all primary and secondary endpoint values will be saved in a secure and unmodifiable database.
- A DMC is established to minimise the risk to study participants. The DMC review outcome will allow to stop the study early if additional risk was found in either treatment arm.

4.3 Justification for Dose

To date, at least 693 participants have been exposed to either baxdrostat at single doses of 1 to 360 mg or to baxdrostat at multiple doses of 1 to 10 mg (for 5 or 10 days) in several

completed Phase I and Phase II clinical studies. In these studies, baxdrostat was safe and well-tolerated. Pharmacokinetic data from Phase I studies showed that plasma peak concentration generally occurred within 4 hours post-dose and the mean half-life is approximately of 29 hours, supporting a once daily dosing regimen. Furthermore, exposure to baxdrostat was not affected by concomitant food intake and baxdrostat may be administered regardless of food intake. The PK of baxdrostat was comparable in healthy participants and patients with hypertension and was not affected by renal impairment (mild to severe) or moderate hepatic impairment.

Studies in human participants demonstrated that baxdrostat was effective in lowering aldosterone levels. After repeat dosing of a dose range of 0.5 to 5 mg during 10 days in participants with low and normal salt dietary intake, the PD response was dose-dependent and maximum suppression of serum aldosterone level was achieved with a once daily dose of 1.5 mg. In patients with rHTN (Study CIN-107-121), 0.5, 1 and 2 mg once daily administration of baxdrostat were studied and the resulting placebo-corrected mean reductions in SBP at Week 12 were 2.7, 8.1 and 10.9 mmHg, respectively. Generally, the baxdrostat 1 and 2 mg doses showed significantly greater decrease in SBP compared to placebo, while the baxdrostat 0.5 mg dose was not significantly different compared to placebo. Thus, the baxdrostat 1 and 2 mg doses are considered efficacious, while the effect of the baxdrostat 0.5 mg dose is regarded as not significant.

Baxdrostat doses up to 2 mg QD were well-tolerated in study participants, with a mild change in mean serum K^+ and sodium, and a slight decrease in eGFR observed. Though individual participants did experience more significant abnormalities, these were infrequent and well-managed. The majority of laboratory parameter changes were not associated with significant clinical AEs. Sporadic hypotension and associated dizziness appeared to be mostly mild.

Based upon the PK, PD, efficacy and safety profiles established in healthy participants and patients in previous studies, 2 mg QD is selected in the present study as a well-tolerated dose with predicted high efficacy.

4.4 End-of-study Definition

For the purpose of Clinical Trial Transparency, the definition of the end of the study differs under FDA and EU regulatory requirements:

- European Union requirements define study completion as the last visit of the last subject for any protocol related activity.
- Food and Drug Administration requirements defines two completion dates:
 - 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 he/she has completed all phases of the study (ie, run-in period, treatment period and safety follow-up period), including the last visit or the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study or the last scheduled procedure shown in the SoA for the last participant in the study, globally.

5 STUDY POPULATION

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

Please refer to Section 5.4 for retesting and rescreening options for some of the criteria presented in the subsections below.

5.1 Inclusion Criteria

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

Age

- 1 Participant must be ≥ 18 years old, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

- 2 Mean seated SBP¹ measured by AOBPM of ≥ 140 mmHg and < 170 mmHg at screening.

¹ After > 5 minute in a seated position (feet flat on floor, back supported, measurement arm supported), 3 measurements, 1 minute interval, average of the last 2 measurements, refer to Section 8.2.1.

- 3 Have a stable regimen of ≥ 3 antihypertensive medications, from different therapeutic classes (at least one must be a diuretic), at maximum tolerated dose in the judgement of the Investigator, for at least 4 weeks prior to screening. 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.
- 4 Have $\text{eGFR} \geq 45 \text{ mL/min/1.73 m}^2$ at screening ².
- 5 Serum K^+ level ≥ 3.5 and $< 5.0 \text{ mmol/L}$ at screening, determined as per central laboratory. See Section 8.3.4.1 for laboratory K^+ measurement details.

Sex and Contraceptive/Barrier Requirements

- 6 Only female participants:

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

- (a) Female participants:

- (i) Females not of child-bearing potential are defined as females who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are post-menopausal. Females will be considered post-menopausal 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:
- (ii) Females < 50 years old would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the post-menopausal range.
- (iii) Females ≥ 50 years old would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- (iv) 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

² Using the eGFR equation developed by [Inker et al 2021](#).

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. Cessation of contraception after this point should be discussed with a responsible physician.

- (v) 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.
- (vi) All females of child-bearing potential must have a negative pregnancy test result at screening and not be at stage of breastfeeding (see SoA for test details; [Table 2]).
- (vii) 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 treatments) ([periodic abstinence - eg, calendar, ovulation, sympto-thermal, post-ovulation methods - declaration of abstinence for the duration of exposure to study intervention and withdrawal are not acceptable methods of contraception]); a vasectomised partner; Implanon[®]; bilateral tubal occlusion; intrauterine device/levonorgestrel intrauterine system; Depo-Provera[™] injections; oral contraceptive associated with inhibition of ovulation; and Evra Patch[™], Xulane[™], or NuvaRing[®].

Informed Consent

- 7 Capable of giving signed informed consent (including compliance with the requirements and restrictions listed in the ICF and in this protocol). See Appendix A 3 for details on the informed consent process.
- 8 Provision of signed and dated written Optional Genomics Initiative Research Information and Consent Form prior to collection of samples for optional genomics initiative research that supports the Genomic Initiative. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit (see Appendix D 2).

5.1.1 Randomisation Criteria

Participants are eligible to be randomised to a treatment group only if all the following criteria apply:

- 9 Mean ambulatory SBP $\geq$ 130 mmHg (see Section 8.2.1 for BP measurement procedures).

- 10 Have 80% to 120% adherence to placebo during the run-in period, based on pill counts in the morning of randomisation.
- 11 Have no change in background therapy regimen and dose consisting of ≥ 3 antihypertensive medications (at least one is a diuretic) for at least 4 weeks prior to randomisation. 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.
- 12 Demonstrated good adherence to the prescribed antihypertensive medications by performing DOT.

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 SBP ³ on AOBPM ≥ 170 mmHg. See Section 8.2.1 for BP measurement procedures.
- 3 Mean seated DBP ³ on AOBPM ≥ 110 mmHg. See Section 8.2.1 for BP measurement procedures.
- 4 Current or prior treatment (within the 4 weeks before screening) with angiotensin-receptor blockers and ACEIs (both taken simultaneously).
- 5 Serum sodium level < 135 mmol/L at screening, determined by central laboratory.
- 6 Has the following known secondary causes of hypertension: renal artery stenosis, uncontrolled or untreated hyperthyroidism, uncontrolled or untreated hypothyroidism, pheochromocytoma, Cushing's syndrome, aortic coarctation.
- 7 New York Heart Association functional HF class IV.
- 8 Medical history of stroke, acute coronary syndrome, hypertensive encephalopathy, or hospitalisation for HF in the 6 months prior to screening.

³ Should be measured after > 5 minute in a seated position (feet flat on the floor and back supported).

- 9 Planned percutaneous coronary intervention/coronary artery bypass grafting or percutaneous coronary intervention/coronary artery bypass grafting done within 6 months prior to screening.
- 10 Known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease.
- 11 Left bundle branch block and any cardiac arrhythmia requiring treatment.
- 12 Persistent atrial fibrillation.
- 13 Known severe hepatic impairment, defined as Child-Pugh Class C, based on records that confirm documented medical history.
- 14 Uncontrolled diabetes with HbA1c > 9.5% (80 mmol/mol).
- 15 QTcF > 470 msec.
- 16 Family history of Long QT syndrome.
- 17 Heart rate < 45 or > 110 beats/min in a resting position, as per vital signs assessment.
- 18 Participants suspected to have severe cardiac hypertrophy.
- 19 Participants who are pregnant or breastfeeding.
- 20 Participants with a diagnosis of adrenal insufficiency.
- 21 Any of the following related to COVID-19 infection:
 - a) Suspected (as judged by the PI) 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

- 22 Prior medical treatment with any MRAs, antiarrhythmic medications (beta blockers and calcium channel blockers classified as Class II/IV antiarrhythmics used to treat hypertension, and digoxin are permitted), or potassium-sparing diuretic use within 4 weeks prior to screening.
- 23 Treatment with potassium binders within 2 months prior to screening.
- 24 Is expected to receive or is receiving any of the exclusionary drugs such as strong inducers of cytochrome P450 (CYP) 3A, chronic (taken more than 3 times a week for more than 3 months) use of NSAIDs (use of low-dose aspirin is permitted, as per medical judgement), MRAs, and/or chronic use of systemic steroids within 8 weeks prior to screening.
- 25 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.

- 26 Current or prior treatment within 6 months prior to screening with cytotoxic therapy. See Section 6.9.1 for prohibited concomitant medications during the study.
- 27 Treatment with K^+ supplements are not prohibited but should be continuously assessed and monitored throughout the trial (see Section 8.3.4.1 for K^+ measurements).

Prior/Concurrent Clinical Study Experience

- 28 Known hypersensitivity to baxdrostat or drugs of the same class, or any of its excipients.
- 29 Participation in another clinical study with an investigational product administered in the 3 months prior to randomisation in this study.

Other Exclusions

- 30 Participants working shifts (ie, shifts that comprise working hours at different times on different days).
- 31 Participants working night shifts.
- 32 Participants who cannot complete the 25-hour ABPM assessment at randomisation within two attempts (will be considered screen failures; see Section 8.2.1.1).

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 6.9.1.

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^+ .

Foods that contain high K^+ include:

- High K^+ level fruits: bananas, cantaloupe, honeydew, oranges, nectarines, kiwi, mango, papaya, prunes, watermelon, pomegranate, dates, dried fig, dried fruits. Limit to one small piece or half-a-cup.
- Vegetables: avocados, broccoli, brussels sprouts, sweet potatoes, parsnips, pumpkin, tomato and tomato-based products, white potatoes, vegetable juices, winter squash.
- Other: tofu, milk, yogurt, ice-cream, chocolate, granola, nuts, peanut butter, salt substitutes.

5.3.2 Caffeine, Alcohol and Tobacco

Smoking habits will be collected at Visit 4 (randomisation) and recorded in the eCRF.

Prior to each visit where blood samples are collected for PD measurements, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the PD sample.

Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

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 at randomisation. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Data collected at screening for this study is detailed in Section 8.1.

Two separate processes are described below, one for retesting and one for rescreening. Note that retesting is not the same as rescreening.

5.4.1 Retest

To account for variability of K^+ , sodium, and BP, a retest of these parameters may be performed if the result does not meet the eligibility criteria for participation in this study, at the Investigator's discretion. Retesting may be considered if the initial abnormal result is suspected to have a transient reversible cause and there is no history of similar recurrent findings. Retest must be done prior to the next planned visit specified in the SoA.

Retesting is only allowed once for each parameter. Participants may be eligible for rescreening

after having a retest (see Section 5.4.2). Retesting does not require reconsent or repetition of any preceding visits and assessments.

Additionally, when performing a retest, the following applies:

- Potassium and sodium measurements must be repeated using the central laboratory.
- Only participants who met exclusion criteria 2 or 3 are eligible for a repeated BP measurement.

5.4.2 Rescreening

Participants who do not meet eligibility criteria (screen failure) may be rescreened. Participants may also be rescreened for unforeseen personal or study-related events if they are otherwise eligible for the study. Rescreening is only allowed 2 times for any potential participant in this study. Rescreened participants will be assigned the same participant number they were given during the first Screening.

Rescreening is not allowed in the following cases:

- Mean seated SBP on AOBPM < 140 mmHg at screening (see inclusion criterion 2).
- Estimated glomerular filtration rate < 45 mL/min/1.73m² at screening⁴ (see inclusion criterion 4).
- Serum potassium (K⁺) level ≥ 5.0 mmol/L at screening determined as per central laboratory (see inclusion criterion 5).
- Mean ambulatory SBP < 130 mmHg at randomisation (see randomisation criterion 9).
- Have a placebo adherence < 80% or > 120% during the run-in period, based on pill counts in the morning of randomisation (see randomisation criterion 10).
- Not having demonstrated good adherence to the prescribed antihypertensive medications by performing DOT during Visit 3 (see randomisation criterion 12).
- Serum sodium level < 135 mmol/L at screening, determined as per central laboratory (see exclusion criterion 5).

⁴ Using the eGFR equation developed by Inker et al 2021..

- Have any of the following known secondary causes of hypertension: renal artery stenosis, uncontrolled or untreated hyperthyroidism, uncontrolled or untreated hypothyroidism, pheochromocytoma, Cushing's syndrome, aortic coarctation (see exclusion criterion [6](#)).
- Participants with a diagnosis of adrenal insufficiency (see exclusion criterion [20](#)).
- Participants who cannot complete the 25-hour ABPM assessment at randomisation within two attempts (will be considered screen failures; see Section [8.2.1.1](#)). See exclusion criterion [32](#).

Participants who are rescreened within 10 days of signing the ICF are only required to retake assessments that qualified for rescreening, without having to re consent. Rescreening must be completed within 4 weeks of signing the ICF. If participants are rescreened more than 10 days after signing the initial ICF, participants must sign a new ICF, repeat all screening assessments, and complete the screening within 4 weeks of signing the new ICF.

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, medical devices and other interventions (eg, surgical and behavioural) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

Study treatments to be administered and investigated in this study are described in [Table 5](#).

Table 5 Study Intervention

Treatment name	2 mg Baxdrostat Treatment	Placebo Treatment
Intervention name	Baxdrostat	Placebo
Type	Drug	Drug
Dose formulation	Tablet	Tablet
Unit dose strengths	2 mg per tablet	N/A
Dosage level	2 mg baxdrostat once daily	Placebo once daily
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

Note: the external label and appearance of all tablets, for both study treatments, 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.

Study participants will take the study intervention tablet daily during the treatment period, for a total of 12 weeks (starting at baseline and taking the last study intervention dose the day before the EoT visit [see SoA; Section 1.3]). If another ABPM attempt is needed, the last dose of study intervention will be part of the repeated DOT (see Section 8.2.1). Please refer to Section 8.2.1.4 for details on study intervention administration during DOT.

Study intervention will be administered to participants at site during study visits (see SoA, Section 1.3) after BP measurements are performed, with the exception of the days of Study Visits 5.1 and 5.2, when participants will self-administer the study intervention at home.

The first dose of placebo should be given at site during Visit 2. Please note that during the run-in period (see Section 4.1.2), the last dose of placebo should be taken on the day before randomisation, so that participants can receive their first dose of study intervention at site, after randomisation.

The following medicinal products are defined as NIMP/AxMP in this study and will be obtained by the study participants. All NIMP/AxMPs used in this clinical trial are authorised

and are to be used in accordance with the terms of their marketing authorisations:

- **Background Antihypertensive Medication:** 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 treatment.
- **Rescue Antihypertensive Medications:** The rescue antihypertensive medicine(s) that participants may receive during the study (see Section 6.9.2).

Please see [Appendix G](#) for details on NIMPs/AxMPs ATC class codes for this study.

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 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 0) will be centrally assigned to randomised study intervention using an automated IRT/RTSM system that will allocate

participants into 1 of the 2 different treatment arms (ie, baxdrostat 2 mg or placebo). Study intervention will be dispensed at the study visits summarised in the SoA (see Section 1.3).

Randomisation will be performed after the run-in period to allocate approximately 212 participants into receiving either 2 mg baxdrostat QD or placebo QD, using a 1:1 ratio. The randomisation will be stratified by mean ambulatory SBP at baseline (< 140 mmHg, ≥ 140 mmHg).

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

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

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

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

6.4 Blinding

The IRT/RTSM will provide to the Investigator or pharmacist the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each centre.

The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The IRT/RTSM will be programmed with blind-breaking instructions. In the case of a potential medical emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such determination. In this situation, the Investigator will document and report the unblinding action to AstraZeneca, within 24 hours after breaking the blind.

If unblinding occurs, the Investigator has to make sure not to reveal the treatment given to the participant to other clinical sites or blinded study personnel.

Additionally, 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 (PRA, corticosterone, 11-deoxycorticosterone, 18-OH corticosterone, aldosterone) will be blinded.

6.5 Study Intervention Compliance

When participants are dosed at site, during on-site visits specified in the SoA (Section 1.3), they will receive the study intervention directly from the Investigator or designee, under medical supervision. When DOT is performed, the date and time of when study intervention is 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.

Participants will self-administer study intervention at home during non-study visit days, preferably in the morning. Compliance with study intervention will be documented in the source documents and eCRF as follows:

- Study intervention exposure - measured by study treatment interruptions and/or treatment discontinuation - will be recorded in the eCRF using the exposure form. Intervention start and stop dates, including dates for intervention delays, will also be recorded in the eCRF.
- Drug accountability will be reported in the eCRF and must be reconciled with study intervention and compliance records.

6.6 Dose Modification

Investigational medicinal product dose modification 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 IMP greater than one tablet per day will be considered an overdose.

The most likely manifestations of an overdose based on the mechanism of baxdrostat action would be hypotension, hypovolemia 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.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate until at least the next scheduled Follow-up Visit. Refer to Section 8.4 for details of AE/SAE reporting related to overdose.
- Document the quantity of the excess dose as well as the duration of the overdose.
- Treat overdose symptoms using clinical judgement.

The Sponsor does not recommend specific treatment for an overdose.

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 participants (except for screen failures) are receiving at the time of enrolment or receive 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).
- Systemic corticosteroids (eg, prednisone, prednisolone, dexamethasone [topical and inhaled steroids are allowed]).
- Strong CYP3A4 inducers (eg, apalutamide, avasimibe, carbamazepine, enzalutamide, lumacaftor, mitotane, phenytoin, rifampin, rifapentine, St. John's wort).
- Simultaneous use of angiotensin-receptor blockers and ACEIs are not allowed during the study. Participants should be on stable dose of either drug class; any changes to drug dose or class must be closely monitored (see Section 8.3.4.1).
- Tacrolimus, calcineurin inhibitors and cyclosporin. Topical/inhaled immunosuppressants are permitted.

The following medications and supplements listed below are permitted only under certain circumstances:

- Potassium binders (prohibited at screening but can be started as a corrective action during the study).
- Treatment with K⁺ supplements are not prohibited but should be continuously assessed and monitored throughout the trial. See Section 8.3.4.1 for K⁺ laboratory measurements.
- Chronic NSAID use. If occasional NSAID usage (less than 3 times a week for less than 3 months) is required, the Investigator should determine the extent and frequency of additional monitoring based on their clinical judgement, taking into account factors such as kidney function, hydration status, NSAID dose, concurrent medication usage, and severity of concomitant diseases. See Section 8.3.4.1 for K⁺ monitoring.

6.9.2 Rescue Medicine

The study sites will be responsible for prescribing rescue antihypertensive medication, which is categorised as NIMP/AxMP in this study (see Section 6.1). Please see [Appendix G](#) for details on rescue antihypertensive medication ATC codes for this study.

If a participant has a SBP or DBP that exceeds 170 or 105 mmHg, respectively, an unscheduled visit will be planned for the following 24 to 48 hours to take the SBP measurement again. If the new SBP reading falls under the same criteria (SBP or DBP exceeds

170 or 105 mmHg, respectively) during the unscheduled visit, rescue therapy will be permitted. Participants receiving rescue therapy should continue with the study intervention.

The choice of rescue therapy is based on the Investigator's best clinical judgement. The use of potassium-sparing diuretics and MRAs are prohibited. In the exceptional circumstance that the Investigator considers there is a medical need for a participant to receive MRAs, study treatment must be permanently discontinued (see Section 7.1).

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

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, are handled as part of [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).

7.1.1 Temporary Interruption of Study Intervention

Study intervention will be temporarily interrupted in the following situations:

- If a participant has a QTcF ≥ 500 ms study treatment will be temporarily interrupted at first and may be permanently discontinued afterwards. See details in Section 7.1.4.
- If a participant has a QTcF increase from baseline ≥ 60 ms study treatment will be temporarily interrupted at first and may be permanently discontinued afterwards. See details in Section 7.1.4.
- Hypotension: if the participant's SBP is ≤ 90 mmHg and the participant has symptoms, 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, BP should be re-checked either during an unscheduled visit within 10 days (± 4 days) from restart of study intervention, or during a scheduled visit where SBP is measured, within that time window.
- Hyponatraemia: if the participant's sodium level is < 130 mmol/L the participant may remain on study intervention, however, the sodium should be re-checked within 72 hours by the central laboratory and if the laboratory retest confirms sodium < 130 mmol/L, the study intervention should be temporarily interrupted. The study intervention may be restarted when the sodium has increased to > 135 mmol/L. If

study intervention is resumed, sodium level should be re-checked either during an unscheduled visit within 10 days (± 4 days) from restart of study intervention by the central laboratory, or during a scheduled visit where sodium level is measured, within that time window.

- Hyperkalaemia should be managed as per local standard-of-care. Participants may be treated acutely or chronically with potassium 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 the central laboratory may result in falsely elevated K^+ levels in the centrally 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 ≥ 5.5 to < 6.0 mmol/L, the participant may remain on study intervention, however, the K^+ should be re-checked within 72 hours by the local and central laboratory and if confirmed $K^+ \geq 5.5$ mmol/L, the study intervention should be temporarily interrupted.
- If K^+ is ≥ 6.0 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 central laboratory. If the repeated K^+ measurement is also ≥ 6.0 mmol/L, refer to Section 7.1.2 for permanent study intervention discontinuation details.
- The IMP may be restarted when K^+ level returns to ≤ 5.0 mmol/L. Potassium should then be re-checked by the local or central laboratory within 2 to 7 days from restart of study intervention.

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

Please refer to Section 8.4.4 for AEs based on examinations and tests and Section 8.4.6 for AESIs.

7.1.2 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 (see Section 7.2).
- An AE that, in the opinion of the Investigator, warrants discontinuation from further dosing.

- Severe non-compliance with the CSP, as judged by the Investigator.
- If the participant becomes pregnant during the study (see Section 8.4.9).
- If at any time during the study, the Investigator decides that a participant must be treated with an MRA or potassium-sparing diuretic (see Section 6.9).
- The participant has a mean seated SBP or seated DBP that exceeds 170 mmHg or 105 mmHg, respectively, in 2 separate occasions, despite rescue therapy being given after each of these 2 occasions (see Section 6.9.2). See Section 8.2.1 for BP measurement procedures.
- Hypotension: if the participant's SBP is ≤ 90 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-baseline sodium level is < 130 mmol/L) after a previous event (see Section 7.1.1), 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 ($K^+ \geq 6.0$ mmol/L) after a previous event (see Section 7.1.1), 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 should discontinue the study treatment and remain in the study for continued safety surveillance. In this situation, it is preferred that an attempt is made to establish whether the participant has primary or secondary adrenal insufficiency.

If study intervention is permanently discontinued, the participant will attend an early EoT Visit, which should be performed as soon as possible following the decision to discontinue, preferably within 2 weeks. During this EoT Visit, the same assessments indicated for Visit 9 will be performed (see Section 1.3).

Thereafter, the participant will attend the rest of the study visits (including the Week 12 EoT Visit) and perform the study assessments as indicated in the SoA, except for the requirement to continue receiving the study intervention for the rest of the study.

See Section 7.2 for details on permanent discontinuation or withdrawal from the study. Please see Section 8.4.4 for AEs based on examinations and tests and Section 8.4.6 for AESIs.

7.1.3 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, if the Investigator believes that it is in best interest of the participant.

Any new clinically relevant finding in liver tests which require interruption or discontinuation of study intervention should be reported as an AE (please refer to Section [8.4.4](#)).

7.1.4 QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline [which is the Randomisation Visit value] in QTcF) after enrolment, the Investigator or qualified designee will determine if the participant can continue 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 ≥ 500 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, participant is taking 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 [7.1.1](#)). On the contrary, if there are no other factors that could explain the QTcF value being 500 ms or higher, study treatment will have to be permanently discontinued.

Additionally, any QTcF value that increases from baseline ≥ 60 ms will be evaluated as specified in the paragraph above, and study treatment will be temporarily or permanently discontinued based on this evaluation (see Section [7.1.1](#)).

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

- Sponsor board approval is granted.
- Independent Ethics Committee and/or IRB approval is obtained, if required, and
- Separate consent for intervention restart is signed by the participant.

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, and reconsented before resumption of dosing.

Refer to [Appendix E](#) for details on the study intervention restart process.

If Sponsor board approval to restart/rechallenge 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. A participant may be discontinued from the study at any time at the discretion of the Investigator for behavioural, or compliance reasons.

If a participant is discontinued from the study, as per Investigator's discretion, efforts should be made to allow the participant to complete a Safety Follow-up Visit. Please refer to Section [4.1.4](#).

Withdrawal from the study describes a participant's voluntary decision to end his/her participation in the study. 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. During this EoT Visit, the same assessments indicated in Visit 9 (see Section [1.3](#)) will be performed and a Safety Follow-up Visit should be scheduled (please refer to Section [4.1.4](#) for details). The EoT Visit does not apply to participants who are not randomised.
- A participant who prematurely withdraws from study treatment will have an early EoT Visit performed at the time of the study treatment discontinuation. After performing the EoT Visit, the participant will complete the rest of the study visits (including the EoT Visit [ie, Visit 9]), as per SoA (Section [1.3](#)). A participant who wishes to withdraw from study treatment must also 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 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.

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 (see Section 1.3), 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 (see Section 1.3).

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.

8.1 Administrative and General/Baseline Procedures

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

For all participants, the following data will be collected at screening:

- Eligibility criteria (see Section 5).
- Demography details (see Section 8.1.1).
- Participant's height and body weight (see Section 8.3.1 and 8.3.2, respectively).
- Participant's medical/surgical history (see Section 8.1.2).
- Concomitant medication data (see Section 6.9).
- Safety assessments data (ie, vital signs, ECG and physical examination, see Section 8.3).
- Other safety data which will be only analysed at screening (ie, FSH and HbA1c) or only at screening and randomisation (pregnancy test), see Section 8.3.4).
- Any SAEs occurring after ICF is signed (see Section 8.4.8).
- Seated BP at screening (see Section 8.2.1.2).

Note that smoker status will be collected at Visit 4, along vital signs (see Section 8.3.2).

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

8.1.1 Demographics

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

8.1.2 Medical and Surgical History

The Investigator, or designee, should record 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

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

8.2.1 Blood Pressure Measurements

Blood pressure devices will be delivered by the Sponsor.

If an error occurred when measuring BP, during the procedures specified in Section 8.2.1.1 or Section 8.2.1.2, please refer to the dedicated manual for the centrally provided AOBPM device.

8.2.1.1 Ambulatory Blood Pressure Measurements

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

The ABPM device will record BP measurements every 20 minutes during a 16-hour daytime period (from 6 AM to 9.59 PM) and every 30 minutes during an 8-hour night-time period (from 10 PM to 5.59 AM).

Study personnel will fit the ABPM device on the participant's arm during the visits indicated in the SoA (see Section 1.3), thereafter, the participant will take the study intervention (corresponding to that day) and his/her prescribed background antihypertensive medications. The ABPM device will be fitted on the participant's non-dominant arm. Participants will wear the ABPM device for at least 25 hours before its removal at the study site, the following day.

Participants should not interrupt their stable regimen of prescribed antihypertensive

medications while wearing the ABPM device.

The ABPM device will be placed on the participant's arm between 6.30 AM and 11.30 AM, and it will start recording BP readings (after the participant takes the study intervention corresponding to that day and his/her prescribed background antihypertensive medications) at the timepoints corresponding to the 20 minutes; 40 minutes; and 00 minutes of every hour.

Participants will be instructed to refrain from strenuous exercise or showering while wearing the ABPM device, but to keep normal daily activities throughout the assessment period.

During the Randomisation Visit, the study intervention can only be dispensed to a participant after the 25-hour ABPM assessment is completed successfully (see Section 1.3).

The following situations should be considered:

- If the ABPM 25-hour period is not completed, the assessment must be repeated at an unscheduled visit. The ABPM assessment will be considered completed when all the following criteria are fulfilled:
 - ≥ 20 hours are recorded by the ABPM device.
 - $\geq 70\%$ of the ABPM readings are recorded.
 - ≤ 2 consecutive hours of recordings are missing.
- Participants who cannot complete the 25-hour ABPM assessment at randomisation within two attempts will be considered screen failures (see Section 5.2).
- If a participant cannot complete the 25-hour ABPM assessment at EoT (from Visit 8 to Visit 9) within two attempts, the data will be considered missing.

8.2.1.2 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.
- On study visits, when study intervention is administered at site, seated and orthostatic BP will be assessed pre-dose.
- Blood pressure measurements should be obtained prior to performing ECG recordings.
- For measuring BP by AOBPM, the following additional standardised procedures are recommended:

- The participant should be seated for at least 5 minutes in the examination room with the back supported, feet flat on the floor and the measurement arm supported so that the midpoint of the manometer cuff is at heart level.
- A designated AOBPM device will be provided to each clinical site and must be used for all study-related measurements.
- An appropriately sized cuff should be used with the bladder centred over the brachial artery.
- The cuff size and arm used for the measurement should be recorded.
- The arm with the higher mean BP value at screening should be used for screening and subsequent BP measurements. Note that for rescreening (see Section 5.4.2), the arm selection is not required, and the BP rescreening measurement should be performed using the arm with which the higher SBP was previously obtained.
- All BP measurements should be obtained at approximately the same time of the day when the screening measurements were obtained.
- Three seated BP measurements (each approximately 1 minute apart) should be obtained using the same arm and AOBPM device at each clinical site visit. Mean seated BP is defined as the average of the last 2 seated BP measurements of the total 3 measurements, at any single clinical site visit.
- If the difference between the last 2 SBP measurements is > 20 mmHg, additional readings should be performed (up to 6 additional measurements; performed as 3 seated BP readings measured twice). If the difference between the last 2 SBP measurements of these 2 additional triple measurements is still > 20 mmHg, the average of the last two measurements will be used.
- Right after the seated BP has been determined, orthostatic BP will be measured (see Section 8.2.1.3), only at the visits specified in the SoA (see Section 1.3).

The criteria for when a large reduction in BP should be reported as an AE is described in Section 8.4.4.

Additionally, the following details should be considered when measuring seated BP during screening:

- The arm with the higher seated SBP determined as per local standard procedures, will be used to take the screening SBP measurements and for all subsequent seated SBP measurements at all visits. Both, the dedicated centrally provided AOBPM device or the local blood pressure monitor can be used to determine laterality.
- Seated SBP measurements will be obtained three times, and the mean seated SBP will be calculated using the last 2 seated BP measurements of the total 3 measurements,

following the procedures described above (see Section 8.2.1.2). If the difference between the last 2 SBP measurements at screening is > 20 mmHg, additional readings should be performed (up to 6 additional measurements; performed as 3 seated BP readings measured twice). If these 2 additional triple measurements still fail the criteria, an unscheduled visit should be performed on the next available day. If an acceptable reading is not obtained at this additional visit, the participant must be considered a screen failure (see Section 5.2). Subsequent BP measurements should preferably be obtained at approximately the same time of day as when the screening measurements are obtained.

For safety reasons, if the standardised automated BP machines provided by the Sponsor were faulty or could not be used for any reason, the study site will use their BP measuring machines, making sure this occurrence is reported on the eCRF.

8.2.1.3 Orthostatic Blood Pressure Measurements

Orthostatic BP measurements include standing BP and will be measured using the AOBPM device during the visits specified in the SoA (Section 1.3). The following standardised procedures are recommended:

- After the seated SBP has been determined (see Section 8.2.1.2), the participant will be asked to stand and after approximately 1 minute a single standing BP measurement will be obtained, as required.
- Participants should not exercise, smoke, or consume caffeinated beverages or food 30 minutes prior to assessment of AOBPM.
- On study visits, when study intervention is administered at site, BP will be assessed pre-dose.
- Blood pressure measurements should be obtained prior to ECG recordings.
- For measuring BP by AOBPM, the following additional standardised procedures are recommended:
 - A designated AOBPM device will be provided to each clinical site and must be used for all study-related measurements.
 - An appropriately sized cuff should be used with the bladder centred over the brachial artery.
 - The cuff size and arm used for the measurement should be recorded.
 - The arm with the higher mean BP value at screening should be used for screening and subsequent BP measurements.
 - All BP measurements should be obtained at approximately the same time of the day when the screening measurements were obtained.

8.2.1.4 Direct Observed Therapy

Direct observed therapy will be performed by study personnel at Visit 3 (run-in period) and at Visit 8, see Section 1.3.

Direct observed therapy procedure is as follows:

- On the day of a DOT procedure, participants will not take their background antihypertensive medications at home (ie, their morning and mid-day prescribed antihypertensive medications), but at study site.
- During the study visit, participants will have ABPM device fitted.
- Thereafter, study personnel will administer the participant's prescribed background antihypertensive medications as well as the study intervention (placebo or baxdrostat), and study personnel will witness the participant taking these medications.
- After the participant takes the background antihypertensive medication and the study intervention, the participant will be monitored for any adverse effects for at least 1 hour. The exact length of the observation period will be determined by the Investigator, who will take the number of background antihypertensive medications and the patient's medical background into account.
- The participant's mean systolic ABPM will be assessed upon completion of the ABPM assessment at Visit 4 (randomisation). If the mean systolic ABPM value < 130 mmHg, the participant will not be randomised to study treatment (see Section 5.1.1).
- If the ABPM assessment has to be repeated at randomisation or at Week 12, the DOT assessment will also be repeated.

8.3 Safety Assessments

Planned time points for all safety assessments are specified in the SoA (see Section 1.3).

8.3.1 Physical Examinations

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.

The targeted physical examination performed at the visits indicated in the SoA (see Section 1.3) should include cardiovascular and lung evaluations and examination of any peripheral oedema.

8.3.2 Vital Signs

Vital signs will include heart rate and BP measurements. Orthostatic vitals will include standing heart rate and BP. Vital signs will be measured using the standardised procedures described in Section 8.2.1.

Body weight (kg) will be measured together with vital signs assessments. Data regarding smoker status will also be collected during Visit 4 (at randomisation).

Deterioration of vital signs compared to baseline 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.

8.3.3 Electrocardiograms

Electrocardiograms will be performed after the participant has been resting in supine position.

Twelve-lead ECGs will be printed and will be interpreted as soon as possible by the Investigator (or sub-Investigator for the Screening Visit only). All ECGs collected at all time points specified in the SoA must be evaluated 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:

- QRS interval
- Heart rate
- Heart rhythm
- RR interval
- QT interval
- QTc (QTcF). See Section 7.1.4 for QTc stopping criteria details.

Investigators should contact the Sponsor or designee if any clinically meaningful changes from baseline are noted on review. See Section 8.4.4 for ECG results that should be reported as AEs.

8.3.4 Clinical Safety Laboratory Tests

Blood and urine samples for determination of clinical chemistry, haematology, coagulation and urinalysis will be taken at the visits indicated in the SoA (see Section 1.3). All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoA.

Clinical chemistry, haematology and urinalysis will be performed at the central laboratory.

The date of sample collection will be recorded in the appropriate CRF. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. Sample tubes and sample sizes will be described in the Laboratory Manual. Please see Section 8.3.4.1 for details on K⁺ measurements.

See Section 7.1 for detailed information of how laboratory parameters outside normal range will be handled.

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

Laboratory variables to be measured are presented in Table 6.

Table 6 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum)
Haemoglobin (Hb)	Creatinine ^d
Leukocyte count	Bilirubin, total
Leukocyte differential count (absolute count)	Alkaline phosphatase (ALP)
Platelet count	Aspartate transaminase (AST)
Glycosylated haemoglobin (HbA1c) ^a	Alanine transaminase (ALT)
Urinalysis (dipstick; urine) ^b	Albumin
Hb/Erythrocytes/Blood	Calcium, total
Protein/Albumin	Sodium
Glucose	Potassium
Leucocytes	Creatine kinase (CK)
Nitrites	Phosphate
Human chorionic gonadotropin (β-hCG) ^c	Magnesium
	Bicarbonate
	Follicle stimulating hormone (FSH) ^a

^a Only measured at screening.

^b Urinalysis tests are only performed at Visit 4 (except β-hCG pregnancy test; see footnote 'c').

^c Urine pregnancy test (β-hCG) will be performed at the Screening and Randomisation Visits (please see Section 1.3 for more details).

^d Estimated glomerular filtration rate will be calculated using the creatinine results obtained from blood samples.

- 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 adverse event (see Section 8.4.4 for AEs based on examination tests).
- The eGFR will be monitored systemically throughout the study by the central laboratory (see SoA in Section 1.3). 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:

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

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](#)).

- If a participant shows AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN, please refer to [Appendix E](#) for further instructions. See also Section 8.4.4 for AEs based on examination tests. If total bilirubin value is elevated the laboratory should also report the direct and indirect bilirubin values. Further details are described in the Laboratory Manual.

Laboratory Analyses Performed at Screening

Laboratory analyses that are only performed at screening (see SoA; Section 1.3), are as follows:

- Analysis of FSH for confirmation of post-menopausal status of women < 50 years old.
- Pregnancy tests for woman of child-bearing potential. A urine pregnancy tests to measure β -hCG will be performed at the Screening and Randomisation Visits. The urine pregnancy test can be replaced by a serum pregnancy test, if required by local authorities. Additionally, if required by local authorities, additional pregnancy tests can be done during the study. Ad hoc pregnancy test can be used at the discretion of the Investigator during the treatment period if there is a suspected pregnancy. Participants who become pregnant should be withdrawn from the study and the Sponsor notified according to the procedures outlined in Section 8.4.9.
- The HbA1c test will be performed to exclude poorly controlled diabetes at screening (see Section 5.2).

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 [Table 2](#). 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 in the CRF only if they meet AE criteria (see Section 8.4.4).

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/angiotensin-receptor

blockers/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 7.1.1 and Section 7.1.2 for temporary interruption and permanent discontinuation criteria of the study intervention, respectively, based on K⁺ levels.

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:

- Adverse Event (verbatim).
- The date when the AE started and stopped.
- Maximum intensity (mild, moderate, severe).
- Whether the AE is serious (yes or no).
- Investigator causality rating against the IMP (yes or no).
- Action taken with regard to IMP.
- Outcome.
- Whether the AE is an AESI (yes or no).
- Whether the AE requires treatment with a concomitant medication.

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

- Date AE met criteria for SAE.
- Date when Investigator became aware of the SAE.

- AE description.
- Reason as to why AE is considered serious ([Appendix B](#)).
- Date of hospitalisation.
- Date of discharge.
- Probable cause of death (verbatim).
- Date of death.
- Autopsy performed (yes or no).
- Causality assessment in relation to study procedure(s) (yes or no).
- Causality assessment to other medication (yes or no).

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse Events will be collected from randomisation throughout the entire treatment period and during the follow-up period.

Serious Adverse Events will be recorded from the time of signing of the ICF and throughout the whole treatment period, including the follow-up period.

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 will be 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 study intervention?'.

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 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.
- The analysis/assessment results are the reason for discontinuation of the IMP.
- The analysis/assessment results 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, 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 vs 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 assessment will be reported as an AE.

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 Differential Diagnosis for Adrenal Insufficiency

Due to theoretical risk, adrenal insufficiency should be considered in the differential diagnosis of participants who develop unexplained signs and symptoms such as anorexia, weight loss, hypoglycaemia, hyperpigmentation, hypotension, nausea, vomiting, abdominal pain, diarrhoea, fatigue, weakness, etc. The evaluation and management of the participant should be at the discretion of the Investigator, including testing to establish the diagnosis according to clinical guidelines/local practise and if needed, in consultation with an Endocrinologist.

If an ACTH stimulation test is performed, the results should be recorded in the eCRF (including the spot ACTH assessment and the stimulated cortisol level).

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 the AESI status and category, on an AE form, which must be submitted as per standard timelines for AEs. The Investigator should assess factors that potentially contribute to the AESIs and record these in the eCRF.

For this clinical study, AESIs include the following: hyperkalaemia, hyponatraemia and hypotension events that require medical intervention. These events consist of abnormally high K^+ in blood, abnormally low sodium concentration in blood and abnormally low BP, respectively (please see subsections below). These AESIs will be confirmed by a clinician.

Potassium and sodium levels will be measured in the clinical laboratory analysis (see Section 8.3.4), using the blood samples collected at the time points specified in the SoA (see Section 1.3). Blood pressure will be measured as detailed in Section 8.2.1.

During the course of the study, additional AESIs may be identified by the Sponsor. All AESIs must be recorded in the eCRF.

8.4.6.1 Hyperkalaemia

An AESI of hyperkalaemia is an event of high K^+ levels (> 5.0 mmol/L) that requires medical intervention.

Local laboratory K^+ values for all events of hyperkalaemia that fulfil the AE reporting criteria should be recorded in the specific CRF 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 sodium levels (< 135 mmol/L) in serum that requires medical intervention.

8.4.6.3 Hypotension

An AESI of hypotension is an event of low SBP that requires medical intervention.

8.4.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation, and occurrences of $AST \text{ or } ALT \geq 3 \times ULN$ together with $TBL \geq 2 \times ULN$ 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 considered causally related to the IMP or not. 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 data entry site **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 and **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 (occurring in study participants and in sexual partners of study participants) and all pregnancy outcomes 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 the Sponsor 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 data entry site **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.

8.4.9.2 Paternal Exposure

Male study participants are not required 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 will inform 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 will work 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 form and on the overdose form in the eCRF.
- An overdose without associated symptoms is only reported on the overdose form in the eCRF.

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 data entry site **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

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

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

Pre-dose blood samples will be collected for measurement of plasma concentrations of baxdrostat as specified in the SoA (Section 1.3). All PK samples will be collected pre-dose; thus, participants should be reminded not to take their study medication at home on the day of their clinic visit as they will receive study medication in the clinic on these days. At Visit 9, PK samples will be collected after ABPM measurements are completed (except for early EoT Visit, see SoA).

For participants who are discontinued from investigational product due to hyperkalaemia, a PK sample should be collected at the EoT Visit (see SoA; Section 1.3).

Samples may be collected at additional time points during the study if warranted and agreed 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.

Blood samples for PK analysis will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

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

For storage, re-use and disposal or destruction of PK samples see [Appendix C](#).

8.5.2 Determination of Drug Concentration

Blood 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 would 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. For more details on unblinding please see Section 6.4.

8.6 Pharmacodynamics

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

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

Aldosterone, 11-deoxycorticosterone, 18-OH corticosterone and corticosterone will be measured using the liquid-chromatography with tandem mass spectrometry method. These results will be obtained for PD analyses purposes only.

8.6.1 Collection of Samples for Pharmacodynamics

Pre-dose blood samples for PD analysis will be collected at the time points specified in the SoA (Section 1.3). Collection of blood samples should be performed in the morning at the clinical site, after the participant has been out of bed for approximately more than 2 hours. The participant must be seated for 5 to 15 minutes prior to blood extraction.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual and according to local regulatory authorities.

Additional PD samples may also be collected in the event of an SAE, AE leading to withdrawal, or any other safety event at the discretion of the Investigator and/or Sponsor.

The remaining PD samples may be used to evaluate biomarkers related to hypertension and its comorbidities, if consented by participants.

For storage, re-use and destruction of samples for PD see [Appendix C](#).

8.7 Optional Genomics Initiative

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA and is subject to participant agreement in the optional Genomics Initiative research information ICF.

Blood samples for DNA isolation will be collected at baseline from participants who have consented to participate in the genomic and multi-omics analysis component of the study. Participation is optional. Participants who do not wish to participate in genomic and multi-omics research may still participate in the study.

See [Appendix D](#) for information regarding the Genomics Initiative genomic and multi-omics 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

Biomarkers will be evaluated in this study. Please refer to Section [8.6.1](#) for details.

Already collected PD samples may be analysed for additional biomarkers thought to play a role in hypertension and its comorbidities, and to evaluate their association with observed clinical responses to baxdrostat.

For details on the ICF section that addresses the collection and use of any optional HBS, see [Appendix A 3](#). For storage, re-use and destruction of biomarker samples see [Appendix C](#).

8.9 Immunogenicity Assessments

Not applicable.

8.10 Medical Resource Utilisation and Health Economics

Not applicable.

8.11 Study Participant Feedback Questionnaire

Not applicable.

9 STATISTICAL CONSIDERATIONS

The SAP will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Any changes to the methods described in the SAP will be described and justified as needed in the CSR.

9.1 Statistical Hypotheses

The hypothesis for the primary objective is as follows:

- H_0 : no difference in mean change from baseline in ambulatory 24-hour average SBP at Week 12 between 2 mg baxdrostat versus placebo.
- H_1 : difference in mean change from baseline in ambulatory 24-hour average SBP at Week 12 between 2 mg baxdrostat versus placebo.

9.2 Sample Size Determination

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

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

9.3 Populations for Analyses

Study populations defined for this study are presented in [Table 7](#).

Table 7 Populations for Analysis

Population/Analysis Set	Description
Randomised Set	Includes all randomised participants. This population will be used for the purpose of subject disposition.
Full Analysis Set	All randomised participants who received at least one administration of study intervention. Data from participants will be analysed according to the treatment group to which they were randomly assigned. Unless otherwise stated, the FAS will be used for the efficacy endpoints.
Safety Analysis Set	All randomised participants who received at least one administration of IMP. Treatment classification will be based on IMP that participants actually receive (ie, erroneously treated participants will be classified according to the treatment they actually received and not to the treatment they were meant to receive). This population will be the primary population for the safety analyses.
PK Analysis Set	All randomised participants who have at least one evaluable post-dose plasma concentration data for PK analysis and who received active treatment.

FAS = full analysis set; IMP = investigational medicinal product; PK = pharmacokinetic.

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. The SAP will also describe in detail how all the study endpoints will be analysed to determine whether the intervention being studied is superior to placebo.

All 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, standard deviation, median, minimum and maximum values. Analysis of categorical variables will include frequency and percentage.

The SAP will provide further details on estimands for the study objectives together with the corresponding intercurrent event strategies. Details concerning the handling of the ABPM data in the statistical analyses, including the validity criteria and calculation of the 24-hour average BP, night-time average BP and daytime average BP, will be described in the SAP.

9.4.2 Efficacy

9.4.2.1 Primary Endpoints

The analysis of the primary endpoints assesses the difference in change in ambulatory 24-hour average SBP from baseline at Week 12 as measured by ABPM between participants treated with baxdrostat 2 mg and participants treated with placebo.

As the primary analysis, the primary endpoints will be analysed using an ANCOVA model with fixed effects for treatment and baseline ambulatory 24-hour average SBP as a covariate, based on the FAS, including participants with completed ABPM assessments at both baseline and Week 12. The least squares mean, standard error and 2-sided 95% confidence interval for the group of participants receiving baxdrostat, together with the comparison with the placebo group, will be provided.

The primary analysis will be conducted in accordance with the primary estimand and the strategies for specific types of intercurrent events outlined in Section 3. The primary analysis will include all available ABPM measurements regardless of treatment discontinuation or initiation of rescue therapy. The reasons and patterns of missing data will be assessed. Impact of missing data on the robustness of the primary analysis results will be assessed in sensitivity analyses, including multiple imputations.

9.4.2.2 Secondary Endpoint(s)

The continuous secondary endpoints, ie, change from baseline in ambulatory night-time average SBP at Week 12, change from baseline in ambulatory daytime average SBP at

Week 12, change from baseline in seated SBP at Week 12, change from baseline in ambulatory 24-hour average DBP at Week 12, change from baseline in ambulatory night-time average DBP at Week 12, change from baseline in ambulatory daytime average DBP at Week 12 and change from baseline in seated DBP at Week 12, will be analysed analogous to the primary analyses of the primary endpoint (see Section 9.4.2.1).

The binary secondary endpoints will be analysed as follows:

- Participants achieving ambulatory 24-hour average SBP < 130 mmHg at Week 12 will be analysed via a logistic regression model, including baseline ambulatory 24-hour average SBP measurement as a covariate and treatment as a factor.
- Participants achieving a nocturnal SBP dipping of $\geq 10\%$ at Week 12 will be analysed similarly, via a logistic regression model, including a baseline dipping status as covariate and treatment as a factor.

Definition of Nocturnal Dip and Dipper

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

Nocturnal dipping rate (%) = $100 \times (\text{average daytime SBP} - \text{average night-time SBP}) / (\text{average daytime SBP})$.

Participants who have $\geq 10\%$ reduction in night-time SBP compared to daytime SBP will be characterised as dippers. Participants who have < 10% reduction in night-time SBP compared to daytime SBP will be characterised as non-dippers.

9.4.3 Safety

Safety analyses will be performed using the safety analysis set. Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory variables and ECG. In addition, extra evaluation will be done for the following AESIs: hyperkalaemia, hyponatraemia and hypotension, based on Investigator reported AEs. For AESI descriptions and details please see Section 8.4.6.

Safety parameters to be evaluated are presented in Table 8.

Table 8 Statistical Safety Parameters

Safety Parameter	Safety Endpoint
Adverse Events	General safety objective: to assess the safety and tolerability of baxdrostat as compared to placebo in patients with rHTN.
	Occurrence and time to first occurrence of AE, SAE, SAE with outcome of death, AE leading to discontinuation of IMP, possibly related AE as assessed by the Investigator, possibly related SAE as assessed by the Investigator.
Clinical laboratory	Observed laboratory value (complete list of parameters is presented in Section 8.3.4), change from baseline and time to first treatment emergent abnormality.
Vital Signs	Observed vital sign value (including blood pressure and pulse rate), change from baseline and time to first treatment emergent abnormality.
Electrocardiogram	Observed ECG parameter, change from baseline.
Other	Occurrence and time to first event for AESIs (see Section 8.4.6 for AESIs definitions); pre-specified AE/safety categories.

AE = adverse event; AESI = adverse event of special interest; ECG = electrocardiogram; IMP = investigational medicinal product; rHTN = resistant hypertension; SAE = serious adverse event.

On-study Analysis Period Definition

The on-study analysis period starts on the date when the first dose of study intervention is taken by study participants and ends on the date when the last clinical assessment is performed, unless the subject dies while under follow-up, then the date of death is taken as the end of the period. If a subject withdraws consent to continue in the study, then the on-study analysis period ends on this date at the latest.

On-treatment Analysis Period Definition

The on-treatment analysis period starts on the date when the first dose of study intervention is taken by study participants and ends 10 days after the last dose of study intervention is taken by participants, or at the end of the on-study analysis period.

Safety Estimand Definition

The aim with the analyses of safety data is to assess the general safety objective, evaluated in a scenario where study treatment is not prematurely discontinued. Two analysis approaches are considered complementary to assess this hypothetical scenario for all the safety endpoints:

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

Hence, the general safety objective will be assessed through an estimand defined by the following attributes:

- Population: participants with rHTN, defined as per the inclusion and exclusion criteria. Implemented through the use of the safety analysis set.
- Treatment: 2 mg baxdrostat QD and stable regimen of background antihypertensive medication.
- Intercurrent events (ICEs):
 - Premature study treatment discontinuation: all analyses will be provided using 2 complementary approaches, unless otherwise stated in SAP;
 - Hypothetical, as if this ICE cannot happen. It will be implemented by excluding/censoring data after premature study treatment discontinuation plus 10 days, using the on-treatment analysis period.
 - Treatment policy by ignoring this ICE. It will be implemented by including all available data, using the on-study analysis period.
 - Initiation or change of concomitant medication, including rescue therapy: these ICEs will be ignored, ie, handled using a treatment policy approach.
 - Death: this ICE will be handled hypothetically as if it cannot happen. It will be implemented by censoring time to event data at death and not imputing any data after death.

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

9.4.4 Pharmacokinetic Analyses

The PK analysis set will be the primary population for the PK analysis.

Plasma concentrations of baxdrostat will be summarised by timepoints and dose level. If PK data permit, other PK parameters will be derived. A population PK model will be developed with the support of PK data from other studies, using nonlinear mixed effects regression analysis in non-linear mixed effects modelling. Moreover, the derived PK parameters and the results of any such modelling will be provided in a separate PK population report (as an appendix to the CSR or as a stand-alone report).

9.4.5 Pharmacodynamic Analyses

The FAS will be the primary population for the PD analysis. All PD variables will be summarised descriptively.

9.4.6 Pharmacokinetic-Pharmacodynamic Analysis

An attempt will be made to correlate plasma concentrations and parameters with measures of safety, PD and/or efficacy, if the data allows. All PK/PD modelling will be described in a separate data analysis plan. The results of any such modelling will be provided in a separate PK/PD report, if applicable, (as an appendix to the CSR or as a stand-alone report).

9.4.7 Methods for Multiplicity Control

A multiplicity testing procedure will be used to strongly control the familywise Type I error rate 0.05 (two-sided), between the primary and secondary endpoints. In the first step of the confirmatory testing, the primary endpoint change from baseline in ambulatory 24-hour average SBP at Week 12 will be tested at two-sided alpha of 0.05. Thereafter, the secondary endpoints will be tested in sequence until a test fails to reject the null hypothesis or until all the listed null hypotheses are rejected:

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

9.5 Interim Analyses

No interim analysis will be performed for this study.

9.6 Data Monitoring/Other Committee

A Data Monitoring Committee has been appointed for this study. The Data Monitoring Committee is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention and to make recommendations to AstraZeneca regarding the stopping of a study due to any harm. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the study.

For details on Data Monitoring Committee, refer to Appendix [A 5](#).

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 World Medical Association General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences 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 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 trial.

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

- Where the EU Clinical Trials Regulation 536/2014 applies, AstraZeneca has in place processes to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

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 the 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 centre.
- 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 re-consented 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 not always required to sign a new ICF. Please see Section [5.4.2](#) for further details.

The ICF will contain a separate section that addresses and documents the collection and use of any 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 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 Controller⁵ 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.

⁵ The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission.

- Whilst 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.

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.
- 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 information technology (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

The DMC shares responsibility with AstraZeneca for monitoring subject safety, with a focus on hypotension, hyperkalaemia and hyponatraemia, and ensuring that study subjects are not exposed to undue risk. In addition, the DMC agrees to provide support for study integrity. The DMC is responsible for periodically assessing study data according to an agreed upon schedule (as well as on an ad hoc basis) and making a recommendation to AstraZeneca and the EC. The processes, roles and responsibilities will be described in a Data Monitoring Committee Charter.

The DMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing.

An EC will be formed to provide scientific oversight and approval of the overall study design, of the CSP and any protocol amendments. The EC will provide oversight of the study conduct and advise AstraZeneca on the execution of the trial. The EC will review the SAP, assist in the interpretation of data and is responsible for public reporting of the study results by publications in major peer reviewed journals and by presentations at international congresses. Details are described in an EC Charter.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global end of study date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on www.astrazenecaclinicaltrials.com <http://www.clinicaltrials.gov> and <https://euclinicaltrials.eu/> as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

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 will be predefined in the Integrated Quality Risk Management Plan 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 noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring 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 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 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 is considered related to the medicinal (investigational) product (see the ICH-E2D Guideline).

The term AE is used to include both serious and non-serious AEs and 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 in-patient 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.

Some examples of important medical events are as follows:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion) or convulsions that do not result in hospitalisation.
- Development of drug dependency or drug abuse.

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.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- 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** 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 centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst 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 and other sample archive facilities for future research.

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

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 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 Optional Genomics Initiative Research

D 1 Use/Analysis of DNA and blood derivatives

- AstraZeneca intends to collect and store DNA and blood derivatives (such as plasma and serum) for genomic, and comprehensive omics characterisation research (such as protein, nucleotides and other entities in circulation), which may include metabolomic, proteomic and lipidomic analysis, to explore how genomic, and time-point omics variations may affect clinical parameters, risk and prognosis of diseases, and the response to medicinal product.
- This genomic, and multi-omics 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 blood sample will be collected for DNA and multi-omics analysis from consenting participants.
- This optional genomic, and multi-omics research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of these genetic, and multi-omics analyses may be reported in a separate study summary.
- AstraZeneca will store the DNA, and blood derivative samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Multi-omics Research Plan and Procedures

Selection of Multi-omics Research Population

All participants will be asked to participate in this genomic, and multi-omics 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 genomic, and multi-omics research, participants must fulfil all of the inclusion criteria described in the main body of the protocol and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

Exclusion from this genomic, and multi-omics research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant.
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection.

- Healthy volunteers and paediatric participant samples will not be collected for the Genomics Initiative.

Withdrawal of Consent for Multi-omics Research

- Participants may withdraw from this genomic, and multi-omics 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 Multi-omics Research

- The blood sample for this genomic, and multi-omics research will be obtained from the participants at Visit 4 (randomisation). Although DNA 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 Visit 4, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics, and multi-omics research during the study.

Coding and Storage of DNA and Multi-omics Samples

The processes adopted for the coding and storage of samples for genomic, and multi-omics 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. DNA, and blood derivatives 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 DNA, or blood derivatives).
- 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 genotypic, or multi-omics 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 genomics, and multi-omics research component, are outlined in [Appendix A](#).

Informed Consent

- The genomic, and multi-omics component of this study is optional, and the participant may participate in other components of the main study without participating in this multi-omics component. To participate in the genomic, and multi-omics component of the study the participant must sign and date both the consent form for the main study and the Optional Genomics Initiative Research 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 centre. The Principal Investigators is responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdraw from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual sequencing, genotype, or multi-omics 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 genomic, and multi-omics data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic 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 have access to his or her genomic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genomic files would remain physically separate.

Data management

- Any genomic, or multi-omics 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 genetic differences from groups of individuals with a disease) from this genomics, and multi-omics 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 multi-omics data in a suitable secure environment separate from the clinical database.
- Genetic data results will be reported in a separate report.

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 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 $\geq 3 \times \text{ULN}$ **together with** TBL $\geq 2 \times \text{ULN}$ at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law

Aspartate aminotransferase or ALT $\geq 3 \times \text{ULN}$ **together with** TBL $\geq 2 \times \text{ULN}$, 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:

- $ALT \geq 3 \times ULN$
- $AST \geq 3 \times ULN$
- $TBL \geq 2 \times ULN$

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:

- 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 ^a 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 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

Hy's Law Laboratory Kit for Central Laboratories

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

^a Routine laboratory tests.

^b HBV DNA is only recommended when IgG anti-HBc is positive.

^c HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.

^d CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly.
anti-CMV = anti-cytomegalovirus; ALT = alanine transaminase; AST = aspartate transaminase; anti-HSV = anti-herpes simplex virus; anti-EBV; anti-Epstein-Barr virus; CD-transferrin = carbohydrate-deficient transferrin; GGT = gamma-glutamyl-transferase; HBV = Hepatitis B Virus; HBsAg = hepatitis B surface antigen; HCV = Hepatitis C Virus; HEV = Hepatitis E Virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalised ratio; LDH = lactate dehydrogenase.

Appendix F Country-specific Requirements

There are no applicable European country-specific requirements for this study protocol.

Appendix G Anatomical Therapeutic Chemical Codes for NIMPs/AxMPs

Anatomical Therapeutic Chemical level 3 codes for NIMPs/AxMPs are detailed in the table below.

ATC Code	ATC Name	ATC Level
C02B	ANTIADRENERGIC AGENTS, GANGLION-BLOCKING	3
C02C	ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING	3
C02D	ARTERIOLAR SMOOTH MUSCLE, AGENTS ACTING ON	3
C02L	ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	3
C03A	LOW-CEILING DIURETICS, THIAZIDES	3
C03B	LOW-CEILING DIURETICS, EXCL. THIAZIDES	3
C03C	HIGH-CEILING DIURETICS	3
C03D	ALDOSTERONE ANTAGONISTS AND OTHER POTASSIUM-SPARING AGENTS	3
C03E	DIURETICS AND POTASSIUM-SPARING AGENTS IN COMBINATION	3
C07A	BETA BLOCKING AGENTS	3
C07B	BETA BLOCKING AGENTS AND THIAZIDES	3
C07C	BETA BLOCKING AGENTS AND OTHER DIURETICS	3
C07D	BETA BLOCKING AGENTS, THIAZIDES AND OTHER DIURETICS	3
C07E	BETA BLOCKING AGENTS AND VASODILATORS	3
C07F	BETA BLOCKING AGENTS, OTHER COMBINATIONS	3
C08C	SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS	3
C08D	SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS	3
C08E	NON-SELECTIVE CALCIUM CHANNEL BLOCKERS	3
C08G	CALCIUM CHANNEL BLOCKERS AND DIURETICS	3
C09A	ACE INHIBITORS, PLAIN	3
C09C	ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), PLAIN	3
C09B	ACE INHIBITORS, COMBINATIONS	3
C09D	ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), COMBINATIONS	3
C09X	OTHER AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	3
C02A	ANTIADRENERGIC AGENTS, CENTRALLY ACTING	3

ATC = Anatomical Therapeutic Chemical

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