A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group, Dose-Ranging Study to Evaluate CIN-107 for the Treatment of Patients With Uncontrolled Hypertension and Chronic Kidney Disease

ClinicalTrials.gov Identifier: NCT05432167

Protocol: Version 4.0 dated 17 August 2023

Clinical Study Protocol	
Study Intervention	Baxdrostat [CIN-107]
Study Code	D6972C00001
Version	4.0
Date	17 August 2023
Original Protocol Name	FigHtn-CKD CIN-107-123
NCT Number	NCT05432167

CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group, Dose-Ranging Study to Evaluate CIN-107 for the Treatment of Patients With Uncontrolled Hypertension and Chronic Kidney Disease

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

NCT Number: NCT05432167

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study 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.

SIGNATURE PAGE

STUDY TITLE: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group, Dose-Ranging Study to Evaluate CIN-107 for the Treatment of Patients With Uncontrolled Hypertension and Chronic Kidney Disease

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature Date

PPD

AstraZeneca

Protocol Number: 4.0

Amendment Number: 3

Study Intervention: CIN-107

Study Phase: II

Indication: Treatment of hypertension in patients with uncontrolled hypertension and chronic kidney disease

Short Title: N/A

Study physician name and contact information will be provided separately.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3 - CSP Version 4.0	17 August 2023
Amendment 2 - CSP Version 3.0	29 March 2023
Amendment 1 - CSP Version 2.0	20 November 2022
Original Protocol Version 1.0	19 January 2022

CSP version 4.0 (17 August 2023)

Overall Rationale for the Amendment

The study was originally designed to be overpowered (98.9%) for evaluation of the primary endpoint with 300 patients randomized. Based on sponsor recalculation of sample size, the protocol is being amended to stop further enrollment of patients. The decision was made in the absence of sponsor review of unblinded interim results. Randomization of eligible patients from the pool of patients in screening or run-in after stopping new enrollments will be permitted, resulting in approximately 174 patients randomized, sufficient for 90% power for the primary endpoint.

Summary of Changes

List of Modifications

Section Number and Name	Description of Change	Brief Rationale
Throughout	CSP updated to AstraZeneca housestyle	To comply with the current company housestyle
Throughout	Some sections were reorganized	Reorganization of CSP was done to comply with AstraZeneca's CSP template guidelines
Throughout	Minor updates to footnotes were added as needed.	Revisions were made to correct typos, add new definitions, and correct format as needed.
List of Abbreviations	The abbreviations list was updated as needed.	List updated per AstraZeneca CSP template requirements
1.1 Synopsis	The synopsis was reorganized. In addition, the following sections were added: • Rationale • Brief Summary • Disclosure Statement • Number of Patients	Revisions were made to comply with the structure of the synopsis in the current AstraZeneca CSP template.
1.1 Synopsis	The definition of "screened" was added.	Clarification - Template text added to comply with AstraZeneca CSP template guidelines.

List of Modifications

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis and 3 Study Objectives and Endpoints	Objectives and Endpoints were reorganized together in tabular form. The secondary objectives for CCI and CCI were moved to be CCI	Reorganization made to comply with AstraZeneca template guidelines. Endpoints were moved to secondary in accordance with the sample size reanalysis.
1.1 Synopsis, 4.2 Summary of Study Design; 8.4.6 Safety Surveillance and Management of Serum Potassium Levels	Updated instructions on hyperkalemia management	Information added at the request of the DSMB.
1.1 Synopsis, 1.3 Schedule of Activities, 6.3 Dose Titration	Updated information regarding up-titration and down-titration assessment	Information added at the request of the DSMB.
1.1 Synopsis 9.3 Population for Analysis	Per-protocol study population was removed.	For consistency with internal statistical standards.
1.1 Synopsis 9.4.2.1 Primary Endpoint	Text was added (underlined): An ~~mixed model for repeated measures (~~MMRM~~)~~ will be used to perform this analysis. The analysis will include fixed effects for treatment, visit, stratification variables (SGLT2 inhibitor use and CKD category), and the treatment-by-visit interaction, along with a covariate of the baseline seated SBP value and the baseline seated SBP by visit interaction.	For consistency with internal statistical standards.
1.1 Synopsis 9.4.2.2 Secondary and CCI Endpoints	Text was added (underlined): The analyses will include fixed effects for treatment, visit, stratification variables (SGLT2 inhibitor use and CKD category), and treatment-by-visit interaction, along with a covariate of the corresponding baseline value and the baseline by visit interaction. Text in Section 9.4.2.2 was revised (text deleted is strikethrough, text added is underlined): Achieving CCI of treatment will be analyzed using logistic regression with terms for treatment, ~~and the~~ baseline SBP value, and stratification variables. ~~As supportive analyses of the primary and secondary efficacy endpoints, the treatment group comparison will be repeated for the PP population. Additional~~	For consistency with internal statistical standards and alignment with endpoints
1.1 Synopsis 9.6 Data Monitoring Committees	Information about the URC was added to the Synopsis and new Sections 9.6 and 9.7.5.	Information was added to comply with AstraZeneca's CSP template guidelines.

List of Modifications

Section Number and Name	Description of Change	Brief Rationale
9.7.5 Committees Structure	Information about the Data and Safety Monitoring Board (DSMB) was added to Sections 9.6 and 9.7.5.	
4.1.1.3 Follow-Up Period	Information about the DSMB was removed from Section 3.1.1.3 Follow-Up Period of Version 3 protocol	Information not needed in the section describing the follow-up period; DSMB information was moved to the new Sections 9.6 and 9.7.6.
4.3 End-of-Study Definition	Clarified definition of the end of study according to EU and FDA requirements.	For consistency and alignment in terms of posting study results
5.3 Lifestyle Considerations	Section heading added. Information was added here from Section 5.6.2 "Restricted Medications and/or Procedures"	Section heading was added to comply with AstraZeneca's CSP template guidelines.
5.4 Screen Failures	New heading added and template definition of screen failure was added.	Section heading was added to comply with AstraZeneca's CSP template guidelines.
6.1 Treatment Groups	Added the number of tablets administered	For clarification of dosing
6.2.1 Formulation and Packaging	Revisions were made as follows (text underlined is new; text deleted is strikethrough) • One pack consists of CCI [redacted] for one-week supplies of run-in drug. At Visit 2, patients will be provided with 2-week supplies of single-blind CIN-107 placebo run-in drug. • One pack consists of CCI [redacted] for one-week supplies of double-blind study drug.	The packaging information has been updated to reflect a new pack design where CCI [redacted] for previous stocks.
6.6 Treatment of Overdose	New heading and template text indicating what the investigator should do in case of an overdose was added.	Section heading and template text was added to comply with AstraZeneca's CSP template guidelines.
6.7.1 Excluded Medications and/or Procedures	Information moved from original Appendix D (in v3.0) "Excluded Medications" to this section.	Revision made to comply with AstraZeneca's CSP template guidelines.
7 DISCONTINUATION OF STUDY DRUG AND PATIENT DISCONTINUATION /WITHDRAWAL	The following revisions were made: • New heading added • Original Section 6.4 (in v3.0) "Early Termination Visit and Withdrawal Procedures" was moved here (now Section 7.2). • Original Section 4.3 (in v3.0) "Withdrawal Criteria" was moved here (now Section 7.3 "Patient Discontinuation/Withdrawal Criteria") • New Section 7.4 Lost to Follow-up was added.	All revisions were made to comply with AstraZeneca's CSP template guidelines and structure.
8.1 Administrative and General/Baseline Procedures	New heading added. The original (v3.0) Sections 6.1 "Informed Consent", 6.2 "Screening Period", and 6.3 "Double-Blind Treatment Period" are now under Section 8.1.	All revisions were made to comply with AstraZeneca's CSP template guidelines and structure.

List of Modifications

Section Number and Name	Description of Change	Brief Rationale
8.2 Efficacy Assessments	New section added – Efficacy variables to be measured in the study were added.	This revision was made to comply with AstraZeneca's CSP template guidelines and structure.
8.3.4 Clinical Laboratory Evaluations	Information about "Clinical Safety Laboratory Analytes" was moved from Appendix B (in v3.0) to this section (now Table 6).	This revision was made to comply with AstraZeneca's CSP template guidelines and structure.
8.4 AEs, SAEs, and Other Safety Reporting	The following revisions were made: • New section heading was added. Original Sections 9.1 to 9.7 were moved under this heading; these sections are 8.4.1 to 8.4.9. • Original Section 9.8 "Special Situations Reports" is now Section 8.4.10 Medication Error, Drug Abuse, Drug Misuse, and Product Compliance. • CSP template text was added to the sections as needed	This revision was made to comply with AstraZeneca's CSP template guidelines and structure.
8.4.4 Serious Adverse Event Reporting – Procedures for Investigators	Text was revised (text deleted is strikethrough, text added is underlined): If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone. 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 1 or 5 calendar days for SAEs. When the EDC is temporarily not accessible, the AstraZeneca study representative should confirm that the investigator/site staff enters the SAE in the EDC when access resumes. The SAE information must be entered into EDC within 24 hours of the system becoming available. ~~If the event meets serious criteria and it is not possible to access the EDC system, a paper SAE form should be completed and sent to the Safety staff via email (medpace-safetynotification@medpace.com) within 24 hours of awareness. If email notification of Medpace safety staff is not available as an alternative notify them by telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3 or Fax: +1-866-336-5320 or +1-513-570-5196. When the EDC system becomes available, the SAE information must be entered into EDC within 24 hours of the system becoming available.~~	CSP template text added comply with current AstraZeneca CSP template requirements/ guidelines and AE/SAE reporting requirements.
8.4.10 Medication Error, Drug Abuse,	Updated section (timelines and definitions) as applicable	Update required due to CT-3 Regulation and corporate safety CAPA.

List of Modifications

Section Number and Name	Description of Change	Brief Rationale
Drug Misuse, and Product Complain		
8.5 CCI [redacted]	Updated section to include sample disposal timeline.	Addition to comply with AstraZeneca's CSP template guidelines and structure.
8.6 CCI [redacted] CCI [redacted]	Tables with CCI [redacted] to be collected from blood and urine was moved from the original Appendix B "clinical Laboratory Analytes" to this section (now Tables 7 and 8)	Reorganization to comply with AstraZeneca's CSP template guidelines and structure.
8.7 CCI [redacted] CCI [redacted]	Text was revised (text deleted is strikethrough, text added is underlined): Blood samples for CCI [redacted] will be stored at ~~Cincinnati Children's Hospital Discover Together Biobank~~ the AstraZeneca Biobank or designated organization (Cincinnati Children's Hospital Discover Together Biobank).	Revisions were made to allow flexibility as CCI [redacted] may be stored or analyzed at AstraZeneca or other designated organizations.
8.7.1 Collection, Storage, and Destruction of CCI [redacted] CCI [redacted]	AZ's sample retention recommendation for CCI [redacted] was added (ie, maximum of 15 years from the date of last subject last visit, after which they will be destroyed.)	Clarification – template text added to comply with AstraZeneca's CSP template guidelines
9.2 Sample Size Determination	Text was revised (text deleted is strikethrough, text added is underlined): The sample size for the study **was** ~~is~~ planned to adequately power the study for the primary endpoint and first 2 secondary efficacy endpoints. Assuming an early withdrawal rate of 8% and a common SD of 11 mmHg, with 300 randomized patients (randomization ratio of 1:1:1; 100 patients in the low dosing strategy, high dosing strategy, or placebo group), the study would have 95.7% power to detect a 6 mmHg difference in change from baseline in SBP between a CIN-107 dosing strategy group versus the placebo group at Week 26 and 98.9% power to detect a difference between the pooled CIN-107 group and the placebo group using a 2-sided significance level of 0.05. **Based on sponsor recalculation of sample size, the protocol is being amended to stop further enrollment of patients once 90% power is reached for the primary endpoint. The decision was made in the absence of sponsor review of unblinded interim results. Randomization of eligible patients from the pool of patients in screening or run-in after stopping new enrollments will be permitted, resulting in approximately 174 patients randomized (randomization ratio of 1:1:1 with approximately 58 patients each in the low dosing strategy, high dosing strategy, or placebo group), sufficient for 90% power for**	Updated sample size and power for early stop to the study

List of Modifications

Section Number and Name	Description of Change	Brief Rationale
	the primary endpoint assuming a treatment difference of 6 mmHg and a SD of 11 mmHg.	
9.4.2.1 Primary Endpoint	Updated intercurrent event strategies; original Section 10.2.1.1 was moved under this heading	Relationship of discontinuation to study drug is not collected
9.4.2.2 Secondary and CCI Endpoints	Section revised to align with new order of endpoints; original Section 10.2.1.2 was moved under this heading	Update to reflect change in order of endpoints
9.7.6 Dissemination of Clinical Study Data	Section added with updated information about timelines for submission of trial results summaries to EU CTIS	Added section to comply with AstraZeneca's CSP template requirements. Update required to comply with EU CTR
9.8.1 Data Quality Assurance	Section added with updated information about retention timelines of records and documents to [25 years after study archiving or as required by local regulations]	Added section to comply with AstraZeneca's CSP template requirements. Retention timelines update required to comply with EU CTR and global company requirement
Appendix A Medication Error, Drug Abuse, and Drug Misuse	Added detailed Drug Abuse and Drug Misuse definition and examples	Update required due to CT-3^ Regulation and corporate safety CAPA
References	Duplicate references were removed: Duprez 2007, Funder 2009, and Sato and Saruta 2004	Duplicated

AE = adverse event; ANCOVA = analysis of covariance; CAPA = Corrective Action and Preventive Action; CKD = chronic kidney disease; CSP = clinical study protocol; CCI; DSMB = Data and Safety Monitoring Board; EDC = electronic data capture; EU CTIS = European Union Clinical Trials Information System; EU CTR = European Union Clinical Trial Register; FDA = Food and Drug Administration; MMRM = mixed-model for repeated measures; CCI SAE = serious adverse event; SBP = systolic blood pressure; SGLT2 = sodium-glucose cotransporter 2; CCI; URC = Unblinded Review Committee

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
ACEi	Angiotensin-converting enzyme inhibitor
ACTH	Adrenocorticotropic hormone
AE(s)	Adverse event(s)
AESI(s)	Adverse event(s) of special interest
ANCOVA	Analysis of covariance
AOBPM	Automated office blood pressure monitoring
ARB	Angiotensin receptor blocker
AV	atrioventricular
AUC	Area under the concentration-time curve
AUCinf	Area under the plasma-time concentration curve extrapolated to infinity
AUClast	Area under the plasma-time concentration curve from time 0 to the last time point
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CI(s)	Confidence interval(s)
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology
Cmax	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CRA	Clinical research associate
CRO	Contract research organization
CV	Cardiovascular
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DES	Data Entry Site
DSMB	Data and Safety Monitoring Board
ECG(s)	Electrocardiogram(s)
eCRF	Electronic consent report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ET	Early termination
EU	European Union

Abbreviation or special term	Explanation
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GFR	Glomerular filtration rate
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HCV	Hepatitis C virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICF	Informed consent form
IRB(s)	Institutional review board(s)
IRT	Interactive response technology
ITT	Intent-to-treat
CCI	CCI
MAD	Multiple-ascending dose
MATE	Multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model for repeated measures
mITT	Modified Intent-to-Treat
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor agonist
CCI	CCI
NOAEL	No-observed-adverse-effect level
CCI	CCI
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
CCI	CCI
CCI	CCI
PK	Pharmacokinetic(s)
CCI	CCI
QD	Once daily
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RAAS	Renin-angiotensin-aldosterone system
RNA	Ribonucleic acid

Abbreviation or special term	Explanation
SAD	Single-ascending dose
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SGLT2	Sodium-glucose cotransporter 2
SUSAR	Suspected unexpected serious adverse reaction
TEAE(s)	Treatment-emergent adverse event(s)
CCI	CCI
uHTN	Uncontrolled hypertension
ULN	Upper limit of normal
URC	Unblinded Review Committee
WHO	World Health Organization

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel-group, Dose Ranging Study to Evaluate CIN-107 for the Treatment of Patients With Uncontrolled Hypertension and Chronic Kidney Disease

Protocol Number:

D6972C00001

Original Protocol Number:

FigHtn-CKD CIN-107-123

Regulatory Agency Identifier Number(s):

NCT05432167

Rationale:

Inappropriate high levels of aldosterone in patients with chronic kidney disease (CKD) have been suggested to contribute to CKD-associated hypertension by promoting inflammation, oxidative stress, fibrosis, mesangial cell proliferation, and podocyte injury. The blockade of aldosterone thereby represents a potential means to reduce blood pressure (BP) as well as to mitigate end-organ damage.

CIN-107 is a highly potent, selective, and competitive inhibitor of aldosterone synthase and may be a novel treatment to provide added benefit for CKD patients when given in combination with an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) and/or other antihypertensive agents to reduce BP and improve renal function.

Patients with CKD have a higher propensity to develop hyperkalemia resulting from taking antihypertension agents that can produce increases in serum potassium. Study CIN-107-123 aims to characterize the safety, tolerability, and effectiveness of CIN-107 using dose titration to mitigate potential adverse effects including hyperkalemia.

Objectives and Endpoints:

The objectives and endpoints for this clinical study are presented in the Table 1.

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary [a]	
To evaluate the treatment effect of CIN-107 on SBP compared to placebo at Week 26 in patients with uHTN and CKD	Change in mean seated SBP from baseline to Week 26 in patients receiving CIN-107 compared to placebo. [b]
Secondary [a]	
To evaluate the treatment effect of CIN-107 on SBP compared to placebo at Week 26 by dosing strategy	• The change from baseline of SBP in CIN-107 compared to placebo at Week 26 in patients assigned to the high-dose strategy group • The change from baseline of SBP in CIN-107 compared to placebo at Week 26 in patients assigned to the low-dose strategy group
Safety	
To evaluate the safety and tolerability of CIN-107 from the time of randomization until the end of the follow-up period in patients with uHTN and CKD. • To evaluate TEAEs; • To evaluate treatment-emergent SAEs • To evaluate treatment-emergent adverse events of special interest (AESIs) • To evaluate TEAEs leading to premature discontinuation of study drug; • To evaluate treatment-emergent marked laboratory abnormalities; and • To evaluate the change in standing SBP and DBP (measured pre-dose at the clinical site) from baseline to EOT (Visit 11); and • To evaluate vital signs, standing BP, and heart rate, physical examinations, electrocardiography, weight measurement, and clinical laboratory evaluations, including standard safety chemistry panel, hematology, coagulation, and urinalysis.	• The incidence of TEAEs • The incidence of TESAEs • The incidence of TEAEs leading to premature discontinuation of the study drug • The incidence of treatment-emergent AESIs; AESIs will include the following: hypotension events that require clinical intervention, abnormal potassium laboratory values that require clinical intervention, and abnormal sodium laboratory values that require clinical intervention. • The incidence of treatment-emergent marked laboratory abnormalities • Change in serum potassium and sodium levels from baseline to Week 26 between each dose strength of CIN-107 compared to placebo • The change in standing SBP and DBP (measured at the clinical site prior to administration of study drug) from baseline to Week 26 • Vital signs (heart rate, respiratory rate, and body temperature), mean SBP, mean DBP, orthostatic vitals (standing BP and heart rate), physical examinations, ECG, weight measurement, and clinical laboratory evaluations including standard safety chemistry panel, hematology, coagulation, and urinalysis.
CCI [redacted]	
To determine the percentage of patients CCI [redacted] CCI [redacted]	• The percentage of patients achieving CCI [redacted] in patients assigned to the CCI [redacted] • The percentage of patients achieving CCI [redacted] at CCI [redacted] in patients assigned to the CCI [redacted] CCI [redacted]
To evaluate the change from baseline in CCI [redacted] CCI [redacted] of CIN-107 compared to placebo at CCI [redacted]	• The change from baseline in CCI [redacted] CCI [redacted] of CIN-107 compared to placebo at CCI [redacted]

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
To evaluate the change from baseline in CCI CCI of CIN-107 compared to placebo at CCI	• The percentage of change from baseline in CCI CCI compared to placebo at CCI
CCI of CIN-107 in patients with uHTN and CKD CCI CCI • To evaluate the relationship between change in CCI and CCI and CCI CIN-107 compared to placebo • To evaluate the relationship between change in CCI and CCI with CCI CCI of CIN-107 compared to placebo • To evaluate the relationship between the change in CCI CCI of CIN-107 compared to placebo To CCI CCI of CIN-107 compared to placebo	CCI CCI of CIN-107 compared to placebo at CCI in CCI including, but not limited to, the following: • CCI CCI CCI CCI CCI CCI CCI • CCI CCI CCI • The relationship between percentage of change in CCI and CCI CCI of CIN-107 compared to placebo at CCI • The relationship between change in CCI and CCI of CIN-107 compared to placebo at CCI • The relationship between the change in CCI CCI of CIN-107 compared to placebo at CCI
CCI CCI CCI CCI	• Percentage change from baseline in CCI at CCI CCI in patients assigned to the CCI CCI • Percentage change from baseline in CCI at CCI CCI in patients assigned to the CCI CCI • Change from baseline in CCI CCI • Change from baseline in CCI CCI CCI

- The mITT population will be used for the primary analysis of all efficacy endpoints.
- Estimand description and detailed intercurrent event strategies for the primary analysis of the primary efficacy endpoint are found in Section 9.4.2.1 and Table 9, respectively.

AESI(s) = adverse event(s) of special interest; CCI ; BP = blood pressure; DBP = diastolic blood pressure; CKD = chronic kidney disease; CCI ; ECG = electrocardiogram; CCI ; CCI ; mITT = modified intent-to-treat; CCI ; CCI ; CCI ; CCI ; SAE = serious adverse event; SBP = systolic blood pressure; TEAE(s) = treatment-emergent adverse evets(s); TESAE(s) = treatment-emergent serious adverse event(s); CCI ; uHTN = uncontrolled hypertension

Overall Design Synopsis:

This is a phase II, randomized, double-blind, placebo-controlled, multicenter, parallel-group, dose-ranging study to evaluate the efficacy and safety of CIN-107 for the treatment of hypertension in patients with uncontrolled hypertension (uHTN) and CKD.

The safety of CIN-107 will be assessed from the time of randomization until the end of the follow-up period. Patients will be followed for efficacy and adherence throughout the double-blind treatment period. CCI variables analyzed during the study will include measures of CCI and its relevant precursors. CCI variables analyzed during the study will include CCI of CIN-107.

Safety surveillance will be conducted at specified clinic visits throughout the study. Serum potassium, sodium levels and the estimated glomerular filtration rate (eGFR) value will be measured at the central laboratory at each designated visit. Unscheduled assessments of potassium or sodium levels or renal function should be completed at the investigator's discretion for acute management of the patient (eg, follow-up from elevated central lab potassium, acute changes in clinical condition, suspected dehydration, etc) as recommended below:

- For serum potassium of ≥ 5.5 to < 6.0 mEq/L, the patient should present to the clinical site within 72 hours for repeat testing.
  - If repeat serum potassium is confirmed (by local or central laboratory) to be ≥ 5.5 mEq/L, study drug should be temporarily interrupted and may not resume until serum potassium is < 5.0 mEq/L. If patient's dose had been up-titrated, then study drug should be resumed at the lower dose (if the lower dose is not available, study drug should not be resumed until the lower dose is available). After restart of study drug, serum potassium should be rechecked within 2 to 7 days.

  - If repeat potassium is < 5.5 mEq/L, study drug dose may continue. If patient's dose had been up-titrated, study drug may be down-titrated based on investigator judgment (if down-titration is indicated as per the investigator's judgment but the lower dose is not available, study drug should be interrupted until the lower dose is available).

- For serum potassium of ≥ 6.0 mEq/L, study drug should be interrupted and may not resume until serum potassium is < 5.0 mEq/L. Potassium should be repeated immediately, either at the clinical site or another clinical location (eg, emergency department if considered clinically indicated by investigator). If patient's dose had been up-titrated, study drug should be re-started at lower dose (if the lower dose is not available, study drug should not be resumed until the lower dose is available). After re-start of study drug, serum potassium should be re-checked within 2 to 7 days.
- Permanently discontinue treatment if a patient experiences a recurrent serum potassium ≥ 6.0 mEq/L after a previous event if there was no explanation for the recurring event other than restarting treatment.
- For serum sodium of < 130 mEq/L, the patient should present to the clinical site for repeat testing. The investigator may withhold dosing if sodium is < 125 mEq/L.
- For serum creatinine greater than 1.5 times baseline (creatinine at Visit 3) or a 30% increase from the previous visit, or an eGFR decrease of ≥ 30% from the previous visit, the patient should suspend study drug dosing and present to the clinical site for repeat testing.
- For patients, who have interrupted study drug for any reason, study drug should not be resumed unless potassium has been confirmed to be < 5.0 mEq/L.

Repeat and unscheduled testing for serum sodium, potassium, or eGFR should be measured at the local laboratory and central laboratory for a faster turn-around time to allow clinical assessment. Patients will be instructed to bring their study drug to all clinical site visits after randomization for assessing treatment adherence.

Screening Period including the Mandatory 2-Week Run-in Period

Patients who provide written informed consent at Visit 1 will be assessed for the Inclusion/Exclusion Criteria.

At Visit 1, site staff will perform a pre-screen dipstick urinalysis to exclude patients whose albuminuria level registers as showing negative or only trace albuminuria. Historical albuminuria or proteinuria of > 500 mg/gm from within the past year and entered in the patient's medical history can be used in lieu of a dipstick urinalysis for albuminuria. If a dipstick is performed and registers at levels above trace for albuminuria, the site staff should proceed to measure BP and vitals, obtain blood samples for eGFR and CCI assessment, and perform routine safety evaluations. Patients will be provided with materials to obtain urine via first morning void at their home on 2 consecutive days prior to and on the morning of Visit 2. Visit 2 can be scheduled between 5 and 15 days after the screening visit when the

laboratory testing results (based on samples drawn at screening visit) are available for determining eligibility. At least 4 days prior to Visit 2, site staff will place a reminder call instructing the patient to obtain the samples on the following 3 consecutive mornings. The third sample will be collected such that the date of collection and Visit 2 are the same.

At Visit 2, patients will bring the collected CCI to the clinical site and site staff will send the samples to a central laboratory for CCI determination. Site staff will assess inclusion/exclusion criteria, measure BP, obtain vitals, and assess concomitant medications. Patients will be provided with materials and instructions to collect CCI beginning the morning of Day -1 (day prior to the randomization visit). On Day -3 (± 1 day), site staff will place a reminder call to the patient to obtain the CCI such that the date of completion of the 24-hour period and Visit 3 (randomization visit, Day 1) are the same.

A patient who has consented to participate in the study but does not meet the study inclusion/exclusion criteria may be rescreened no less than 5 days after the last study visit, with sponsor and/or medical monitor consultation and approval.

At Visit 2, the patients will be provided with 2-week supplies of single-blind CIN-107 placebo run-in drug and instructions on lifestyle management, reminders concerning hydration and the expectation that they will continue their background antihypertensive medications and, if relevant, sodium-glucose cotransporter 2 (SGLT2) inhibitor.

Upon return of the screening eligibility laboratory results of CCI, patients will be contacted via telephone to inform them of their eligibility, and if eligible, to begin taking the study drug once per day and schedule their next visit (Visit 3).

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

Double-Blind Treatment Period

At Visit 3 (randomization visit, Day 1/Week 0), inclusion criteria for systolic blood pressure (SBP) will be confirmed. Patients who remain eligible will be randomized 1:1:1 into 1 of the 3 treatment groups (baxdrostat low-dosing strategy, baxdrostat high-dosing strategy, or placebo group). Patients randomized to the low-dose strategy will initially receive a 0.5 mg dose and patients randomized to the high-dose strategy will initially receive a 2 mg dose. Randomization will be stratified by SGLT2 inhibitor use, baseline SBP ($\leq$ 155 mmHg or $>$ 155 mmHg) and CKD category (eGFR $\leq$ 45 mL/min/1.73 m^2 or $>$ 45 mL/min/1.73 m^2).

At Visit 4 (1 week after randomization), all randomized patients will return to the clinic and a blood sample will be drawn for safety parameter measurements. If electrolyte imbalance or clinically significant decline in eGFR occurs, the patients must be monitored at the investigator's discretion for acute management of the patient.

At Visit 5 (3 weeks after randomization), BP will be measured, and a blood sample will be drawn for safety parameter measurements. The CIN-107 dose level may be up-titrated if the following criteria have been met:

1 Patient has not achieved SBP < 130 mmHg target.
2 Patient has not experienced hyperkalemia (defined as potassium ≥ 5.0) at any point during the trial (including screening).
3 Patient has not experienced hyponatremia (defined as sodium < 135) at any point during the trial (including screening).
4 Patient has not experienced declining in renal function (defined as eGFR decrease of ≥ 30% from randomization).

For clarity, if the SBP remains ≥ 130 mmHg and the electrolyte/eGFR safety criteria are acceptable, 3 case scenarios may be encountered:

1 A patient on 0.5 mg CIN-107 dose strength until Visit 5 may receive 1 mg CIN-107 dose strength following Visit 5.
2 A patient on 2 mg CIN-107 dose strength until Visit 5 may receive 4 mg CIN-107 dose strength following Visit 5.
3 Patients randomized at Visit 3 to placebo remain on placebo.

Down-titration based on potassium values can occur following up-titration as follows:

- For patients who have been up-titrated at Visit 5, down-titration is permitted if electrolyte imbalance or declining renal function is a significant risk for the patient (if in the investigator's judgment down-titration is indicated for a patient who has been up-titrated at visit 5, but the lower dose is not available; study drug should be interrupted until the lower dose is available).
- If Visit 5 potassium value is ≥ 5.0, but patient had been up-titrated at Visit 5, then subject should be brought back in for an unscheduled visit to down-titrate IMP immediately.

At Visit 6 (4 weeks after randomization and 1 week after possible dose up-titration), all patients will return to the clinic, BP will be measured and a blood sample will be drawn for serum electrolytes and renal function measurements.

At Visit 7 (6 weeks after randomization), BP will be measured and a blood sample will be drawn for serum electrolyte measurements.

At Visits 8 to 10 (Weeks 9 to 22), patients should be taking study drug tablets as prescribed every day. Vital signs and safety laboratory testing will be measured at clinical visits. CCI [redacted] will be drawn during the designated visits.

At Visit 11 (Week 26), patients will take the last study drug dose and complete the required procedures including return of any unused study drug.

For CCI [redacted], baseline is defined as geometric mean of the 3 samples returned at Visit 2. For BP measurements, baseline is defined as the average of the 3 measurements taken prior to administration of the first dose of investigational product at Visit 3. Measurements of efficacy and safety variables recorded prior to the first dose of double-blind study drug administration will constitute pre-dose measurements.

During clinical site visits, adherence to study drug dosing will be calculated using pill counts.

Pre-dose blood samples for CCI [redacted] will be collected at Visit 3 (baseline), Visit 9 (Week 16), Visit 11 (Week 26), and Visit 12 (Week 28, 2 weeks after the last dose). Pre-dose blood samples for CCI [redacted] will be collected at Visits 9 and 11. If possible, the CCI [redacted] samples should be drawn at Visit 13 (early termination [ET] visit) if a patient withdraws from study participation. CCI [redacted] samples will be collected within approximately 15 minutes prior to dosing.

CCI [redacted] for CCI [redacted] and CCI [redacted] will be obtained over 24 hours (CCI [redacted]) leading up to Visit 3 (baseline), Visit 9 (Week 16), Visit 11 (Week 26), and Visit 12 (Week 28, 2 weeks after the last dose).

CCI [redacted] will be obtained via first morning void on the 2 consecutive days leading up to and morning of Visits 2, 9, 11, and 12. The secondary efficacy endpoint evaluation will take place at the end of treatment (EOT) visit (Visit 11). For visits at which both CCI [redacted] and CCI [redacted] are to be obtained, approximately 10 mL of first void sample should be collected from the CCI [redacted] pan and transferred to the CCI [redacted] container for CCI [redacted] testing before transferring the CCI [redacted] to the CCI [redacted]

Follow-Up Period

At Visit 12, patients will complete a follow-up visit at 2 weeks ± 7 days after the last dose of the study drug.

Brief Summary:

The purpose of this study is to compare the efficacy and safety of CIN-107 versus placebo for the treatment of hypertension in patients with uHTN and CKD. Two tablets per day of CIN-107 or placebo will be self-administered orally.

Study details include:

- A screening period of up to 5 weeks including a mandatory 2-week run-in period
- A double-blind treatment period of 26 weeks
- A follow-up period of 2 weeks

Patients will complete at least 12 visits over a period of approximately 8 months.

Disclosure Statement:

This is a randomized, double-blind, parallel-group, interventional study with 3 treatment arms (CIN-107 versus placebo) that are blinded to patients, site staff, and investigators.

Population:

Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1 Is an adult male or female patient ≥ 18 years of age.

2 Has a mean seated SBP ≥ 140 mmHg at Screening (Visit 1), Visit 2, and Visit 3.

Note: Patients with mean seated SBP ≥ 130 mmHg may be eligible if diabetic.

Note: Mean seated SBP is defined as the average of 3 seated SBP measurements at any single clinical site visit.

3 Has a prior diagnosis of mild-to-severe CKD, defined as eGFR (based on the CKD-EPI equation) of 25 to 75 mL/min/1.73 m^2, inclusive, at Visit 1.

Note: To ensure patients with moderate and severe renal impairment will be represented, the number of patients with an eGFR ≥ 60 and < 75 mL/min/1.73 m^2 will be capped at 45.

4 Has a CCI [redacted] in at least 2 out of 3 measurements based on first CCI collected in the morning on consecutive days during the screening period.

5 Is currently taking an ACEi or ARB at the patient's maximum tolerated daily dose, based on investigator judgment, for > 4 weeks prior to Visit 1.

6 If taking a SGLT2 inhibitor at screening (Visit 1), the regimen must be stable for a period of at least 8 weeks before Visit 1 and be expected to remain at a stable dose over the study period.

Note: It is expected that patients not currently taking an SGLT2 inhibitor at screening (Visit 1) will not initiate this class of medication during the entire study period.

7 Is willing to be compliant with the contraception and reproductive restrictions of the study as follows:

- Female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) must have a documented negative pregnancy test at Visit 1 and the randomization visit (Visit 3); and must use a highly effective method of contraception (ie, < 1% failure rate) from Day 1 through 30 days after the last administration of study drug.

  Note: Acceptable methods of contraception for female patients of childbearing potential enrolled in the study include the following:

  - Surgical sterilization (tubal ligation)
  - Intrauterine device for at least 12 weeks before Visit 1
  - Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before Visit 1
  - Diaphragm used in combination with spermicide
- Postmenopausal women must have not had menstrual bleeding for at least 1 year before initial dosing and either be > 60 years or have an elevated follicle-stimulating hormone (FSH) level > 40 mIU/mL at Visit 1.

8 Is able and willing to give informed consent for participation in the study.

9 After the mandatory run-in period of 2 weeks, investigators must confirm the patient's BP and CCI measurements still meet the eligibility criteria.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1 Have a documented diagnosis of type 1 diabetes.

2 Are not willing or not able to discontinue a mineralocorticoid receptor agonist (MRA) or a potassium-sparing diuretic as part of an existing antihypertensive regimen.

Note: Patients taking an MRA or a potassium-sparing diuretic (eg, triamterene, amiloride, etc) as an antihypertensive agent must be willing to discontinue this agent for study eligibility. The potassium-sparing diuretic may be discontinued and replaced with a non-potassium-sparing diuretic. All patients who remain on a stable regimen of antihypertensive agents, including a non-potassium-sparing diuretic, for at least 6 weeks, will be eligible to enter the single-blind run-in. If the patient discontinues their prior MRA or potassium-sparing diuretic and/or initiates a new antihypertensive for study eligibility or has their antihypertensive dose adjusted after Visit 1, they should remain on a stable regimen of antihypertensive agents for at least 4 weeks and will have an extended

screening period of up to 9 weeks from signing of informed consent to randomization (Visit 3).

3 Have a single occurrence of mean seated SBP > 180 mmHg or diastolic blood pressure (DBP) > 110 mmHg during the screening period (if such a BP is recorded during the screening period, the patient may attend an interim visit for an additional BP measurement and reassessment of inclusion/exclusion criteria).

Note: Mean seated BP is defined as the average of 3 measurements obtained at any one clinical site visit. If the patient missed the regularly scheduled antihypertensive medication(s) prior to the visit (Visits 1 or 2), one BP retest is allowed ≥ 2 hours after taking the medication(s), on the following day, or later after reestablishing the regularly scheduled antihypertensive regimen.

4 Has a body mass index (BMI) > 50 kg/m^2 at Visit 1.

5 Has documented bilateral clinically relevant renal artery stenosis of ≥ 70%; if the imaging evidence is met, the patient should be excluded, since hypertension itself could be considered 'clinically relevant'. Suspected or nondocumented renal artery stenosis is not excluded.

6 Has had dialysis for acute kidney injury/acute renal failure within 12 weeks prior to the screening period or has a planned dialysis or kidney transplantation during the course of the study.

7 Has known documented chronic heart failure New York Heart Association Class III or Class IV and/or hospitalization for heart failure within 6 months of Visit 1.

8 Has had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure within 6 months of Visit 1.

9 Has known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease diagnosed from a prior echocardiogram or another imaging study.

10 Has a planned coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) or any major surgical procedure during the study.

11 Has had PCI, CABG, other major cardiac surgery (eg, valve replacement), or peripheral arterial bypass surgery within 6 months of Visit 1.

12 Has had a prior solid organ transplant or cell transplant.

13 Is expected to receive or is receiving any of the exclusionary drugs such as strong inducers of cytochrome P450 (CYP)3A, chronic (medication is taken more than 3 times a week for more than 3 months) use of non-steroidal anti-inflammatory drugs, spironolactone/eplerenone, and/or chronic use of systemic steroids.

14 Has a known hypersensitivity to any of the following:

- CIN-107 or drugs of the same class
- Excipients in CIN-107 or drugs of the same classes

15 Has received immunotherapy for treatment of CKD within 6 months of Visit 1 or expects to receive immunotherapy for treatment of CKD during participation in the study.

16 Has any clinically relevant medical or surgical conditions including unstable conditions and/or conditions requiring regular transfusion or treatment with systemic immunosuppressants, including corticosteroids that, in the opinion of the investigator, would put the patient at risk by participating in the study.

17 Has evidence of any of the following at Visit 1 (1 retest is allowed):

- White blood cell count > 15×10^9/L or absolute neutrophil count < 1×10^9/L
- Serum potassium < 3.5 mEq/L

Note: Patients with a serum potassium level below normal range may continue in the study without retest if the investigator elects to correct the serum potassium level with supplementation and offers to manage the condition.

- Serum potassium > 5.0 mEq/L
- Serum sodium < 135 mEq/L
- Serum aspartate aminotransferase or alanine aminotransferase >3 × upper limit of normal (ULN) or
- Total bilirubin > 2 × ULN, unless due to Gilbert's syndrome
- eGFR is < 25 or > 75 mL/min/1.73 m^2

18 Has uncontrolled diabetes with glycosylated hemoglobin > 10.5% at Visit 1.

19 Is positive for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen, or hepatitis C virus (HCV) ribonucleic acid (RNA).

20 Has typical consumption of > 14 alcoholic drinks weekly.

Note: One drink of alcohol is equivalent to ½ pint of beer (285 mL), one glass of spirits (25 mL), or one glass of wine (125 mL).

21 Has participated in another clinical study involving any investigational drug within 30 days prior to Visit 1, or plans to participate in another clinical study within 30 days of discontinuation of study drug.

22 Has received experimental therapy for disease intervention with a small molecule within 30 days of Visit 1 or 5 half-lives, whichever is longer, or received experimental therapy with a large molecule within 90 days of the Visit 1 or 5 half-lives, whichever is longer.

Note: Vaccinations, including those for coronavirus disease 2019 (COVID-19), will not be exclusionary.

23 Is pregnant, breastfeeding, or planning to become pregnant during the study.

24 Is considered by the investigator, after reviewing medical and psychiatric history, physical examination, and laboratory evaluations, to be unsuitable for any other reason that may either place the patient at increased risk during participation or interfere with the

interpretation of the study outcomes. History of COVID-19 infection, in of itself, is not an exclusionary criterion unless the patient is subsequently considered unsuitable for the study based on criteria above.

Number of Patients:

It is expected that approximately 174 eligible patients will be randomized at a 1:1:1 ratio to receive either CIN-107 (low or high dose) or matching placebo.

Study Arms, Dosage Forms, Route of Administration, and Duration:

CIN-107 tablets, active or placebo, will be provided in blister packs. Placebo tablets will be indistinguishable from the CIN-107 tablets. Two tablets per day will be self-administered orally.

At Visit 3 (randomization visit, Day 1/Week 0), eligible patients will be randomized 1:1:1 into 1 of the 3 treatment groups (baxdrostat low-dosing strategy, baxdrostat high-dosing strategy, or placebo group).

Dose titration is permitted at Visit 5/Week 3. The CIN-107 dose level may be up-titrated if the following criteria have been met:

1 Patient has not achieved SBP < 130 mmHg target.
2 Patient has not experienced hyperkalemia (defined as potassium ≥ 5.0) at any point during the trial (including screening).
3 Patient has not experienced hyponatremia (defined as sodium < 135) at any point during the trial (including screening).
4 Patient has not experienced declining in renal function (defined as eGFR decrease of ≥ 30% from randomization).

If these conditions are met, dose titration is then permitted as follows:

- A patient on 0.5 mg CIN-107 dose may receive 1 mg CIN-107 following Visit 5.
- A patient on 2 mg CIN-107 may receive 4 mg CIN-107 following Visit 5.
- Patients randomized at Visit 3 to placebo remain on placebo.

Down-titration based on potassium values can occur following up-titration as follows:

- For patients who have been up-titrated at Visit 5, down-titration is permitted if electrolyte imbalance or declining renal function is a significant risk for the patient (if in the investigator's judgment down-titration is indicated for a patient who has been up-titrated at visit 5, but if the lower dose is not available; study drug should be interrupted until the lower dose is available).

- If Visit 5 potassium value is $\geq$ 5.0, but patient had been up-titrated at Visit 5, then subject should be brought back in for an unscheduled visit to down-titrate IMP immediately.

Patients will be allowed to have their normal diet the morning of study drug administration. At the randomization visit (Visit 3), patients will receive either CIN-107 tablets of their assigned dose strength or matching placebo tablets. Patients will self-administer the first dose of study drug as 2 tablets taken orally at the clinical site. Subsequent doses of the study drug are to be taken by the patient by mouth once daily (QD) at approximately the same time each morning at home. On days of clinical site visits, patients will take their scheduled morning doses of their ACEi, ARB, and SGLT2 inhibitor (if applicable) at home and hold their dose of study drug. Patients must bring their study drug and background ACEi/ARB and any other hypertensive medications they are taking to the clinical site at all visits. At the clinical site, patients will self-administer the study drug to be witnessed by site staff after completion of pre-dose evaluations and laboratory sampling. The presence of the background antihypertensive medications and study drug in the urine samples or blood samples drawn at the clinic visit may be tested to verify dosing adherence.

Patients will complete at least 12 visits over a period of approximately 8 months.

The study will consist of the following 3 periods and corresponding visits:

- A screening period of up to 5 weeks (Visits 1 and 2) including a mandatory 2-week run-in period (beginning at Visit 2 until Visit 3)
- A double-blind treatment period of 26 weeks (Visits 3 through 11)
- A follow-up period of 2 weeks (Visit 12)

Data Monitoring/Other Committee:

No formal interim analysis is planned. A Data and Safety Monitoring Board (DSMB) will be formed to conduct data reviews to assess safety and tolerability of CIN-107 and to make recommendations to AstraZeneca regarding the study. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study. Details related to the DSMB responsibilities, authorities, and procedures will be documented in the DSMB Charter.

The sponsor may initiate an Unblinded Review Committee (URC), whose members are not involved in the execution of the study and would be described in a separate URC Charter. The URC would assess the safety and efficacy of baxdrostat in a CKD population in preparation for the initiation of Phase III studies. Review by the URC is not intended to inform any decision making by the sponsor regarding the conduct of the ongoing Phase II trial D6972c00001. The sponsor will take every necessary step to maintain the scientific and data integrity of this study.

Statistical Methods:

The following analysis populations are defined for the different types of data analyses:

- Intent-to-treat (ITT) population – All patients randomized into the study. Treatment classification will be based on the randomized treatment assignment.
- modified Intent-to-treat (mITT) population - The mITT population will include all patients in the ITT population who receive at least 1 dose of any study drug. Treatment classification will be based on the randomized treatment assignment. The mITT population will be used for the primary analysis of all efficacy endpoints.
- Safety population – All patients who receive at least one dose of any study drug. Treatment classification will be based on the actual treatment received. The safety population will be the primary population used for the safety analyses.
- CCI [redacted]

Descriptive statistics (arithmetic mean, standard deviation (SD), median, minimum, and maximum) will be calculated for quantitative variables as well as for the difference from baseline, when appropriate. Categorical variables will be summarized using frequencies and percentages.

Efficacy Analysis

The primary efficacy analysis will compare the mean change in seated SBP from baseline to Week 26 of pooled CIN-107 and placebo using the mITT population. A mixed-model for repeated measures (MMRM) will be used to perform this analysis. The analysis will include fixed effects for treatment, visit, stratification variables (SGLT2 inhibitor use and CKD category), and the treatment-by-visit interaction, along with a covariate of the baseline seated SBP value and the baseline seated SBP by visit interaction. An estimate of the treatment difference in the mean change at Week 26 will be generated, as will a test of the null hypothesis that the true means are equal at a 2-sided 0.05 level of significance. The least squares means, standard errors, and 2-sided 95% confidence intervals (CIs) for the true mean for each treatment group will be provided.

To protect the overall alpha level, the secondary efficacy endpoints will be tested in a hierarchical manner, each at a 2-sided 0.05 level of significance. Hypothesis testing of endpoints will proceed in the sequence shown above until a comparison is not statistically significant. At that point, all remaining sequential tests will be deemed not significant.

CCI [redacted] will compare the change in CCI [redacted] and CCI [redacted] from CCI [redacted]. An CCI [redacted]. The CCI [redacted] will include CCI [redacted] and

the [redacted]. The [redacted] will be used with an [redacted] of each dosing strategy of CIN-107 to the placebo group will be provided.

Achieving [redacted] will be analyzed using [redacted]

Sensitivity analyses may be carried out under secondary estimands and/or various assumptions for missing data. Full details will be provided in the statistical analysis plan (SAP).

Safety Analysis

The safety population will be the primary population for the safety analysis. All safety endpoints will be summarized descriptively.

The assessment of safety will be based primarily on the frequency of adverse events (AEs), clinical laboratory assessments, vital signs, and 12-lead electrocardiograms (ECGs). Other safety data will be summarized as appropriate.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events, defined as those AEs that newly occur or worsen in severity during the double-blind treatment period, will be summarized by system organ class and preferred term. A list of patients with serious adverse events (SAEs), AEs of special interest, and those who withdrawal from the study due to an AE will be provided.

Summary statistics by treatment strategy group at baseline, at each visit, and of changes from baseline to each visit for laboratory parameters, vital signs, and other safety measurements will be provided. The occurrence of significant abnormalities in change from baseline of laboratory values will be summarized by treatment group. Physical examination data will be listed.

[redacted]

[redacted]

[redacted]

Sample Size Determination:

The sample size for the study was planned to adequately power the study for the primary endpoint and first 2 secondary efficacy endpoints. Assuming an early withdrawal rate of 8% and a common SD of 11 mmHg, with 300 randomized patients (randomization ratio of 1:1:1; 100 patients in the low dosing strategy, high dosing strategy, or placebo group), the study would have 95.7% power to detect a 6 mmHg difference in change from baseline in SBP between a CIN-107 dosing strategy group versus the placebo group at Week 26 and 98.9% power to detect a difference between the pooled CIN-107 group and the placebo group using a 2-sided significance level of 0.05.

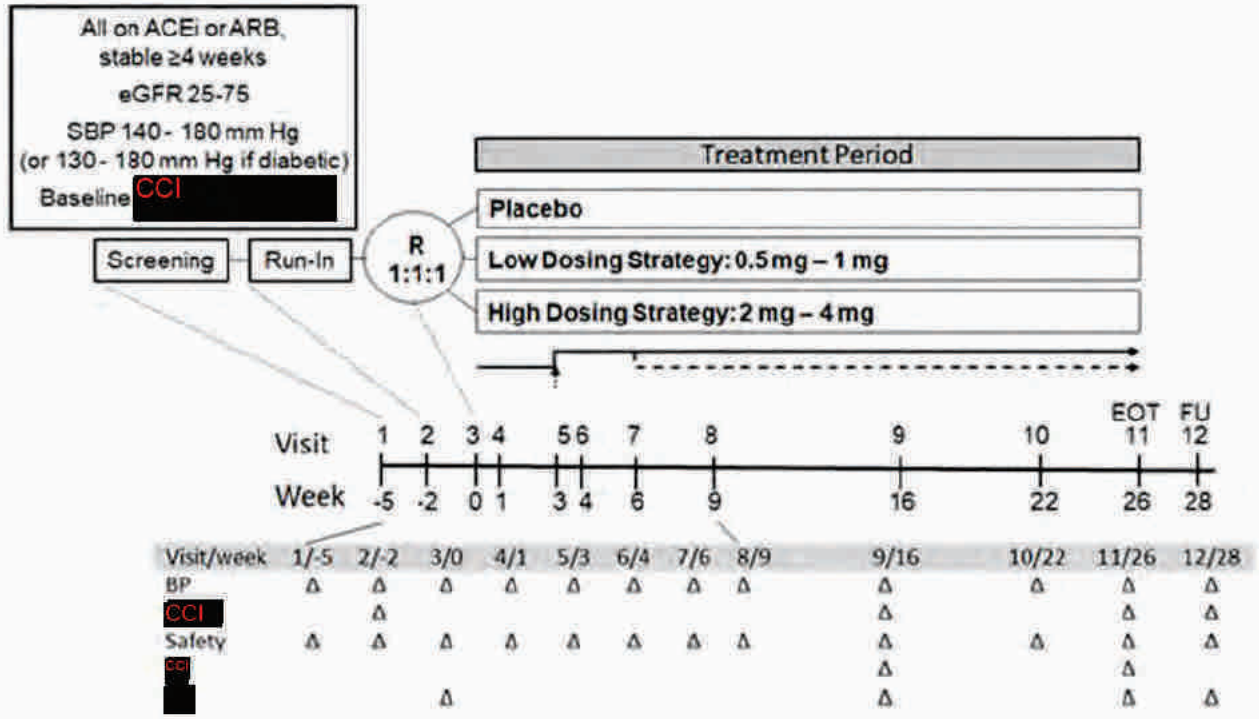
Based on sponsor recalculation of sample size, the protocol is being amended to stop further enrollment of patients once 90% power is reached for the primary endpoint. The decision was made in the absence of sponsor review of unblinded interim results. Randomization of eligible patients from the pool of patients in screening or run-in after stopping new enrollments will be permitted, resulting in approximately 174 patients randomized (randomization ratio of 1:1:1 with approximately 58 patients each in the low dosing strategy, high dosing strategy, or placebo group), sufficient for 90% power for the primary endpoint assuming a treatment difference of 6 mmHg and an SD of 11 mmHg.

Sites:

Approximately 100 clinical sites in the United States

1.2 Schema

The clinical study design is shown in Figure 1.**Figure 1 Study Design**



ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; SBP = systolic blood pressure; CCI EOT = end of treatment; FU = follow-up; R = randomization; CCI .

1.3 Schedule of Activities

Table 2 Schedule of Activities

	Screening		Double-Blind Treatment Period									FU	ET
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Run-in	**Rand.**								**EOT**		
Week	**-5**	**-2**	**1**	**1**	**3**	**4**	**6**	**9**	**16**	**22**	**26**	**28**	
Day (± Visit Window)	**-35 to -19**	**-20 to -14**	**1**	**7 (± 3)**	**21 (± 3)**	**28 (± 7)**	**42 (± 7)**	**63 (± 7)**	**112 (± 7)**	**154 (± 7)**	**182 (± 7)**	**196 (± 7)**	
Informed consent [a]	X												
Inclusion/exclusion criteria [b]	X	X	X[c]										
Demographic information	X												
Medical/surgical history	X												
AEs and SAEs [d]	X	→	→	→	→	→	→	→	→	→	→	→	
Prior/concomitant medications [e]	X [f]	→	→	→	→	→	→	→	→	→	→	→	
Height [g]	X												
Body weight	X		X		X	X	X	X	X	X	X	X	X
Vital signs [h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Seated BP [i]	X [j]	X	X	X	X	X	X	X	X	X	X	X	X
Standing BP and heart rate [k]	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination [l]	X										X		X
Limited physical examination [m]			X		X		X	X	X	X		X	
12-lead ECG [n]	X		X				X				X	X	X
Urine dipstick [o]	X												
Provide CCI CCI [p]	CCI [redacted]												
Collect CCI [q]													
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X
Provide CCI collection kit (for CCI and CCI) [r]		X						X		X	X		
Collect CCI collection kit [s]			X						X		X	X	
Standard safety chemistry, hematology, and coagulation	X		X	X	X	X	X	X	X	X	X	X	X
Serum potassium (local lab)			X [t]	X [t]	X [t]	X [t]	X [t]	X [t]	X [t]	X [t]	X [t]	X [t]	X [t]

Table 2 Schedule of Activities

	Screening		Double-Blind Treatment Period									FU	ET
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Run-in	**Rand.**								**EOT**		
Week	**-5**	**-2**	**1**	**1**	**3**	**4**	**6**	**9**	**16**	**22**	**26**	**28**	
Day (± Visit Window)	**-35 to -19**	**-20 to -14**	**1**	**7 (± 3)**	**21 (± 3)**	**28 (± 7)**	**42 (± 7)**	**63 (± 7)**	**112 (± 7)**	**154 (± 7)**	**182 (± 7)**	**196 (± 7)**	
Glycosylated hemoglobin	X												
HIV, HbsAg, and HCV screen	X												
Pregnancy test [u]	X		X								X		X
FSH [v]	X												
CCI [w]									X		X		X
CCI [x]			X						X		X	X	X
Randomization via IRT [y]			X										
Assessment for potential up-titration					X								
Assessment for potential down-titration [z]						X	X	X	X	X	X		
Dispense study drug [aa]		X	X		X		X	X	X	X			
Administer study drug [bb]			X	X	X	X	X	X	X	X	X		
Collect unused study drug			X		X		X	X	X	X	X		X
Assess treatment adherence [cc]			X		X		X	X	X	X	X		X
Adherence counseling [dd]		X	X		X		X	X	X	X			
Provide instructions for next visit	X	X	X	X	X	X	X	X	X	X	X		
CCI [ee]							X						

[a] Written informed consent must be obtained before any protocol-specific procedures are performed.

[b] Screening laboratory evaluations, if abnormal, may be repeated once no less than 5 days after the last study visit for eligibility purposes before excluding the patient with sponsor and/or medical monitor consultation and approval.

[c] At Visit 3, site should confirm Visit 2 results that patient continues to meet inclusion criterion 2 regarding BP, inclusion criterion 3 regarding eGFR, and inclusion criterion 4 regarding CCI. If these criteria are not met, the patient should not be enrolled in the study.

[d] Clinical sites will record the time of event (hour, minutes) for AEs and SAEs that start at informed consent.

[e] Clinical sites will record the time of concomitant medication administration (hour, minutes) if the medication is initiated and/or stopped on the first randomized study drug administration visit (Visit 3) or at Visit 11 (EOT).

[f] The investigator or designee will record that the patient is currently taking an ACEi or ARB at the maximum tolerated daily dose for > 4 weeks prior to this visit.

g Height will be collected at Visit 1 and will be used to calculate BMI using the weight from this visit. Subsequent BMI calculations will use the same height.

h Vital signs and BP will be measured using the standardized procedures listed in Section 8.3.2.

i At each visit, seated BP should be measured in triplicate in the designated arm (arm identified to have the higher mean SBP value with laterality testing at Visit 1).

j Seated BP will be measured in both upper arms (3 times/arm) using an appropriately sized cuff and monitor provided to the clinical site to detect possible laterality differences. The arm with the higher mean SBP value will then be used to take the screening BP measurements (at least 5 minutes after determining laterality) and for all subsequent measurements. The same BP monitor provided to the clinical site should be used for all subsequent measurements. If the lowest and highest SBP measurements are > 15 mmHg apart, additional readings should be performed. The last 3 consecutive, consistent SBP measurements will be averaged to determine the final value to be used to assess eligibility at Visit 1. If the lowest and highest SBP measurements are > 20 mmHg apart after a total of 6 measurements, the measurements will not be used to assess study eligibility, but measurements may be reassessed after at least 72 hours. If the lowest and highest SBP values remain > 20 mmHg apart after 6 measurements at a subsequent assessment, the patient will be excluded from the study.

k After the seated BP is determined, the patient will be asked to stand and after 60 seconds a single standing BP and a single standing heart rate (orthostatic vitals) measurement will be obtained.

l A complete physical examination will consist of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system.

m A limited physical exam will consist of a minimum of general appearance, skin, heart, lungs, and abdomen.

n Perform 12-lead ECG after the patient has been resting in the supine position for > 10 minutes and after measuring vital signs and BP.

o Urine dipstick assessment should be performed at prescreening. Historical albuminuria or proteinuria of > 500 mg/gm from within the past year and entered in the patient's medical history can be used in lieu of a dipstick urinalysis for albuminuria. If a dipstick is performed and is positive for albuminuria, the site staff should proceed to perform all Visit 1 evaluations.

p Patients will be provided with CCI at Visits 1, 8, 10, and 11 to obtain CCI via first morning void at their home on 3 consecutive days prior to the next scheduled visit. At least 4 days prior to the next scheduled visit, site staff will place reminder calls instructing the patient to obtain the samples on the following 3 consecutive mornings. The third sample will be collected such that the date of collection and the next scheduled visit (Visits 2, 9, 11, or 12) are the same.

q If one of the following occurs during the 3-day collection period, the patient will be asked to repeat the CCI as soon as practical: unusual physical exercise, menstruation, urinary tract infection, febrile illness, or flu.

r Patients will be provided with CCI collection materials (for CCI) at Visits 2, 8, 10, and 11. Patients will be instructed to begin collecting all CCI starting 24 hours prior to these visits and to bring the entire sample to the clinical site.

s A CCI collection can be repeated if the investigator suspects that the sampling is insufficient, and the patient is within the visit window; sites will aliquot CCI into a transfer tube and send to the central laboratory.

t If indicated, repeat and unscheduled testing for serum potassium should be measured at the local laboratory and the central laboratory for a faster turn-around time to allow for timely clinical assessment and acute management of the patient, at the investigator's discretion.

u For female patients of childbearing potential (ovulating, premenopausal, and not surgically sterile), serum pregnancy tests will be performed at screening, EOT, and ET visits. A POC pregnancy test will be performed at randomization (Visit 3) to assess eligibility.

v FSH levels will be measured only for female patients who are postmenopausal for at least 1 year at screening and are not surgically sterile.

[w] Pre-dose blood samples for [redacted] will be collected within approximately 15 minutes prior to dosing.

[x] Pre-dose blood samples for [redacted] will be collected. Samples will be processed following instructions in the lab manual.

[y] Patients who meet all inclusion/exclusion criteria at Visit 3 (randomization visit) will be randomized into the study using an automated IRT system.

[z] Down-titration based on potassium values can occur following up-titration as specified in Section 6.3.

[aa] Patients will be assigned study drug kits via IRT.

[bb] During clinical site visits beginning at Visit 3, patients will self-administer the study drug at the clinical site to be witnessed by site staff after completion of pre-dose evaluations and laboratory sampling. A hand and mouth check will be performed by site staff. Starting the following morning, patients will self-administer the study drug by mouth QD at home at approximately the same time each morning.

[cc] Site staff will assess treatment adherence based on pill counts.

[dd] Instruct patients to take their scheduled morning doses of their ACEi or ARB at home and to hold their dose of study drug on the morning of their next visit. Patients must bring their study drug and background ACEi or ARB medications to the clinical site at all visits.

[ee] For patients who provide written informed consent to participate in the [redacted], a blood sample will be collected at any time after randomization.

ACEi = angiotensin-converting enzyme inhibitor; AE(s) = adverse event(s); ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOT = End of Treatment; ET = Early Termination; FSH = follicle-stimulating hormone; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IRT = interactive response technology; lab = laboratory; [redacted]; POC = point of care; QD = once daily; Rand = randomization; SAE(s) = serious adverse event(s); SBP = systolic blood pressure; [redacted].

2 INTRODUCTION AND BACKGROUND INFORMATION

2.1 Background

Aldosterone is a hormone that has been implicated in a variety of CV and renal diseases. It is the principal mineralocorticoid in humans and is synthesized in the adrenal cortex by the enzyme aldosterone synthase. Aldosterone is a key component of the RAAS and acts as a critical regulator of fluid and electrolyte homeostasis through its agonism of the MR. Its effect on end organs has been shown to occur via its direct interaction with the MR (genomic effect) in addition to mechanisms independent of that direct interaction (non-genomic or non-receptor mediated effects) (Duprez 2007, Funder 2009, Sato and Saruta 2004).

One of the challenges that has impacted the development of aldosterone synthase inhibitors has been the difficulty in selectively inhibiting aldosterone synthase without affecting the synthesis of cortisol. The synthesis pathway of cortisol is catalyzed by 11β-hydroxylase (encoded by the CYP11B1 gene) that shares high sequence similarity with aldosterone synthase (encoded by the CYP11B2 gene). Undesired inhibition of 11β-hydroxylase leads to suppression of cortisol levels, compromised stress and immunologic responses, adverse effects on some metabolic functions, and possibly increased mortality rates (Oelkers 1996, Wagner et al 1984, Wagner and White 1984, Weldon and Brown 2019).

Baxdrostat (formerly CIN-107 or RO6836191) was acquired from Roche Pharmaceuticals, Inc. (hereinafter Roche) by CinCor Pharma, Inc. (hereinafter CinCor). CinCor is a wholly owned subsidiary of the AstraZeneca group of companies. Baxdrostat is a highly potent, selective, and competitive inhibitor of human aldosterone synthase (encoded by the CYP11B2 gene). AstraZeneca is pursuing further clinical development of the compound. In nonclinical in-vivo studies (primarily conducted in primates), CIN-107 significantly lowered aldosterone without affecting cortisol levels over a wide dose range. Using the translational model, the potency and selectivity of CIN-107 on mineralocorticoid and glucocorticoid synthesis was assessed following injection of Synacthen (which acts as ACTH) in Cynomolgus monkeys. CIN-107 CCI in a dose-dependent manner without CCI . To assess overall CCI , CIN-107 was tested in CCI . CCI

2.1.1 Overview of Nonclinical Studies

The potential adverse effects of CIN-107 have been evaluated in standard safety pharmacology, genotoxicity, repeated-dose toxicity, and reproductive toxicity studies. Findings in animal models are available in the IB and are briefly summarized below.

Administration of CIN-107 up to [redacted] for up to [redacted] has been studied in [redacted]. [redacted] study were [redacted] and/or [redacted], with the exception of dose-related [redacted] in both sexes, which were noted at all dose levels. In the [redacted], CIN-107-related [redacted] [redacted]. Mild, dose responsive (females only), non-adverse [redacted] was observed in males administered [redacted] mg/kg/day and females administered [redacted] mg/kg/day. Based on these data, the NOAEL for CIN-107 in male rats, is [redacted]. Due to the CIN-107 related unscheduled sacrifice of 2 females administered [redacted] mg/kg/day, the NOAEL for CIN-107 in female rats is [redacted] mg/kg/day which is equivalent to [redacted] (Study RETOX007).

CIN-107 was administered in cynomolgus monkeys up to [redacted]. No CIN-107-related clinical pathology changes were noted. CIN-107 related [redacted]. Microscopic findings showed evidence of reversibility. Due to the lack of impact on the health and well-being of animals, the NOAEL is [redacted] mg/kg/day for male and female monkeys or a [redacted] (Study RETOX006).

The [redacted] affected in both rats and monkeys. A mechanistic 4-week cynomolgus monkey study demonstrated [redacted]. These pathological changes in the [redacted], indicating that they were [redacted].

Dose- and exposure-dependent inhibition of aldosterone synthesis was confirmed in acute and sub chronic monkey models. In cynomolgus monkeys challenged with an injection of ACTH, CIN-107 blocked aldosterone synthesis without interfering with cortisol levels.

There was no evidence for a mutagenic, clastogenic, or aneugenic potential of CIN-107.

In vitro CV safety was assessed in a human ether à-go-go related gene assay. The concentration needed for [redacted] was approximately [redacted] for the highest anticipated clinical dose of baxdrostat (8 mg QD). This indicated a

very CCI of any QT liability. In a modified Irwin test and in a whole-body plethysmography study in male rats, single oral administrations of CIN-107 up to a dose of CCI mg/kg did not induce any adverse effects on the central nervous system or respiratory function. The NOAEL was considered to be CCI mg/kg CIN-107 for both studies.

2.1.2 Overview of Clinical Studies With CIN-107

2.1.2.1 Clinical Studies in Healthy Subjects

Four clinical pharmacology studies of CIN-107 have been conducted to date in healthy subjects: a SAD study, a MAD study, a study to characterize the effect of food on the PK and to bridge the PK of the solution formulation of CIN-107 to the tablet formulation intended for future development, and a study to assess the effect of CIN-107 on the PK of the MATE substrate metformin.

Results of the SAD study which investigated the safety, tolerability, PK, and PD of CIN-107 in healthy male volunteers demonstrated that single oral doses of CIN-107 up to 360 mg were well tolerated. There were no deaths, SAEs, or dose-limiting events, and the maximum tolerated dose observed was at the highest dose tested of 360 mg (Marney and Brown 2007).

Following oral administration, CIN-107 was CCI A CCI was often observed at CCI . Thereafter, concentrations CCI . Over the anticipated CCI (Marney and Brown 2007).

Single doses of CIN-107 CCI . A CCI effect on CCI was consistently achieved at a dose of CCI mg CIN-107 under the different conditions tested (CCI Although there was CCI may have occurred based on CCI in CCI

Single oral doses of up to 360 mg CIN-107 did not affect serum electrolyte (chloride, potassium, sodium, and phosphate) levels, with no difference for subjects on active treatment versus those on placebo. Urine sodium and the sodium to potassium ratio both increased, with

the sodium loss in urine greater than the potassium retention. No change in urine creatinine was apparent.

Results of the MAD study indicate that MADs of CIN-107 up to 5 mg QD for 10 days were well tolerated by healthy subjects under low salt diet (for CIN-107 2.5 and 5 mg dose groups) and normal salt diet (for CIN-107 0.5, 1.5, and 2.5 mg dose groups). Specifically, there were no deaths, SAEs, or TEAEs leading to withdrawal, and there were no clinically significant changes in ECGs or vital signs. CCI from the MAD study indicate that exposure to CIN-107 (as assessed by CCI) is generally CCI at CCI as compared to that observed CCI. CCI from this study confirmed the ability of CIN-107 to CCI. As expected with a CCI

The drug product used in the Phase I SAD and MAD studies was provided as an oral solution. As a replacement for the oral solution, a tablet formulation was developed and used in the Phase I relative bioavailability and food effect study (CIN-107-112). The study was conducted with a 5 mg solution (fasted) and a 5 mg tablet (fed and fasted). Results of the relative bioavailability assessment indicate that exposure to CIN-107 following administration of the CIN-107 tablet formulation planned for use in future studies is equivalent to that observed following administration of the oral solution used in the SAD and MAD studies. Consumption of a high fat, high calorie meal had CCI did have a small effect on the rate of absorption. CCI when CIN-107 was administered with the specified meal as compared to in a CCI

The metformin drug-drug interaction study demonstrated that systemic exposure to metformin is unchanged when administered with CIN-107. The safety profile of metformin was similar in the presence and absence of CIN-107. Specifically, there were no deaths, SAEs, or TEAEs leading to withdrawal and there were no clinically significant changes in ECGs or vital signs.

2.1.2.2 Clinical Study in Patients with Renal Impairment

Of particular relevance to study subjects who will be enrolled in this trial is the investigation of the PK of CIN-107 in individuals with varying degrees of renal impairment. The PK profiles of CIN-107 following administration of a single 10 mg dose in individuals with renal impairment were qualitatively and quantitatively similar to those measured in healthy subjects. Pairwise comparisons of plasma PK parameters for CIN-107 in the moderate to severe renal impairment group confirmed the lack of noteworthy effect across groups with

geometric mean ratios of [redacted] for Cmax, AUCinf, and AUClast, respectively, as compared to the control group. [redacted] to CIN-107 were not observed in the kidney failure group as compared to the control group with geometric mean ratios [redacted] for Cmax, AUCinf, and AUClast, respectively. The conclusions of these studies demonstrated that a single [redacted] when administered to individuals with varying degrees of renal function, including those with moderate to severe renal impairment or kidney failure (on hemodialysis). There were no noteworthy increases in systemic exposure or decrease in clearance in individuals with impaired renal function. Dose adjustment of CIN-107 based on renal function was therefore not considered necessary.

2.2 Study Rationale

Aldosterone has been implicated in CV and kidney damage by causing inappropriate or excessive distal tubular reabsorption of sodium from the kidney. This can contribute to the development of hypertension and end-organ damage (Marney and Brown). Damage may also occur in permissive milieu with attendant high sodium intake, in which even normal concentrations of aldosterone produce BP-independent end organ damage, acting through inflammatory and profibrotic pathways (Duprez 2007, Funder 2009, Sato and Saruta 2004). Inappropriately high levels of aldosterone in patients with CKD have been suggested to contribute to CKD-associated hypertension by promoting inflammation, oxidative stress, fibrosis, mesangial cell proliferation, and podocyte injury (Gant et al 2017). The blockade of aldosterone thereby represents a potential means to reduce BP as well as to mitigate end organ damage (Ritz and Tomaschitz 2014).

In animal studies, aldosterone given chronically induces proteinuria, glomerular mesangial injury, and tubulointerstitial fibrosis; all of which were prevented by administration of an MRA (Riboulet 2015). Clinical studies have demonstrated that the incidence of proteinuria or albuminuria is higher among patients with primary aldosteronism than among patients with essential hypertension. Among patients with primary aldosteronism, CKD, or diabetic nephropathy, plasma aldosterone levels are positively correlated with urinary protein excretion and negatively correlated with GFR.

In addition to hypertension, albuminuria is a major determinant of disease progression, and both contribute to the key morphologic components of progressive scarring of the kidney: glomerulosclerosis, interstitial inflammation, fibrosis, and tubular atrophy. A change in albuminuria has been linked to hypertension and elevated aldosterone levels and consistently related to the risk of progression to end-stage kidney disease, particularly in patients with high baseline albuminuria. A change in albuminuria is generally observed earlier than a change in GFR allowing for earlier detection of the disease. A change in albuminuria over a 6-month period provides information about longer term risk of progression to end-stage kidney disease and supports the use of average change in albuminuria as a surrogate endpoint for the

treatment of CKD, particularly in populations with moderate-to-severe albuminuria (Coresh et al 2019, Heerspink et al 2019, Levey et al 2015, Levey et al 20).

CIN-107 is a highly potent, selective, and competitive inhibitor of aldosterone synthase and may be a novel treatment to provide added benefit for CKD patients when given in combination with an ACEi/ARB and/or other antihypertensive agents to reduce BP and improve renal function.

Patients with CKD have a higher propensity to develop hyperkalemia resulting from taking antihypertension agents that can produce increases in serum potassium. Study CIN-107-123 aims to characterize the safety, tolerability, and effectiveness of CIN-107 using dose titration to mitigate potential adverse effects (Section 6.3).

2.3 Risk/Benefit Assessments

Taking into account the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with investigational intervention/procedure are justified by the anticipated benefits that may be afforded to patients with indication.

2.3.1 Risk Assessment

2.3.1.1 Risk of Hyperkalemia and Hyponatremia

Aldosterone leads to increased renal reabsorption of sodium and water together with secretion of potassium, thereby increasing blood volume and BP. Based on clinical data from Phase 2 studies and the mode of action for CIN-107, reduction of circulating aldosterone levels may lead to natriuresis and subsequently to increased serum potassium and decreased serum sodium. Hyperkalemia is classified as an important identified risk. Potassium and sodium levels will be closely monitored in this clinical study.

2.3.1.2 Risk of Hypovolemia and Orthostatic Hypotension

As a consequence of the urinary sodium loss described above, osmotic water loss can lead to hypovolemia and consequently to orthostatic hypotension with a corresponding increase in heart rate. These events will be followed in this clinical study by measuring body weight, heart rate, and orthostatic vital signs.

2.3.1.3 Risk of Adrenal Effects

While CIN-107 exhibits a highly selective CYP11B2 inhibition, the possibility of CYP11B1 inhibition cannot be excluded in patients with CKD receiving repeated doses of CIN-107 over multiple weeks. This could result in a reduction in cortisol levels, as seen with very high doses of CIN-107 in preclinical studies and in clinical studies of the non-selective CYP11B1/B2 inhibitor LCI699 (Andersen et al 2001, Calhoun et al 2011, Karns et al 2013).

2.3.1.4 Risk of Sex Hormone-related Adverse Events

Known side effects of MRAs including gynecomastia, mastodynia, and abnormal vaginal bleeding were observed more frequently with spironolactone than with eplerenone. Occurrence of these events will be monitored in this clinical study. A selective inhibitor of aldosterone synthase is nevertheless not expected to interfere with sexual hormone pathways as there is no evidence it could block the sex hormones receptors, as spironolactone does, nor is there any evidence for a reduction in the synthesis of the sex steroid hormones themselves.

2.3.1.5 Risk of Allergic Reactions

Patients with known allergies to CIN-107 or its excipients (including placebo) should not receive CIN-107.

3 STUDY OBJECTIVES AND ENDPOINTS

The objectives and endpoints for this clinical study are presented in Table 3.

Table 3 Study Objectives and Endpoints

Objectives	Endpoints
Primary [a]	
To evaluate the treatment effect of CIN-107 on SBP compared to placebo at Week 26 in patients with uHTN and CKD	Change in mean seated SBP from baseline to Week 26 in patients receiving CIN-107 compared to placebo. [b]
Secondary [a]	
To evaluate the treatment effect of CIN-107 on SBP compared to placebo at Week 26 by dosing strategy	• The change from baseline of SBP in CIN-107 compared to placebo at Week 26 in patients assigned to the high-dose strategy group • The change from baseline of SBP in CIN-107 compared to placebo at Week 26 in patients assigned to the low-dose strategy group
Safety	
To evaluate the safety and tolerability of CIN-107 from the time of randomization until the end of the follow-up period in patients with uHTN and CKD. • To evaluate TEAEs; • To evaluate treatment-emergent SAEs • To evaluate treatment-emergent AESIs • To evaluate TEAEs leading to premature discontinuation of study drug; • To evaluate treatment-emergent marked laboratory abnormalities; and • To evaluate the change in standing SBP and DBP (measured pre-dose at the clinical site) from baseline to EOT (Visit 11); and	• The incidence of TEAEs • The incidence of TESAEs • The incidence of TEAEs leading to premature discontinuation of the study drug • The incidence of treatment-emergent AESIs; AESIs will include the following: hypotension events that require clinical intervention, abnormal potassium laboratory values that require clinical intervention, and abnormal sodium laboratory values that require clinical intervention. • The incidence of treatment-emergent marked laboratory abnormalities • Change in serum potassium and sodium levels from baseline to Week 26 between each dose strength of CIN-107 compared to placebo

Table 3 Study Objectives and Endpoints

Objectives	Endpoints
• To evaluate vital signs, standing BP, and heart rate, physical examinations, electrocardiography, weight measurement, and clinical laboratory evaluations, including standard safety chemistry panel, hematology, coagulation, and urinalysis.	• The change in standing SBP and DBP (measured at the clinical site prior to administration of study drug) from baseline to Week 26 • Vital signs (heart rate, respiratory rate, and body temperature), mean SBP, mean DBP, orthostatic vitals (standing BP and heart rate), physical examinations, ECG, weight measurement, and clinical laboratory evaluations including standard safety chemistry panel, hematology, coagulation, and urinalysis.
CCI	
To determine the percentage of patients achieving CCI CCI	• The percentage of patients achieving CCI CCI • The percentage of patients achieving CCI CCI CCI
To evaluate the change from baseline CCI CCI of CIN-107 compared to placebo at CCI	• The change from baseline in CCI CCI of CIN-107 compared to placebo at CCI
To evaluate the change from baseline in CCI CCI of CIN-107 compared to placebo at CCI	• The percentage of change from baseline in CCI CCI of CIN-107 compared to placebo at CCI
CCI CCI CCI CCI • To evaluate the relationship between change in CCI and CCI and CCI of CIN-107 compared to placebo • To evaluate the relationship between change in CCI and CCI CCI of CIN-107 compared to placebo • To evaluate the relationship between the change in CCI CCI of CIN-107 compared to placebo CCI CCI	CCI CCI CCI CCI: • CCI CCI CCI CCI CCI CCI CCI, • CCI CCI CCI, • The relationship between percentage of change in CCI and changes in CCI compared to placebo at CCI • The relationship between change in CCI and CCI of CIN-107 compared to placebo at CCI • The relationship between the change in CCI CCI of CIN-107 compared to placebo at CCI

Table 3 Study Objectives and Endpoints

Objectives	Endpoints
CCI CCI CCI CCI	• Percentage change from baseline in CCI CCI in patients assigned to the CCI CCI • Percentage change from baseline in CCI CCI in patients assigned to the CCI CCI • Change from baseline in CCI CCI • Change from baseline in CCI CCI CCI

[a] The mITT population will be used for the primary analysis of all efficacy endpoints.

[b] Estimand description and detailed intercurrent event strategies for the primary analysis of the primary efficacy endpoint are found in Section 9.4.2.1 and Table 9, respectively.

AESI(s) = adverse event(s) of special interest; CCI ; BP = blood pressure; DBP = diastolic blood pressure, CKD = chronic kidney disease; CCI ; ECG = electrocardiogram; CCI ; EOT = end of treatment; CCI mITT = modified intent-to-treat; CCI ; CCI ; SAE = serious adverse event; SBP = systolic blood pressure; TEAE(s) = treatment-emergent adverse evets(s); TESAE(s) = treatment-emergent serious adverse event(s); CCI , uHTN = uncontrolled hypertension

4 STUDY DESCRIPTION

4.1 Study Indication

Treatment of hypertension in patients with uHTN and CKD.

4.2 Summary of Study Design

This is a Phase II, randomized, double-blind, placebo-controlled, multicenter, parallel-group, dose-ranging study to evaluate the efficacy and safety of CIN-107 for the treatment of hypertension in patients with uHTN and CKD.

The safety of CIN-107 will be assessed from the time of randomization until the end of the follow-up period. Patients will be followed for efficacy and adherence throughout the double-blind treatment period. CCI analyzed during the study will include measures of CCI and its relevant precursors. CCI analyzed during the study will include CCI of CIN-107.

Safety surveillance will be conducted at specified clinic visits throughout the study. Serum potassium, sodium levels and the eGFR value will be measured at the central laboratory at each designated visit. Unscheduled assessments of potassium or sodium levels or renal function should be completed at the investigator's discretion for acute management of the patient (eg, follow-up from elevated central lab potassium, acute changes in clinical condition, suspected dehydration, etc) as recommended below:

- For serum potassium of ≥ 5.5 to < 6.0 mEq/L, the patient should present to the clinical site within 72 hours for repeat testing.
    - If repeat serum potassium is confirmed (by local or central laboratory) to be ≥ 5.5 mEq/L, study drug should be temporarily interrupted and may not resume until serum potassium is < 5.0 mEq/L. If patient's dose had been up-titrated, then study drug should be resumed at the lower dose (if the lower dose is not available, study drug should not be resumed until the lower dose is available). After restart of study drug, serum potassium should be rechecked within 2 to 7 days.
    - If repeat potassium is < 5.5 mEq/L, study drug dose may continue. If patient's dose had been up-titrated, study drug may be down-titrated based on investigator judgment (if down-titration is indicated as per the investigator's judgment but the lower dose is not available, study drug should be interrupted until the lower dose is available).
- For serum potassium of ≥ 6.0 mEq/L, study drug should be interrupted and may not resume until serum potassium is < 5.0 mEq/L. Potassium should be repeated immediately, either at the clinical site or another clinical location (eg, emergency department if considered clinically indicated by investigator). If patient's dose had been up-titrated, study drug should be re-started at lower dose (if the lower dose is not available, study drug should not be resumed until the lower dose is available). After re-start of study drug, serum potassium should be re-checked within 2 to 7 days.
- Permanently discontinue treatment if a patient experiences a recurrent serum potassium ≥ 6.0 mEq/L after a previous event if there was no explanation for the recurring event other than restarting treatment.
- For serum sodium of < 130 mEq/L, the patient should present to the clinical site for repeat testing. The investigator may withhold dosing if sodium is < 125 mEq/L.
- For serum creatinine greater than 1.5 times baseline (creatinine at Visit 3) or a 30% increase from the previous visit, or an eGFR decrease of $\geq 30\%$ from the previous visit, the patient should suspend study drug dosing and present to the clinical site for repeat testing.
- For patients, who have interrupted study drug for any reason, study drug should not be resumed unless potassium has been confirmed to be < 5.0 mEq/L.

Repeat and unscheduled testing for serum sodium, potassium, or eGFR should be measured at the local laboratory and central laboratory for a faster turn-around time to allow clinical assessment. Local laboratory assessments may also be conducted in addition to central laboratory assessment at any timepoint at the investigator's discretion. Patients will be instructed to bring their study drug to all clinical site visits after randomization for assessing treatment adherence.

4.2.1 Study Visits

Patients will complete at least 12 visits over a period of approximately 8 months.

The study will consist of the following 3 periods and corresponding visits:

- A screening period of 5 weeks (Visits 1 and 2) including a mandatory 2-week run-in period (beginning at Visit 2 until Visit 3)
- A double-blind treatment period of 26 weeks (Visits 3 through 11)
- A follow-up period of 2 weeks (Visit 12)

4.2.1.1 Screening Period Including the Mandatory 2-Week Run-In Period

Patients who provide written informed consent at Visit 1 will be assessed for the Inclusion/ exclusion criteria.

At Visit 1, site staff will perform a pre-screen dipstick urinalysis to exclude patients who only have negative or trace albuminuria. Historical albuminuria or proteinuria of > 500 mg/gm from within the past year and entered in the patient's medical history can be used in lieu of a dipstick urinalysis for albuminuria. If a dipstick is performed and registers at levels above trace for albuminuria, the site staff should proceed to measure BP and vitals, obtain blood samples for eGFR assessment, and perform routine safety evaluations. Patients will be provided with materials to obtain urine via first morning void at their home on 2 consecutive days prior to and on the morning of Visit 2. Visit 2 can be scheduled between 5 and 15 days after the screening visit when the laboratory testing results (based on samples drawn at screening visit) are available for determining eligibility. At least 4 days prior to Visit 2, site staff will place a reminder call instructing the patient to obtain the samples on the following 3 consecutive mornings. The third sample will be collected such that the date of collection and Visit 2 are the same.

At Visit 2, patients will bring the collected CCI [redacted] to the clinical site and site staff will send the samples to a central laboratory for CCI [redacted] determination. Site staff will assess inclusion/exclusion criteria, measure BP, obtain vitals, and assess concomitant medications. Patients will be provided with materials and instructions to collect CCI [redacted] beginning the morning of Day -1 (day prior to randomization). On Day -3 (± 1 day), site staff will place a

reminder call to the patient to obtain the CCI such that the date of completion of the 24-hour period and Visit 3 (randomization visit) are the same.

At Visit 3, site should confirm Visit 2 results that patient continues to meet inclusion criterion 2 regarding BP, inclusion criterion 3 regarding eGFR, and inclusion criterion 4 regarding CCI. If these criteria are not met, the patient should not be enrolled in the study.

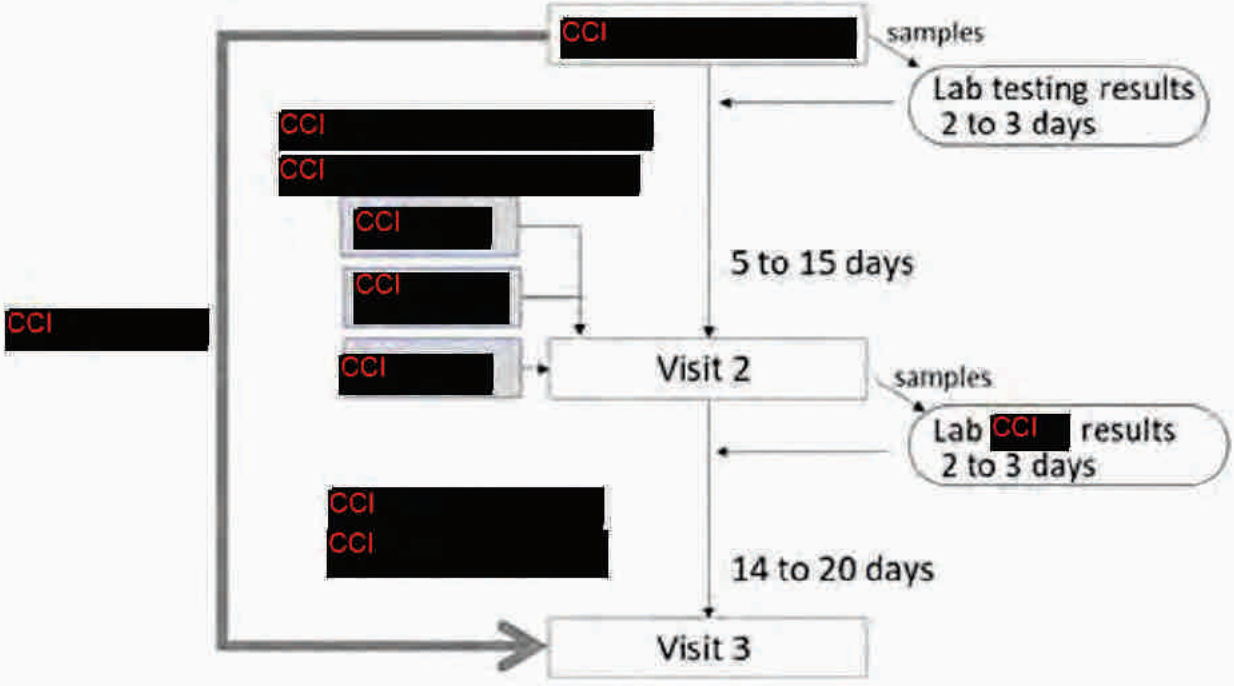
A patient who has consented to participate in the study but does not meet the study inclusion/exclusion criteria may be rescreened no less than 5 days after the last study visit, with sponsor and/or medical monitor consultation and approval.

At Visit 2, the patients will be provided with 2-week supplies of single-blind CIN-107 placebo run-in drug and instructions on lifestyle management, reminders concerning hydration, and the expectation that they will continue their background antihypertensive medications and, if relevant, SGLT2 inhibitor.

Upon return of the screening eligibility laboratory results of CCI, patients will be contacted via telephone to inform them of their eligibility, and if eligible, to begin taking the study drug once per day and schedule their next visit (Visit 3).

The scheduling of clinical visits during the screening period is illustrated in Figure 2.

Figure 2 CCI



[a] CCI.

Note: This guide can be used to determine visit dates; however, site should confirm that visits are scheduled in line with the windows provided in the SOA (Table 2).

CCI [redacted]

4.2.1.2 Double-Blind Treatment Period

At Visit 3 (randomization visit, Day 1/Week 0 in Figure 2), inclusion criteria for SBP will be confirmed. Patients who remain eligible will be randomized 1:1:1 into 1 of the 3 treatment groups (baxdrostat low-dosing strategy, baxdrostat high-dosing strategy, or placebo group). Randomization will be stratified by SGLT2 inhibitor use, baseline SBP (≤ 155 mmHg or >155 mmHg) and CKD category (eGFR ≤ 45 mL/min/1.73 m^2 or > 45 mL/min/1.73 m^2).

At Visit 4 (one week after randomization), all randomized patients will return to the clinic and a blood sample will be drawn for safety parameter measurements. If electrolyte imbalance or clinically significant decline in eGFR occurs, the patients must be monitored at the investigator's discretion for acute management of the patient.

At Visit 5 (3 weeks after randomization), BP will be measured, and a blood sample will be drawn for safety parameter measurements. The CIN-107 dose level may be up-titrated if the following criteria have been met:

1 Patient has not achieved SBP < 130 mmHg target.
2 Patient has not experienced hyperkalemia (defined as potassium ≥ 5.0) at any point during the trial (including screening).
3 Patient has not experienced hyponatremia (defined as sodium < 135) at any point during the trial (including screening).
4 Patient has not experienced declining in renal function (defined as eGFR decrease of ≥ 30% from randomization).

If the SBP remains ≥ 130 mmHg and the electrolyte/GFR safety criteria are acceptable, 3 case scenarios may be encountered:

1 A patient on 0.5 mg CIN-107 dose strength until Visit 5 may receive 1 mg CIN-107 dose strength following Visit 5.
2 A patient on 2 mg CIN-107 dose strength until Visit 5 may receive 4 mg CIN-107 dose strength following Visit 5.
3 A patient randomized at Visit 3 to placebo will remain on placebo.

Down-titration based on potassium values can occur following up-titration as follows:

- For patients who have been up-titrated at Visit 5, down-titration is permitted if electrolyte imbalance or declining renal function is a significant risk for the patient (if in the

investigator's judgment down-titration is indicated for a patient who has been up-titrated at Visit 5, but the lower dose is not available; study drug should be interrupted until the lower dose is available).

- If Visit 5 potassium value is ≥ 5.0, but patient had been up-titrated at Visit 5, then subject should be brought back in for an unscheduled visit to down-titrate IMP immediately.

At Visit 6 (4 weeks after randomization and 1 week after possible dose up-titration), all patients will return to the clinic, BP will be measured and a blood sample will be drawn for serum electrolytes and renal function measurements.

At Visit 7 (6 weeks after randomization), BP will be measured and a blood sample will be drawn for serum electrolyte measurements.

At Visits 8 to 10 (Weeks 9 to 22), patients should be taking study drug tablets as prescribed every day. Vital signs and safety laboratory testing will be measured at clinical visits. CCI [redacted].

At Visit 11 (Week 26), patients will take the last study drug dose and complete the required procedures including return of any unused study drug.

For CCI [redacted] measurements, baseline is defined as geometric mean of the 3 samples returned at Visit 2. For BP measurements, baseline is defined as the average of the 3 measurements taken prior to study drug administration at Visit 3. Measurements of efficacy and safety variables recorded prior to the first dose of double-blind study drug administration will constitute pre-dose measurements.

During clinical site visits, adherence to study drug dosing will be calculated using pill counts.

Pre-dose blood samples CCI [redacted] will be collected at Visit 3 (baseline), Visit 9 (Week 16), Visit 11 (Week 26), and Visit 12 (Week 28, 2 weeks after the last dose). Pre-dose blood samples for CCI [redacted] will be collected at Visits 9 and 11. If possible, the CCI [redacted] samples should be drawn at Visit 13 (ET) if a patient withdraws from study participation. CCI [redacted] blood samples will be collected within approximately 15 minutes prior to dosing.

CCI [redacted] CCI [redacted] and CCI [redacted] will be obtained over 24 hours (CCI [redacted] leading up to Visit 3 (baseline), Visit 9 (Week 16), Visit 11 (Week 26), and Visit 12 (Week 28, 2 weeks after the last dose).

CCI will be obtained via first morning void on the 2 consecutive days leading up to and morning of Visits 2, 9, 11, and 12. The secondary efficacy endpoint evaluation will take place at the EOT visit (Visit 11). For visits at which both CCI and CCI are to be obtained, approximately 10 mL of first void sample should be collected from the CCI pan and transferred to the CCI for CCI testing before transferring the CCI to the CCI .

4.2.1.3 Follow-Up Period

At Visit 12, patients will complete a follow-up visit at 2 weeks ± 7 days after the last dose of the study drug. The assessments to be performed at this visit are indicated in the SoA (Table 2).

The study design is shown in Figure 1.

4.3 End-of-study Definition

Primary completion date is defined as the date that the final patient 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 is defined as the date the final patient 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 patient's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

5 SELECTION OF PATIENTS

5.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1 Is an adult male or female patient ≥ 18 years of age.

2 Has a mean seated SBP ≥ 140 mmHg at Screening (Visit 1), Visit 2, and Visit 3.

Note: Patients with mean seated SBP ≥ 130 mmHg may be eligible if diabetic.

Note: Mean seated SBP is defined as the average of 3 seated SBP measurements at any single clinical site visit.

3 Has a prior diagnosis of mild-to-severe CKD, defined as eGFR (based on the CKD-EPI equation) of 25 to 75 mL/min/1.73 m^2, inclusive, at Visit 1.

Note: To ensure patients with moderate and severe renal impairment will be represented, the number of patients with an eGFR ≥ 60 mL/min/1.73 m^2 and ≤ 75 mL/min/1.73 m^2 will be capped at 45.

4 Has a CCI [redacted] in at least 2 out of 3 measurements based on first CCI collected in the morning on consecutive days during the screening period.

5 Is currently taking an ACEi or ARB at the patient's maximum tolerated daily dose, based on investigator judgment, for > 4 weeks prior to Visit 1.

Note: Taking additional antihypertensive agents is permitted except an MRA or a potassium-sparing diuretic (eg, triamterene, amiloride, etc).

6 If taking a SGLT2 inhibitor at screening (Visit 1), the regimen must be stable for a period of at least 8 weeks before Visit 1 and be expected to remain at a stable dose over the study period.

Note: It is expected that patients not currently taking an SGLT2 inhibitor at screening (Visit 1) will not initiate this class of medication during the entire study period.

7 Is willing to be compliant with the contraception and reproductive restrictions of the study as follows:

- Female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) must have a documented negative pregnancy test at Visit 1 and the randomization visit (Visit 3).
- Female patients of childbearing potential must use a highly effective method of contraception (ie, < 1% failure rate) from Day 1 through 30 days after the last administration of study drug.

  Note: Acceptable methods of contraception for female patients of childbearing potential enrolled in the study include the following:

  - Surgical sterilization (tubal ligation)

- Intrauterine device for at least 12 weeks before Visit 1
- Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before Visit 1
- Diaphragm used in combination with spermicide

– Postmenopausal women must have not had menstrual bleeding for at least one year before initial dosing and either be > 60 years or have an elevated FSH level > 40 mIU/mL at Visit 1.

8 Is able and willing to give informed consent for participation in the study.

9 After the mandatory run-in period of 2 weeks, investigators must confirm the patient's BP and CCI measurements still meet the eligibility criteria.

5.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1 Have a documented diagnosis of type 1 diabetes.

2 Are not willing or not able to discontinue a MRA or a potassium-sparing diuretic as part of an existing antihypertensive regimen.

Note: Patients taking an MRA or a potassium-sparing diuretic (eg, triamterene, amiloride, etc) as an antihypertensive agent must be willing to discontinue this agent for study eligibility. The potassium-sparing diuretic may be discontinued and replaced with a non-potassium-sparing diuretic. All patients who remain on a stable regimen of antihypertensive agents, including a non-potassium-sparing diuretic, for at least 6 weeks, will be eligible to enter the single-blind run-in. If the subject discontinues their prior MRA or potassium-sparing diuretic and/or initiates a new antihypertensive for study eligibility or has their antihypertensive dose adjusted after Visit 1, they should remain on a stable regimen of antihypertensive agents for at least 4 weeks and will have an extended screening period of up to 9 weeks from signing of informed consent to randomization (Visit 3).

3 Have a single occurrence of mean seated SBP > 180 mmHg or DBP > 110 mmHg during the screening period (if such a BP is recorded during the screening period, the patient may attend an interim visit for an additional BP measurement and reassessment of inclusion/exclusion criteria).

Note: Mean seated BP is defined as the average of 3 measurements obtained at any one clinical site visit. If the patient missed the regularly scheduled antihypertensive medication(s) prior to the visit (Visits 1 or 2), one BP retest is allowed ≥ 2 hours after taking the medication(s), on the following day, or later after reestablishing the regularly scheduled antihypertensive regimen.

4 Has a BMI > 50 kg/m^2 at Visit 1.

5 Has documented bilateral clinically relevant renal artery stenosis of ≥ 70%; if the imaging evidence is met, the subject should be excluded since hypertension itself could be considered 'clinically relevant'. Suspected or nondocumented renal artery stenosis is not excluded.

6 Has had dialysis for acute kidney injury/acute renal failure within 12 weeks prior to the screening period or has a planned dialysis or kidney transplantation during the course of the study.

7 Has known documented chronic heart failure New York Heart Association Class III or Class IV and/or hospitalization for heart failure within 6 months of Visit 1.

8 Has had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure within 6 months of Visit 1.

9 Has known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease, diagnosed from a prior echocardiogram or another imaging study.

10 Has a planned coronary revascularization (PCI or CABG) or any major surgical procedure during the study.

11 Has had PCI, CABG, other major cardiac surgery (eg, valve replacement), or peripheral arterial bypass surgery within 6 months of Visit 1.

12 Has had a prior solid organ transplant or cell transplant.

13 Is expected to receive or is receiving any of the exclusionary drugs such as strong inducers of CYP3A, chronic use (medication is taken more than 3 times a week for more than 3 months) of non-steroidal anti-inflammatory drugs, spironolactone/eplerenone, and/or chronic use of systemic steroids.

14 Has a known hypersensitivity to any of the following:
- CIN-107 or drugs of the same class
- Excipients in CIN-107 or drugs of the same classes

15 Has received immunotherapy for treatment of CKD within 6 months of Visit 1 or expects to receive immunotherapy for treatment of CKD during participation in the study.

16 Has any clinically relevant medical or surgical conditions including unstable conditions and/or conditions requiring regular transfusion or treatment with systemic immunosuppressants, including corticosteroids that, in the opinion of the investigator, would put the patient at risk by participating in the study.

17 Has evidence of any of the following at Visit 1 (1 retest is allowed):
- White blood cell count > 15×10^9/L or absolute neutrophil count < 1×10^9/L
- Serum potassium < 3.5 mEq/L

Note: Patients with a serum potassium level below normal range may continue in the study without retest if the investigator elects to correct the serum potassium level with supplementation and offers to manage the condition.

- Serum potassium > 5.0 mEq/L
- Serum sodium < 135 mEq/L
- Serum aspartate aminotransferase or alanine aminotransferase > 3 × ULN or
- Total bilirubin > 2 × ULN, unless due to Gilbert's syndrome
- Estimated GFR is < 25 or > 75 mL/min/1.73 m^2

18 Has uncontrolled diabetes with glycosylated hemoglobin > 10.5% at Visit 1.

19 Is positive for HIV antibody, HBsAg, or HCV RNA.

20 Has typical consumption of > 14 alcoholic drinks weekly.

Note: One drink of alcohol is equivalent to ½ pint of beer (285 mL), one glass of spirits (25 mL), or one glass of wine (125 mL).

21 Has participated in another clinical study involving any investigational drug within 30 days prior to Visit 1, or plans to participate in another clinical study within 30 days of discontinuation of study drug.

22 Has received experimental therapy for disease intervention with a small molecule within 30 days of Visit 1 or 5 half-lives, whichever is longer, or received experimental therapy with a large molecule within 90 days of the Visit 1 or 5 half-lives, whichever is longer.

Note: Vaccinations, including those for COVID-19, will not be exclusionary.

23 Is pregnant, breastfeeding, or planning to become pregnant during the study.

24 Is considered by the investigator, after reviewing medical and psychiatric history, physical examination, and laboratory evaluations, to be unsuitable for any other reason that may either place the patient at increased risk during participation or interfere with the interpretation of the study outcomes. History of COVID-19 infection, in of itself, is not an exclusionary criterion unless the patient is subsequently considered unsuitable for the study based on criteria above.

5.3 Lifestyle Considerations

Patients should not exercise, smoke, or consume caffeinated beverages or food 30 minutes prior to assessment of vital signs.

5.4 Screen Failures

A screen failure occurs when a patient who has consented to participate in the clinical study is not subsequently assigned to study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from

regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

A patient who has consented to participate in the study but does not meet the study inclusion/exclusion criteria may be rescreened no less than 5 days after the last study visit, with sponsor and/or medical monitor consultation and approval.

6 STUDY TREATMENTS

6.1 Treatment Groups

At Visit 3 (randomization visit), eligible patients will be randomly assigned in a 1:1:1 ratio to 1 of the 3 treatment groups:

- Low-dosing strategy group: to take CIN-107 0.5 mg (as one 0.5 mg tablet and one placebo tablet) and may up-titrate to take CIN-107 1 mg (as one 1 mg tablet and one placebo tablet) at Week 3 (Visit 5)
- High-dosing strategy group: to take CIN-107 2 mg (as one 2 mg tablet and one placebo tablet) and may up-titrate to take CIN-107 4 mg (as two 2 mg tablets) at Week 3 (Visit 5)
- Placebo group: to take placebo (as two placebo tablets) for CIN-107

Missed doses of CIN-107 or placebo should not be compensated for (ie, if a dose is missed, the next regularly scheduled dose should be taken and should not be doubled).

6.2 Drug Supplies

6.2.1 Formulation and Packaging

CIN-107 will be provided as 0.5, 1, and 2 mg tablets in blister packs. CIN-107 tablets will contain the active ingredient and CCI [redacted] as inactive ingredients.

Matching placebo tablets will contain no active ingredient and the same inactive ingredients. Placebo tablets will be indistinguishable from the CIN-107 tablets. The study drug will be packaged as the following:

Study Drug for Run-in Period: (to be dispensed at Visit 2)
One pack consists of CCI [redacted] for 1-week supplies of run-in drug. At Visit 2, patients will be provided with 2-week supplies of single-blind CIN-107 placebo run-in drug.

Study Drug for Double-blind Treatment Period: (to be dispensed at Visit 3 to Visit 10)
One pack consists of CCI [redacted] for 1-week supplies of double-blind study drug.

The number of packs to be dispensed to each patient will depend on the number of weeks until the next clinical visit. One extra kit may be provided to accommodate the allowed visit windows, if necessary.

6.2.2 Study Drug Preparation and Dispensing

Blinded study drug will be delivered from the central depot to the clinical site. Once a patient has been assigned a randomized treatment via IRT, site staff who have been delegated the task of drug dispensing by the investigator will dispense the appropriate treatment. Study drug (CIN-107 or placebo) will be dispensed at Visit 3 (randomization visit) and Visits 5, 7, 8, 9, and 10.

At Visit 2, patients will be provided with 2-week supplies of single-blind CIN-107 placebo run-in drug.

6.2.3 Study Drug Administration

Patients will be instructed to take 2 tablets per day by mouth during the mandatory run-in period and during the double-blind treatment period.

Patients will be allowed to have their normal diet the morning of study drug administration. At the randomization visit, patients will receive either CIN-107 tablets of their assigned dose strength or matching placebo tablets. At Visit 3 (randomization visit), patients will self-administer the first dose of study drug in 2 tablets at the clinical site. Subsequent doses of the study drug are to be taken by the patient by mouth QD at approximately the same time each morning at home. On days of clinical site visits, patients will take their scheduled morning doses of their regular antihypertensive medications and SGLT2 inhibitor (if applicable) at home and hold their dose of study drug. Patients must bring their study drug and regular antihypertensive medications to the clinical site at all visits. At the clinical site, patients will self-administer the study drug to be witnessed by site staff after completion of pre-dose evaluations and laboratory sampling.

A tablet administration guide outlining the best practices for administering study drug will be provided to clinical sites.

6.2.4 Treatment Compliance

Patients will self-administer the study drug at the clinical site to be witnessed by site staff after completion of pre-dose evaluations and laboratory sampling; the date and time of study drug administration will be recorded. A hand and mouth check will be performed by site staff.

On days of clinical site visits, patients will bring their medications (study drug and all antihypertensive medications) to the clinical site for assessment of treatment adherence. Site staff will assess treatment adherence based on pill counts. If pill count is not feasible, the site

staff may record the compliance based on patient's attestation; however sites should strive for accurate pill counts at each visit. Site staff will record date and time of last dose prior to PK sampling on the eCRF.

For all protocol-specified doses when the patient is not at the clinical site, patients will self-administer study drug at home and continue taking their background antihypertensive medications. Site staff will counsel patients about the importance of adhering to their antihypertensive medications and study drug regimen. During clinical site visits, adherence to study drug will be calculated using pill counts. The presence of the background antihypertensive medications and study drug in the urine samples and blood samples drawn at the clinic visit may be tested to verify dosing adherence.

Missed doses of CIN-107 or placebo should not be compensated for (ie, if a dose is missed, the next regularly scheduled dose should be taken and should not be doubled).

6.2.5 Storage and Accountability

The study drug will be stored at CCI [redacted]

A drug accountability log will be maintained by the clinical sites indicating the receipt and dispensation of all study drug supplies. The log will indicate date dispensed, quantity dispensed, and the patient to whom the study drug was dispensed.

At the conclusion of the study and after final accountability, all unused study drug should be collected by site staff and destroyed at the clinical site per the clinical site's standard operating procedures. Clinical sites that do not allow destruction may return any unused study drug to the central depot for final drug accountability and destruction. It is the investigator's responsibility to ensure that the sponsor has provided written authorization prior to the return or destruction of the study drug and that appropriate records of the disposal are documented and maintained. A certificate of return will be provided to the clinical sites by the central depot. If no study drug remains, this will be indicated in the drug accountability log.

6.3 Dose Titration Criteria

Three weeks after randomization (Visit 5), the CIN-107 dose level may be up-titrated if the following criteria have been met:

1 Patient has not achieved SBP < 130 mmHg target.
2 Patient has not experienced hyperkalemia (defined as potassium ≥ 5.0) at any point during the trial (including screening).
3 Patient has not experienced hyponatremia (defined as sodium < 135) at any point during the trial (including screening).

4 Patient has not experienced declining in renal function (defined as eGFR decrease of ≥ 30% from randomization).

Down-titration based on potassium values can occur following up-titration as follows:

- For patients who have been up-titrated at Visit 5, down-titration is permitted if electrolyte imbalance or declining renal function is a significant risk for the patient (if in the investigator's judgment down-titration is indicated for a patient who has been up-titrated at Visit 5, but the lower dose is not available; study drug should be interrupted until the lower dose is available).
- If Visit 5 potassium value is ≥ 5.0, but patient had been up-titrated at Visit 5, then subject should be brought back in for an unscheduled visit to down-titrate IMP immediately.

Detailed information about dose titration is provided in Section 4.2.1.2.

6.4 Randomization and Blinding

Patients who meet all inclusion/exclusion criteria at Visit 3 (randomization visit) will be randomized into the study using an automated IRT system in a 1:1:1 ratio into 1 of the 3 treatment groups (placebo, low dose treatment strategy and high dose treatment strategy). It is anticipated that a total of approximately 174 patients will be randomized.

Randomization information will be concealed from the investigators, the patients, and the study team until the end of the study, with the exception of an emergency situation involving a patient that requires unblinding of the treatment assignment (Section 6.5).

Bioanalytical staff involved in CCI will be unblinded to treatment either via receipt of the randomization code to allow for analysis of samples from patients receiving CIN-107 only, or by the nature of the results of sample analysis. The CCI will be deidentified before being provided to any other individuals, including those involved in calculating CCI and associated descriptive statistics and/or plotting CCI in order to maintain blinding. Similar measures will be undertaken for CCI, which have the potential to unblind (eg, being deidentified before being provided to the investigator, other site staff, study team members), as deemed reasonable and appropriate.

Randomization will be stratified by SGLT2 inhibitor use, baseline SBP (≤ 155 mmHg or > 155 mmHg) and CKD category (eGFR ≤ 45 mL/min/1.73 m^2 or > 45 mL/min/1.73 m^2).

The number of patients with eGFR 60 to 75 mL/min/1.73 m^2 at the time of randomization (as shown with a laboratory test at screening [Visit 1]) will be monitored, and randomization in IRT will be capped to ensure that the number of patients in this subpopulation does not exceed 45 (approximately 25% of the total population).

6.5 Breaking the Blind

Individual treatment assignments may be unblinded when immediate knowledge of the treatment assignment is needed to optimize the clinical management of the patient. The investigator should contact the medical monitor to discuss the event prior to unblinding. In the event this is not possible, the investigator should contact the AZ medical monitor as soon as possible to discuss the event. If unblinding is deemed necessary, the investigator will perform the unblinding in IRT. Documentation of the blind break must be retained in the patient's source documentation at the clinical site in such a way as to avoid unblinding the treatment assignment to other clinical sites or blinded study staff. The number of individuals at the study site who become aware of treatment status should be kept to minimum (including keeping the patient blinded if possible).

Designated personnel who are not involved with the study operation will hold the treatment codes. The unblinded treatment information can be provided to the DSMB to facilitate the evaluation of any clinically important increase in the rate of a serious suspected adverse reaction or to the designated safety contact when the treatment information is required to determine if an expedited safety report must be submitted to regulatory agencies.

6.6 Treatment of Overdose

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

Clinical judgment should always be applied when determining overdose. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s), or the investigator has a reason to suspect that the patient has taken additional dose(s).

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Evaluate the patient, in consultation with the medical monitor or the Study Clinical Lead, if possible, to determine whether study drug should be interrupted or whether the dose should be reduced.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities as medically appropriate. Refer to Section 8.4.5 for details of AE/SAE reporting related to overdose.

6.7 Prior and Concomitant Medications and/or Procedures

6.7.1 Excluded Medications and/or Procedures

Use of the following investigational, prescription, and/or over-the-counter medications is not permitted during the study:

- Strong inducers of CYP3A
- Chronic use of non-steroidal anti-inflammatory drugs. Chronic use is defined as medication is taken more than 3 times a week for more than 3 months
- Spironolactone/eplerenone
- Chronic use of systemic steroids (inhaled/topical steroids are allowed)

Note: Examples of the above excluded products are provided in Table 4.

- Immunotherapy for treatment of CKD within 6 months of Visit 1 or expected to receive immunotherapy for treatment of CKD during participation in the study
- Experimental therapy with a small molecule within 30 days of Visit 1 or 5 half-lives, whichever is longer, or received experimental therapy with a large molecule within 90 days of the Visit 1 or 5 half-lives, whichever is longer
- MRAs
- Potassium-sparing diuretics (eg, triamterene and amiloride) within 4 months of Visit 1
- Coronary revascularization (PCI or CABG) within 6 months of Visit 1 or planned during the study
- Any major surgical procedure within 6 months of Visit 1 or planned during the study

Table 4 Examples of Excluded Medications

Group	Excluded Medications Examples
Strong inducers of CYP3A [a]	Apalutamide, carbamazepine [b], enzalutamide [c], mitotane, phenytoin [d], rifampin [e], St. John's wort [f]
Medications known to prolong QT	Amiodarone, azithromycin, cilostazol, ciprofloxacin, cisapride, citalopram, ciprofloxacin, clarithromycin, dofetilide, domperidone, donepezil, erythromycin, escitalopram, fluconazole, hydroxychloroquine, levofloxacin, methadone, moxifloxacin, ondansetron, pentamidine, quinidine, sotalol, thioridazine, vandetanib
NSAIDS	Naproxen sodium, indomethacin, ibuprofen, (only chronic use [chronic use is defined as medication is taken more than 3 times a week for more than 3 months] is excluded.)
Systemic steroids	Prednisone, prednisolone, dexamethasone (topical and inhaled steroids are allowed)

[a] Examples of clinical inducers for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (12/03/2019). Strong, moderate, and weak inducers are drugs that decrease the AUC of sensitive index substrates of a given metabolic pathway by ≥ 80%, ≥ 50% to < 80%, and ≥ 20% to < 50%, respectively

[b] Strong inducer of CYP2B6 and CYP3A, and weak inducer of CYP2C9

[c] Strong inducer of CYP3A and moderate inducer of CYP2C9 and CYP2C19

[d] Strong inducer of CYP2C19 and CYP3A, and moderate inducer of CYP1A2, CYP2B6, CYP2C8, and CYP2C9

[e] Strong inducer of CYP3A and moderate inducer of CYP1A2 and CYP2C19; and

[f] The effect of St. John's wort varies widely and is preparation dependent.

AUC = area under the concentration-time curve; CYP = cytochrome P450; DDI = drug-drug interaction; NSAIDS = non-steroidal anti-inflammatory drugs

Sources: (a) Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed 15 April 2021; (b) Drugs with known TdP risk. Available at www.crediblemeds.org. Accessed 15 April 2020.

Each concomitant medication should be assessed individually for its potential for a drug-drug interaction. For examples of clinical inhibitors and substrates of the listed transporters and clinical inducers for P450-mediated metabolisms, see the online reference at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers and at www.CredibleMeds.org.

Non-RAAS-modifying antihypertensive drug(s) may be utilized to manage BP and include mono- or combination therapy consisting of non-dihydropyridine calcium channel blockers (eg, diltiazem, verapamil), hydralazine, or an alpha blocker. Non-RAAS-modifying antihypertensive drug(s), defined as mono- or combination therapy with a non-dihydropyridine calcium channel blocker (eg, diltiazem, verapamil), hydralazine, or an alpha blocker, are allowed for BP management.

6.7.2 Restricted Medications and Procedures

It is expected that patients not currently taking SGLT2 inhibitor(s) will not initiate this class of medication during the entire study.

6.7.3 Allowed Medications and/or Procedures

ACEi or ARB at the maximum tolerated daily dose by the patient based on investigator judgment for > 4 weeks prior to Visit 1 is required for inclusion into the study.

If a patient is taking a SGLT2 inhibitor at screening (Visit 1), the regimen must be stable for a period of at least 8 weeks before Visit 1 and be expected to remain at a stable dose over the study period. It is expected that patients not currently taking SGLT2 inhibitor(s) will not initiate this class of medication during the entire Treatment Period.

Female patients of childbearing potential enrolled into the study are permitted to take hormonal contraception (oral, implant, ring, or patch) from Day 1 through 30 days after the last administration of study drug.

Vaccinations, including those for COVID-19, will not be exclusionary.

Non-RAAS-modifying antihypertensive drug(s), defined as mono- or combination therapy with a non-dihydropyridine calcium channel blocker (eg, diltiazem, verapamil), hydralazine, or an alpha blocker, are allowed for BP management.

Medications other than those excluded (Section 6.7.1) are allowed during the study period.

6.7.4 Documentation of Prior and Concomitant Medication Use

All medications used within 30 days of the screening period will be recorded. All concomitant medications and concurrent therapies will be documented in the patient's eCRF as indicated in Section 1.3. Dose, route, unit frequency of administration, indication for administration, and dates of medication administration will also be captured in source documents and on the appropriate eCRF.

All concomitant medications and concurrent therapies (including fluids, electrolytes, vitamins, and supplements) [including potassium supplements]), as well as "as needed" medications will be documented as indicated in Section 1.3. Dose, route, unit frequency of administration, indication for administration, and dates of medication administration will also be captured in source documents and on the appropriate eCRF.

6.7.5 Rescue Medication Use

Every effort will be made to secure the continued participation of the patients. Rescue medication use is permitted and recommended at any time in the study if SBP shows an increase of 30 mmHg from baseline or BP exceeds 170/105 mmHg (either measurement) in office measurements or home measurements by the patient over 3 consecutive days. Choice of rescue therapy should take into consideration current antihypertensive treatment, as well as co-morbidities, such as CV or renal disease, and severity of BP elevation. Site investigators should use their best clinical judgment when determining rescue medications. Blood pressure must be determined prior to initiation of the rescue medication.

7 DISCONTINUATION OF STUDY DRUG AND PATIENT WITHDRAWAL FROM STUDY

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 (Section 7.2).

If study intervention is permanently discontinued, the patient should, if at all possible, remain in the study and continue to complete planned visits and assessments per the SOA, with the exception of CCI assessments.

7.2 Early Termination Visit and Withdrawal Procedures

The EOT visit for patients completing the study is Visit 11. For patients who are withdrawn from the study prior to completion, all EOT visit (Visit 11) procedures will be performed at an ET visit (Visit 13). Refer to Section 7.3 for withdrawal criteria. The ET procedures include the following:

- Assess and record AEs
- Record concomitant medications
- Measure body weight
- Record vital signs and seated BP

  Note: The arm with the higher mean SBP value identified at Visit 1 during laterality testing should be used for all BP measurements. At each visit, seated BP should be measured in triplicate in the designated arm (arm identified with laterality testing at Visit 1). The same BP monitor originally provided to the clinical site should be used for all measurements.
- Record standing BP and heart rate

  Note: Once the seated BP has been determined, the patient will be asked to stand and after 60 seconds a single standing BP and a single standing heart rate measurement will be obtained.
- Perform a complete physical examination (general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system)
- Perform 12-lead ECG after the patient has been resting in the supine position for > 10 minutes and after measuring vital signs and BP
- Collect CCI determination if available
- Collect CCI collection if available
- Collect urine samples for urinalysis
- Collect blood samples for the following:
  - Clinical laboratory assessments including standard safety chemistry panel, hematology, and coagulation

    Note: Serum potassium levels of patients will be monitored systematically throughout the study. If indicated, repeat and unscheduled testing for serum potassium should be measured at the local laboratory and central laboratory (Section 8.4.6).
  - Serum pregnancy test
  - CCI

- CCI
- Collect unused study drug
- Assess treatment adherence by pill counts

7.3 Patient Withdrawal Criteria

Patients may withdraw consent or request withdrawal from the study participation for any reason. The site staff should make every effort to complete the assessments scheduled for the ET visit (Table 2). The reason for patient withdrawal must be documented in the eCRF. The sponsor or the regulatory authority may terminate the study.

A patient may be withdrawn from the study for any of the following reasons:

- The patient has a mean seated BP > 170/105 mmHg at 2 separate occasions during the double-blind treatment period
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol
- Pregnancy (Section 8.4.7 for reporting requirements)
- Requirement of prohibited concomitant medications (Section 6.7.1)
- Patient failure to comply with protocol requirements or study-related procedures.

If a patient withdraws dosing prematurely from the study due to the above criteria, the site staff should make every effort to schedule the remaining protocol-specified visits and retrieve as much safety and efficacy data as possible.

In the case of a patient lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records (Section 7.4). Patients who withdraw from the study will not be replaced.

7.4 Lost to Follow-up

A patient will be considered lost to follow-up if the patient 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 patient fails to return to the study site for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible. The patient should be counseled on the importance of maintaining the assigned visit schedule. At this time ascertain whether the patient should or wishes to or continue in the study.

- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient. These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, the patient will be considered to have been lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Administrative and General/Baseline Procedures

8.1.1 Informed Consent

Written consent will be obtained from all patients before any protocol-specific procedures are performed.

Information about the study will be given to the patient both verbally and in writing. The written patient information will explain the objectives of the study, potential risks and benefits, and the impact of early withdrawal on the scientific validity of the study. The patient must have adequate time to read the information and to ask the investigator any questions. The investigator must be satisfied that the patient has understood the information provided before written consent is obtained. If there is any doubt as to whether the patient has understood the written or verbal information, the patient must not enter the study.

Patients will be given the option to participate in the CCI [redacted] during the consenting process. The written informed consent for CCI [redacted] will be included in the main ICF. For patients who provide written informed consent to participate in the CCI [redacted], a blood sample will be collected at any time after randomization during the patient's participation in the study.

Section 9.7.3 provides additional details on informed consent.

8.1.2 Screening Period (Visits 1 to 2)

8.1.2.1 Visit 1 (35 to 19 days prior to day of randomization)

For patients that require withdrawal of MRA, Visit 1 would be up to 9 weeks prior to the day of randomization.

The following procedures will be performed at Visit 1:

- Obtain informed consent
- Assess eligibility based on inclusion/exclusion criteria
- Record demographic information and medical/surgical history
- Record prior/concomitant medication
- Measure height and body weight

- Record vital signs and seated BP

  Note: Seated BP will be measured in both upper arms (3 times/arm) using an appropriately sized cuff and monitor provided to the clinical site to detect possible laterality differences at screening. The arm with the higher mean SBP value will then be used to take the screening BP measurements (at least 5 minutes after determining laterality) and for all subsequent measurements at subsequent visits. The same BP monitor provided to the clinical site should be used for all subsequent measurements.
- Record standing BP and heart rate

  Note: Once the seated BP has been determined, the patient will be asked to stand and after 60 seconds a single standing BP and a single standing heart rate measurement will be obtained.
- Perform a complete physical examination (general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system)
- Perform 12-lead ECG after the patient has been resting in the supine position for > 10 minutes and after measuring vital signs and BP
- Provide CCI [redacted] measurements
- Conduct urine dipstick assessment
- Collect blood samples for the following:
  - Clinical laboratory assessments including standard safety chemistry panel, hematology, and coagulation
  - Glycosylated hemoglobin
  - HIV, HBsAg, and HCV screen
  - Serum pregnancy test (if applicable)
- FSH (if applicable)
- Provide instructions for next visit

8.1.2.2 Visit 2 (14 to 20 days prior to day of randomization)

The following procedures will be performed at Visit 2:

- Assess eligibility based on inclusion/exclusion criteria
- Assess and record AEs
- Record concomitant medications
- Record vital signs and seated BP

  Note: The arm with the higher mean SBP value identified at Visit 1 during laterality testing should be used for all BP measurements. At each visit, seated BP should be measured in triplicate in the designated arm (arm identified with laterality testing at Visit 1). The same BP monitor originally provided to the clinical site should be used for all measurements.
- Record standing BP and heart rate

Note: Once the seated BP has been determined, the patient will be asked to stand and after 60 seconds a single standing BP and a single standing heart rate measurement will be obtained.

- Collect CCI determination by the central lab
- Collect urine samples for urinalysis
- Provide CCI collection kits
- Dispense run-in study drug
- Advise patient to take run-in study drug after Visit 2 once laboratory data (CCI) confirms eligibility
- Perform adherence counseling
- Provide instructions for next visit

8.1.3 Double-Blind Treatment Period (Visit 3 through 10)

8.1.3.1 Randomization – Visit 3 (Day 1)

The following procedures will be performed at Visit 3 (Day 1):

- Confirm eligibility based on inclusion/exclusion criteria
- Assess and record AEs
- Record concomitant medications
- Measure body weight
- Record vital signs and seated BP

  Note: The arm with the higher mean SBP value identified at Visit 1 during laterality testing should be used for all BP measurements. At each visit, seated BP should be measured in triplicate in the designated arm (arm identified with laterality testing at Visit 1). The same BP monitor originally provided to the clinical site should be used for all measurements.
- Record standing BP and heart rate

  Note: Once the seated BP has been determined, the patient will be asked to stand and after 60 seconds a single standing BP and a single standing heart rate measurement will be obtained.
- Perform a limited physical examination (general appearance, skin, heart, lungs, and abdomen)
- Perform 12-lead ECG after the patient has been resting in the supine position for > 10 minutes and after measuring vital signs and BP
- Collect urine samples for urinalysis
- Collect CCI collection kits
- Collect blood samples for the following:
  - Clinical laboratory assessments including standard safety chemistry panel, hematology, and coagulation

Note: Serum potassium levels of patients will be monitored systematically throughout the study. If indicated, repeat and unscheduled testing for serum potassium should be measured at the local laboratory and central laboratory (Section 8.4.6).

- Point of care pregnancy test (if applicable)
- CCI [redacted]

- Perform randomization via IRT
- Dispense study drug
- Administer study drug
- Collect unused study drug
- Assess treatment adherence by pill counts
- Perform adherence counseling
- Provide instructions for next visit

8.1.3.2 Visit 4 (Week 1)

The following procedures will be performed at Visit 4 (Day 7 ± 3 days):

- Assess and record AEs
- Record concomitant medications
- Record vital signs and seated BP

  Note: The arm with the higher mean SBP value identified at Visit 1 during laterality testing should be used for all BP measurements. At each visit, seated BP should be measured in triplicate in the designated arm (arm identified with laterality testing at Visit 1). The same BP monitor originally provided to the clinical site should be used for all measurements.
- Record standing BP and heart rate

  Note: Once the seated BP has been determined, the patient will be asked to stand and after 60 seconds a single standing BP and a single standing heart rate measurement will be obtained.
- Collect urine samples for urinalysis
- Collect blood samples for the following:
  - Clinical laboratory assessments including standard safety chemistry panel, hematology, and coagulation

    Note: Serum potassium levels of patients will be monitored systematically throughout the study. If indicated, repeat and unscheduled testing for serum potassium should be measured at the local laboratory and central laboratory (Section 8.4.6).
- Administer study drug
- Provide instructions for next visit

8.1.3.3 Visit 5 (Week 3)

The following procedures will be performed at Visit 5 (Day 21 ± 3 days):

- Assess and record AEs
- Record concomitant medications
- Measure body weight
- Record vital signs and seated BP

  Note: The arm with the higher mean SBP value identified at Visit 1 during laterality testing should be used for all BP measurements. At each visit, seated BP should be measured in triplicate in the designated arm (arm identified with laterality testing at Visit 1). The same BP monitor originally provided to the clinical site should be used for all measurements.
- Record standing BP and heart rate

  Note: Once the seated BP has been determined, the patient will be asked to stand and after 60 seconds a single standing BP and a single standing heart rate measurement will be obtained.
- Perform a limited physical examination (general appearance, skin, heart, lungs, and abdomen)
- Collect urine samples for urinalysis
- Collect blood samples for the following:
  - Clinical laboratory assessments including standard safety chemistry panel, hematology, and coagulation

    Note: Serum potassium levels of patients will be monitored systematically throughout the study. If indicated, repeat and unscheduled testing for serum potassium should be measured at the local laboratory and central laboratory (Section 8.4.6)
- Perform up-titration assessment (if needed, per Section 6.3)
- Dispense study drug
- Administer study drug
- Collect unused study drug
- Assess treatment adherence by pill counts
- Perform adherence counseling
- Provide instructions for next visit

8.1.3.4 Visit 6 (Week 4)

The following procedures will be performed at Visit 6 (Day 28 ± 7 days):

- Assess and record AEs
- Record concomitant medications

- Measure body weight
- Record vital signs and seated BP

  Note: The arm with the higher mean SBP value identified at Visit 1 during laterality testing should be used for all BP measurements. At each visit, seated BP should be measured in triplicate in the designated arm (arm identified with laterality testing at Visit 1). The same BP monitor originally provided to the clinical site should be used for all measurements.
- Record standing BP and heart rate

  Note: Once the seated BP has been determined, the patient will be asked to stand and after 60 seconds a single standing BP and a single standing heart rate measurement will be obtained.
- Collect urine samples for urinalysis
- Collect blood samples for the following:
  - Clinical laboratory assessments including standard safety chemistry panel, hematology, and coagulation

    Note: Serum potassium levels of patients will be monitored systematically throughout the study. If indicated, repeat and unscheduled testing for serum potassium should be measured at the local laboratory and central laboratory (Section 8.4.6).
- Administer study drug
- Provide instructions for next visit

8.1.3.5 Visit 7 (Week 6)

The following procedures will be performed at Visit 7 (Day 42 ± 7 days):

- Assess and record AEs
- Record concomitant medications
- Measure body weight
- Record vital signs and seated BP

  Note: The arm with the higher mean SBP value identified at Visit 1 during laterality testing should be used for all BP measurements. At each visit, seated BP should be measured in triplicate in the designated arm (arm identified with laterality testing at Visit 1). The same BP monitor originally provided to the clinical site should be used for all measurements.
- Record standing BP and heart rate

  Note: Once the seated BP has been determined, the patient will be asked to stand and after 60 seconds a single standing BP and a single standing heart rate measurement will be obtained.
- Perform a limited physical examination (general appearance, skin, heart, lungs, and abdomen)

- Perform 12-lead ECG after the patient has been resting in the supine position for > 10 minutes and after measuring vital signs and BP
- Collect urine samples for urinalysis
- Collect blood samples for the following:
  - Clinical laboratory assessments including standard safety chemistry panel, hematology, and coagulation

    Note: Serum potassium levels of patients will be monitored systematically throughout the study. If indicated, repeat and unscheduled testing for serum potassium should be measured at the local laboratory and central laboratory (Section 8.4.6).
- Dispense study drug
- Administer study drug
- Collect unused study drug
- Assess treatment adherence by pill counts
- Perform adherence counseling
- Provide instructions for next visit

8.1.3.6 Visit 8 (Week 9)

The following procedures will be performed at Visit 8 (Day 63 ± 7 days):

- Assess and record AEs
- Record concomitant medications
- Measure body weight
- Record vital signs and seated BP

  Note: The arm with the higher mean SBP value identified at Visit 1 during laterality testing should be used for all BP measurements. At each visit, seated BP should be measured in triplicate in the designated arm (arm identified with laterality testing at Visit 1). The same BP monitor originally provided to the clinical site should be used for all measurements.
- Record standing BP and heart rate

  Note: Once the seated BP has been determined, the patient will be asked to stand and after 60 seconds a single standing BP and a single standing heart rate measurement will be obtained.
- Perform a limited physical examination (general appearance, skin, heart, lungs, and abdomen)
- Provide CCI [redacted] determination
- Provide CCI [redacted] collection kits
- Collect urine samples for urinalysis
- Collect blood samples for the following:

  - Clinical laboratory assessments including standard safety chemistry panel, hematology, and coagulation

    Note: Serum potassium levels of patients will be monitored systematically throughout the study. If indicated, repeat and unscheduled testing for serum potassium should be measured at the local laboratory and central laboratory (Section 8.4.6).

- Dispense study drug
- Administer study drug
- Collect unused study drug
- Assess treatment adherence by pill counts
- Perform adherence counseling
- Provide instructions for next visit

8.1.3.7 Visit 9 (Week 16)

The following procedures will be performed at Visit 9 (Day 112 ± 7 days):

- Assess and record AEs
- Record concomitant medications
- Measure body weight
- Record vital signs and seated BP

  Note: The arm with the higher mean SBP value identified at Visit 1 during laterality testing should be used for all BP measurements. At each visit, seated BP should be measured in triplicate in the designated arm (arm identified with laterality testing at Visit 1). The same BP monitor originally provided to the clinical site should be used for all measurements.
- Record standing BP and heart rate

  Note: Once the seated BP has been determined, the patient will be asked to stand and after 60 seconds a single standing BP and a single standing heart rate measurement will be obtained.
- Perform a limited physical examination (general appearance, skin, heart, lungs, and abdomen)
- Collect CCI [redacted] determination by the central lab
- Collect CCI [redacted] collection kits
- Collect urine samples for urinalysis
- Collect blood samples for the following:
  - Clinical laboratory assessments including standard safety chemistry panel, hematology, and coagulation

    Note: Serum potassium levels of patients will be monitored systematically throughout the study. If indicated, repeat and unscheduled testing for serum

potassium should be measured at the local laboratory and central laboratory (Section 8.4.6).

  - CCI [redacted]
  - CCI [redacted]

- Dispense study drug
- Administer study drug
- Collect unused study drug
- Assess treatment adherence by pill counts
- Perform adherence counseling
- Provide instructions for next visit

8.1.3.8 Visit 10 (Week 22)

The following procedures will be performed at Visit 8 (Day 154 ± 7 days):

- Assess and record AEs
- Record concomitant medications
- Measure body weight
- Record vital signs and seated BP

  Note: The arm with the higher mean SBP value identified at Visit 1 during laterality testing should be used for all BP measurements. At each visit, seated BP should be measured in triplicate in the designated arm (arm identified with laterality testing at Visit 1). The same BP monitor originally provided to the clinical site should be used for all measurements.
- Record standing BP and heart rate

  Note: Once the seated BP has been determined, the patient will be asked to stand and after 60 seconds a single standing BP and heart rate measurement will be obtained.
- Perform a limited physical examination (general appearance, skin, heart, lungs, and abdomen)
- Provide CCI [redacted] determination
- Provide CCI [redacted] collection kits
- Collect urine samples for urinalysis
- Collect blood samples for the following:
  - Clinical laboratory assessments including standard safety chemistry panel, hematology, and coagulation

  Note: Serum potassium levels of patients will be monitored systematically throughout the study. If indicated, repeat and unscheduled testing for serum potassium should be measured at the local laboratory and central laboratory (Section 8.4.6).
- Dispense study drug
- Administer study drug

- Collect unused study drug
- Assess treatment adherence by pill counts
- Perform adherence counseling
- Provide instructions for next visit

8.1.3.9 End of Treatment Visit – Visit 11 (Week 26)

The following procedures will be performed at Visit 11 (Day 182 ± 7 days):

- Assess and record AEs
- Record concomitant medications
- Measure body weight
- Record vital signs and seated BP

  Note: The arm with the higher mean SBP value identified at Visit 1 during laterality testing should be used for all BP measurements. At each visit, seated BP should be measured in triplicate in the designated arm (arm identified with laterality testing at Visit 1). The same BP monitor originally provided to the clinical site should be used for all measurements.
- Record standing BP and heart rate

  Note: Once the seated BP has been determined, the patient will be asked to stand and after 60 seconds a single standing BP and a single standing heart rate measurement will be obtained.
- Perform a complete physical examination (general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system)
- Perform 12-lead ECG after the patient has been resting in the supine position for > 10 minutes and after measuring vital signs and BP
- Collect CCI [redacted] determination
- Collect CCI [redacted] collection kits
- Collect urine samples for urinalysis
- Provide CCI [redacted] determination
- Provide CCI [redacted] collection kits
- Collect blood samples for the following:
  - Clinical laboratory assessments including standard safety chemistry panel, hematology, and coagulation

    Note: Serum potassium levels of patients will be monitored systematically throughout the study. If indicated, repeat and unscheduled testing for serum potassium should be measured at the local laboratory and central laboratory (Section 8.4.6).
  - Serum pregnancy test
  - CCI [redacted]

  - CCI [redacted]
- Administer study drug
- Collect unused study dug
- Assess treatment adherence by pill counts
- Provide instructions for next visit

8.1.4 Follow-Up Period – (Visit 12/Week 28)

Patients will complete the follow-up visit at 2 weeks ± 7 days following the last dose of the study drug.

- Assess and record AEs
- Record concomitant medications
- Measure body weight
- Record vital signs and seated BP

  Note: The arm with the higher mean SBP value identified at Visit 1 during laterality testing should be used for all BP measurements. At each visit, seated BP should be measured in triplicate in the designated arm (arm identified with laterality testing at Visit 1). The same BP monitor originally provided to the clinical site should be used for all measurements.
- Record standing BP and heart rate

  Note: Once the seated BP has been determined, the patient will be asked to stand and after 60 seconds a single standing BP and a single standing heart rate measurement will be obtained.
- Perform a limited physical examination (general appearance, skin, heart, lungs, and abdomen)
- Perform 12-lead ECG after the patient has been resting in the supine position for > 10 minutes and after measuring vital signs and BP
- Collect CCI [redacted] determination
- Collect CCI [redacted] collection kits
- Collect urine samples for urinalysis
- Collect blood samples for the following:
  - Clinical laboratory assessments including standard safety chemistry panel, hematology, and coagulation

    Note: Serum potassium levels of patients will be monitored systematically throughout the study. If indicated, a repeat and unscheduled testing for serum potassium should be measured at the local laboratory and central laboratory (Section 8.4.6).
  - CCI [redacted]

8.2 Efficacy Assessments

Efficacy variables are shown in Table 5.

Table 5 Laboratory Efficacy Variables

Primary endpoint variable	CCI
mean seated SBP [a]	• CCI • CCI • CCI [b]

[a] SBP and CCI will be measured with a AOBPM device (Section 8.3.2).
[b] The CCI will be calculated by the central laboratory.
AOBPM = automated office blood pressure monitoring; CCI = CCI; SBP = systolic blood pressure; CCI

Analyses will be performed at a central laboratory contracted by AstraZeneca; the timing of the sample collection is indicated in the SoA (Section 1.3).

For instructions on the sampling process for CCI refer to Section 4.2.1.2.

For measurements of CCI, refer to Section 8.3.2.

8.3 Safety Assessments

8.3.1 Physical Examinations

A complete physical examination will consist of assessment of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system and will be performed as indicated in the SoA (Section 1.3).

A limited physical examination will consist of a minimum of general appearance, skin, heart, lungs, and abdomen, and will be performed as indicated in the SoA (Section 1.3).

8.3.1.1 Height and Weight

Height will be collected at Visit 1 only and will be used to calculate BMI using the weight from this Visit. Subsequent BMI calculations will use height collected at Visit 1. Height will be measured with the patient's shoes off.

Weight will be measured at visits as indicated in the SoA (Section 1.3). Weight will be measured with the patient's shoes off and after the patient's bladder has been emptied.

8.3.2 Vital Signs

Vital signs will include mean seated heart rate (determined by 3 seated heart rate measurements), respiratory rate, and body temperature. Orthostatic vital signs will include a

single standing BP and a single standing heart rate. Vitals signs and BP will be measured at visits as indicated in the SoA (Section 1.3) using the following standardized procedures:

- Patients must be seated for at least 5 minutes in the examination room before measurement of vital signs and BP.
- Patients should not exercise, smoke, or consume caffeinated beverages or food 30 minutes prior to assessment of vital signs and AOBPM.
- On visits when study drug will be administered, vital signs and BP will be assessed pre-dose.
- Vitals signs and BP measurements should be obtained prior to ECG recordings.

For measuring seated BP by AOBPM, the following additional standardized procedures are recommended:

- The patient 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 centered over the brachial artery.
- The cuff size and arm used for the measurement should be recorded.
- Seated BP will be measured in both upper arms (3 times/arm) (each measurement 1 to 2 minutes apart) to detect possible laterality differences using the same AOBPM device at Visit 1.
- The arm with the higher mean SBP value will then be used to take the screening BP measurements (at least 5 minutes after determining laterality) and for all subsequent measurements at subsequent visits.
- All BP measurements should be obtained at approximately the same time of day as the screening measurements are obtained.
- At Visit 1, if the lowest and highest screening SBP measurements are > 15 mmHg apart, additional readings should be performed. The last 3 consecutive, consistent SBP measurements will be averaged to determine the final value to be used to assess eligibility at Visit 1. If the lowest and highest SBP measurements are > 20 mmHg apart after a total of 6 measurements, the measurements will not be used to assess study eligibility, but measurements may be reassessed after at least 72 hours. If the lowest and highest SBP values remain > 20 mmHg apart after 6 measurements at a subsequent assessment, the patient will be excluded from the study.
- Once the seated BP has been determined, the patient should be asked to stand and after 60 seconds a single standing BP and heart rate (orthostatic vitals) measurement will be obtained.

8.3.3 Electrocardiograms

Standard 12-lead ECGs will be collected as indicated in the SoA (Section 1.3).

ECGs will be performed after the patient has been resting in the supine position for at least 10 minutes. Twelve-lead ECGs will be printed and will be interpreted as soon as possible by a qualified investigator (or subinvestigator). All ECGs collected at the time of randomization, EOT, and ET visits must be evaluated for the presence of abnormalities by a qualified physician.

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

- Heart rate
- QRS interval
- PR interval
- RR interval
- QT interval
- QTc (ie, QTcF) duration

Investigators should contact the sponsor or designee if there are any clinically meaningful changes from baseline ECGs based on the ECG alert criteria guidance in Appendix B.

8.3.4 Clinical Laboratory Evaluations

The laboratory variables to be collected are listed in Table 6.

Blood samples for chemistry panel, hematology, and coagulation will be obtained as indicated in the SoA (Section 1.3) and assessed at the central laboratory per institutional guidelines. All blood samples will be obtained after vital signs have been measured and prior to dosing of study drug.

Serum or point-of-care pregnancy tests will be performed only for female patients of childbearing potential (ovulating, premenopausal, and not surgically sterile) as indicated in the SoA (Section 1.3). FSH levels will be measured only for female patients who are postmenopausal for at least one year at screening and are not surgically sterile as indicated in the SoA (Section 1.3).

CCI [redacted] will be obtained as indicated in the SoA (Section 1.3) and assessed at the central laboratory per institutional guidelines for complete urinalysis. If one of the following occurs during the 3-day collection period, the patient will be asked to repeat the CCI [redacted] collection as soon as practical:

- Unusual physical exercise
- Menstruation
- Urinary tract infection
- Febrile illness
- Flu

Screening laboratory evaluations, if abnormal, may be repeated once for eligibility purposes.

Table 6 Laboratory Variables

Standard Safety Chemistry Panel	
Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid
Additional Chemistry Parameters	
Glycosylated hemoglobin (HbA1c)	
Hematology	
Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential [a]	
Coagulation	
Activated partial thromboplastin time	Prothrombin time
International normalized ratio	
Urinalysis	
Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [b]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	
Additional Urinalysis Analytes	

Table 6 Laboratory Variables

Sodium	Chloride
Potassium	Phosphate
Creatinine	Albumin
Endocrinology	
Follicle-stimulating hormone (FSH) [c]	β-human chorionic gonadotropin [d]
Serology	
Hepatitis B surface antigen	Hepatitis C virus RNA
Human immunodeficiency virus antibody	

[a] Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

[b] Microscopy is performed only as needed based on positive dipstick test results.

[c] FSH levels will be measured only for female patients who are postmenopausal for at least one year at screening and are not surgically sterile.

[d] Serum or point-of-care pregnancy tests will be performed only for female patients of childbearing potential (ovulating, premenopausal, and not surgically sterile).

FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1C; RNA = ribonucleic acid

8.4 AEs, SAEs, and Other Safety Reporting

8.4.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse Events, which include clinical laboratory test variables, will be monitored and documented from the time of signing of informed consent until the end of the follow-up period. Patients should be instructed to report any AE that they experience to the investigator, whether or not they think the event is due to study treatment. Beginning at signing of informed consent, investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery,

endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at signing of informed consent should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present starting from informed consent and significantly worsen during the study should be reported as AEs or SAEs, depending on their seriousness as described below. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action taken with the study drug is required as a result of the abnormality
- Based on the clinical judgment of the investigator

8.4.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

8.4.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.4.1.3 Adverse Events of Special Interest

The investigator will monitor each patient for clinical and laboratory evidence for pre-defined AESIs throughout the patient's participation in this clinical study.

The investigator will assess and record any additional information on the AESI in detail on an AE form which must be submitted within 24 hours of awareness of the event.

For this clinical study, AESIs include the following:

- Hypotension events that require clinical intervention
- Abnormal potassium laboratory values that require clinical intervention
- Abnormal sodium laboratory values that require clinical intervention

During the course of the study, additional AESIs may be identified by the sponsor.

AESIs must be recorded in the eCRF.

8.4.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations
  Note: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event
  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.4.3 Assessment of Adverse Events by the Investigator

The investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of not related, unlikely related, possibly related, and related.

8.4.3.1 Assessment of severity

- Mild – An event that is easily tolerated and generally not interfering with normal daily activities.
- Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.
- Severe – An event that is incapacitating with inability to work or perform normal daily activities.

8.4.3.2 Causality assessment

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant drug - The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug - Clinical and/or nonclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.4.4 Serious Adverse Event Reporting – Procedures for Investigators

Initial reports

All SAEs (whether or not considered causally related to the study drug) occurring from signing of informed consent until 30 days following the last administration of study drug must be reported to clinical safety within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the investigator considers related to study drug must be reported to clinical safety or the sponsor/designee.

To report the SAE, sites complete the SAE form electronically in the EDC system for the study. When the form is completed, the CRO Study Representative (ie, site monitor/CRA) will be notified electronically by the EDC system and will retrieve the SAE form and submit it electronically via email to the AstraZeneca DES.

If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the investigator/study site staff how to proceed. 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 1 calendar day for fatal or life threatening SAEs or 5 calendar days for all other SAEs. When the EDC is temporarily not accessible, the AstraZeneca study representative should confirm that the investigator/site staff enters the SAE in the EDC when access resumes. The SAE information must be entered into EDC within 24 hours of the system becoming available.

Follow-up reports

The investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to clinical safety.

8.4.5 Overdose Reporting

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

In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s), or the Investigator has reason to suspect that the patient has taken additional dose(s). Clinical judgment should always be applied in determining overdose.

If an overdose of the study drug, as described above, occurs in the course of the study, the investigator or other site personnel must inform the designated study representative no later than 24 hours of knowledge of the event. All AEs and SAEs associated with the overdose should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form.

The designated study representative works with the investigator to ensure that all relevant information is provided to clinical safety within 1 calendar day (initial fatal/life-threatening or follow-up fatal/life-threatening) or 5 calendar days (other serious initial and follow-up) if the overdose is associated with an SAE, and within 30 calendar days if no SAE is associated with the overdose.

8.4.6 Safety Surveillance and Management of Serum Potassium Levels

Patients who present during the screening period (Visits 1 or 2) with a serum potassium level below normal range may continue in the study if the Investigator elects to correct the serum potassium level with supplementation and offers to manage the condition.

Serum potassium levels of patients will be monitored systematically throughout the study. In addition to the clinical laboratory tests pre-defined in the SoA (Section 1.3), interim assessments of serum potassium levels are recommended under certain situations (eg, overdose of potassium supplements, vomiting and/or diarrhea for $\geq$ 1 day) that may impact patients' electrolyte levels or fluid balance.

- For serum potassium of $\geq$ 5.5 to < 6.0 mEq/L, the patient should present to the clinical site within 72 hours for repeat testing.
  - If repeat serum potassium is confirmed (by local or central laboratory) to be $\geq$ 5.5 mEq/L, study drug should be temporarily interrupted and may not resume until serum potassium is < 5.0 mEq/L. If patient's dose had been up-titrated, then study drug should be resumed at the lower dose (if the lower dose is not available, study drug should not be resumed until the lower dose is available). After restart of study drug, serum potassium should be rechecked within 2 to 7 days.
  - If repeat potassium is < 5.5 mEq/L, study drug dose may continue. If patient's dose had been up-titrated, study drug may be down-titrated based on investigator judgment (if down-titration is indicated as per the investigator's

judgment but the lower dose is not available, study drug should be interrupted until the lower dose is available).

- For serum potassium of ≥ 6.0 mEq/L, study drug should be interrupted and may not resume until serum potassium is < 5.0 mEq/L. Potassium should be repeated immediately, either at the clinical site or another clinical location (eg, emergency department if considered clinically indicated by investigator). If patient's dose had been up-titrated, study drug should be re-started at lower dose (if the lower dose is not available, study drug should not be resumed until the lower dose is available). After re-start of study drug, serum potassium should be re-checked within 2 to 7 days.
- Permanently discontinue treatment if a patient experiences a recurrent serum potassium ≥ 6.0 mEq/L after a previous event if there was no explanation for the recurring event other than restarting treatment.
- For patients, who have interrupted study drug for any reason, study drug should not be resumed unless potassium has been confirmed to be < 5.0 mEq/L.

Repeat and unscheduled testing for serum sodium, potassium, or eGFR should be measured at the local laboratory and central laboratory for a faster turn-around time to allow clinical assessment. Local laboratory assessments may also be conducted in addition to central laboratory assessment at any timepoint at the investigator's discretion. Patients will be instructed to bring their study drug to all clinical site visits after randomization for assessing treatment adherence.

8.4.7 Pregnancy Reporting

If a patient becomes pregnant during the study or within the safety follow-up period defined in the protocol, the investigator is to stop dosing with study drug(s) immediately. The patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, the investigator or other site personnel will inform the designated clinical study monitor within 24 hours of knowledge of the event.

The designated study representative will work with the investigator to ensure that all relevant information is provided to clinical safety within 1 calendar day (initial fatal/life-threatening or follow-up fatal/life-threatening) or 5 calendar days (other serious initial and follow-up) if the pregnancy is associated with an SAE, and within 30 calendar days if no SAE is associated with the pregnancy.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety follow-up period defined in the protocol, the investigator should notify the clinical safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, and documented even if the patient was discontinued from the study. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

8.4.8 Expedited Reporting

All relevant information about SUSARs that are fatal or life-threatening will be reported as soon as possible to the FDA by of the sponsor, and in any case no later than 7 days after knowledge. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the sponsor.

Sponsor or designated CRO will also inform all investigators as required per local regulations. The requirements above refer to the requirements relating to the study drug.

8.4.9 Medication Error, Drug Abuse, Drug Misuse, and Product Complaint

If a medication error, drug abuse, or drug misuse, as described below, occurs during the study, then the investigator or other site personnel informs the appropriate study representative within 24 hours of knowledge of the event. The study representative works with the investigator to ensure all relevant information is completed in the respective paper form and provided to clinical safety within 1 calendar day (initial fatal/life-threatening or follow-up fatal/life-threatening) or 5 calendar days (other serious initial and follow-up) if an SAE is associated with the medication error, drug abuse, or drug misuse, and within 30 calendar days if no SAE is associated with the medication error, drug abuse, or drug misuse.

Misuse: Refers to situations where the medicinal product is intentionally and inappropriately used not in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.

Abuse: Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Medication error: Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of investigational product are not considered reportable as medication error.

The full definition and examples of drug misuse, drug abuse, and medication errors can be found in Appendix A.

8.5 CCI

CCI will be obtained as indicated in the SoA (Section 1.3). CCI . CCI will be analyzed to measure CCI .

Additional details regarding the CCI collection, processing, and shipment can be found in the laboratory manual.

CCI will be disposed of after the CCI or 6 months after issuance of the CCI (whichever is earlier), unless requested for future analyses.

8.6 CCI

CCI will be obtained as indicated in Section 1.3. Refer to Table 7 and Table 8 for the complete list of CCI

Additional details regarding the CCI collection, processing, and shipment can be found in the laboratory manual. Information on the CCI can be found in Appendix C.

CCI

CCI [redacted]

8.7 CCI [redacted]

A single, CCI [redacted] may be collected at any time during the patient's participation in the Double-Blind Treatment Period of the study. The CCI [redacted] may be used for CCI [redacted]

Patients will be given the option to participate in the CCI [redacted] during the consenting process. The written informed consent for CCI [redacted] will be included in the main ICF. For patients who provide written informed consent to participate in the CCI [redacted] assessment, a blood sample will be collected at any time after randomization. The patient may withdraw consent to participate in the CCI [redacted] at any time during the study without withdrawing consent to participate in the study. Refer to Section 8.7.1 for details regarding sample and data destruction following withdrawal of consent.

The CCI [redacted]

If analysis of the CCI [redacted] is undertaken, details of sample and data analyses will be provided in a separate protocol and/or analysis plan. The results obtained from analysis of the CCI [redacted] will be accessible to the sponsor, the party(ies) performing sample analysis and data analyses, and the party involved in maintenance of the sponsor's database. The results may be disclosed to the investigator but are not intended to be provided to the patient. The CCI [redacted] may be reported or published without any of the patient's personal identification information. CCI [redacted] will be stored at the CCI [redacted]

Information on the CCI [redacted] can be found in Appendix C.

8.7.1 Collection, Storage, and Destruction of CCI [redacted]

The date and time of the CCI [redacted] collection will be documented in the patient's source documents. Each sample must be labeled with a unique identifier. Good Laboratory Practice requires a chain of custody that is traceable to the sample donor. In order to ensure patient confidentiality, sample tubes will be identified only by patient identification number.

Samples will be stored for a maximum of 15 years from the date of last subject last visit, after which they will be destroyed. CCI [redacted] 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.

If the patient withdraws consent, the blood samples will be promptly managed for proper disposition. However, the data will not be discarded if CCI [redacted] has been completed before the patient withdraws consent.

9 STATISTICAL CONSIDERATIONS

This section describes statistical aspects of the study. The SAP will be developed and finalized before database lock and will describe in detail the planned statistical analyses.

9.1 Statistical Hypotheses

9.2 Sample Size Determination

The sample size for the study was planned to adequately power the study for the primary endpoint and first 2 secondary efficacy endpoints. Assuming an early withdrawal rate of 8% and a common SD of 11 mmHg, with 300 randomized patients (randomization ratio of 1:1:1; 100 patients in the low dosing strategy, high dosing strategy, or placebo group), the study would have 95.7% power to detect a 6 mmHg difference in change from baseline in SBP between a CIN-107 dosing strategy group versus the placebo group at Week 26 and 98.9% power to detect a difference between the pooled CIN-107 group and the placebo group using a 2-sided significance level of 0.05.

Based on sponsor recalculation of sample size, the protocol is being amended to stop further enrollment of patients. The decision was made in the absence of sponsor review of unblinded interim results. Randomization of eligible patients from the pool of patients in screening or run-in after stopping new enrollments will be permitted, resulting in approximately 174 patients randomized (randomization ratio of 1:1:1 with approximately 58 patients each in the low dosing strategy, high dosing strategy, or placebo group), sufficient for 90% power for the primary endpoint assuming a treatment difference of 6 mmHg and an SD of 11 mmHg.

9.3 Populations for Analyses

The following analysis populations are defined for the different types of data analyses:

- ITT population – All patients randomized into the study. Treatment classification will be based on the randomized treatment assignment.
- mITT population – The mITT population will include all patients in the ITT population who receive at least 1 dose of any study drug. Treatment classification will be based on

the randomized treatment assignment. The mITT population will be used for the primary analysis of all efficacy endpoints.

- Safety population – All patients who receive at least one dose of any study drug. Treatment classification will be based on the actual treatment received. The safety population will be the primary population used for the safety analyses.
- CCI [redacted]

9.4 Statistical Analyses

9.4.1 General Considerations

Descriptive statistics (arithmetic mean, SD, median, minimum, and maximum) will be calculated for quantitative variables, as well as for the difference from baseline, when appropriate. Categorical variables will be summarized using frequencies and percentages.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint

The primary efficacy endpoint is the change in mean seated SBP from baseline to Week 26 of CIN-107 compared to placebo. The SBP will be measured by seated AOBPM.

Definition of Estimand

For the primary efficacy objective of evaluating the treatment effect of CIN-107 in SBP compared to placebo at Week 26 in patients with uHTN and CKD, the estimand is defined as follows:

Treatment condition:

- Placebo: placebo for CIN-107.
- Low-dosing CIN-107 strategy group: CIN-107 0.5mg and may up-titrate to take CIN-107 1 mg at Week 3 (Visit 5)
- High-dosing CIN-107 strategy group: CIN-107 2 mg and may up-titrate to take CIN-107 4 mg at Week 3 (Visit 5).

The dose strength may revert to the lower dose level in the patient's assigned group at Week 6 (Visit 7) if the higher dose is not tolerated (Section 6.3).

Target patient population: Adult male and female patients with uHTN and CKD.

Endpoint: Change in seated SBP from baseline to Week 26.

Population-level summary: The treatment difference (placebo – pooled CIN-107) in the mean change from baseline at Week 26.

Intercurrent events and strategies: Intercurrent events include discontinuation of assigned study treatment for reasons unrelated to study drug, discontinuation of assigned study treatment for reasons related to study drug, receipt of other treatment for hypertension and CKD prior to Week 26, use of prohibited medication, and death. The strategies are described in Table 9.

Table 9 Intercurrent Event Strategies for the Primary Analysis of the Primary Efficacy Endpoint

Intercurrent Event	Strategy
Discontinuation of assigned study treatment	Treatment policy strategy: Primary efficacy endpoint data collected after treatment discontinuation will be included in the analysis.
Other treatment for hypertension received prior to Week 26	Treatment policy strategy: Primary efficacy endpoint data collected after use of other treatment for hypertension will be included in the analysis.
Use of prohibited medication	Treatment policy strategy: Primary efficacy endpoint data collected after use of prohibited medication will be included in the analysis.
Death	Hypothetical strategy: The hypothetical strategy is that the patient did not die. The primary efficacy endpoint will be considered missing.

The primary efficacy analysis will compare the mean change in seated SBP from baseline to Week 26 of pooled CIN-107 and placebo using the mITT population. An MMRM will be used to perform this analysis. The analysis will include fixed effects for treatment, visit, stratification variables (SGLT2 inhibitor use and CKD category), and the treatment-by-visit interaction, along with a covariate of the baseline seated SBP value and the baseline seated SBP by visit interaction. An estimate of the treatment difference in the mean change at Week 26 will be generated, as will a test of the null hypothesis that the true means are equal at a 2-sided 0.05 level of significance. The least squares means, standard errors, and 2-sided 95% CIs for the true mean for each treatment group will be provided.

9.4.2.2 Secondary and CCI

The secondary efficacy endpoints as follows:

- The change from baseline of SBP on CIN-107 compared to placebo at Week 26 in patients assigned to the high-dose strategy group
- The change from baseline of SBP on CIN-107 compared to placebo at Week 26 in patients assigned to the low-dose strategy group

The CCI endpoints as follows:

- CCI
- CCI

- CCI [redacted]
- CCI [redacted]

The CCI [redacted] are the CCI [redacted] including, but not limited to, the following:

- CCI [redacted]
- CCI [redacted]
- The relationship between percentage of change in CCI [redacted] and CCI [redacted] of CIN-107 compared to placebo at CCI [redacted]
- The relationship between change in CCI [redacted] and CCI [redacted] of CIN-107 compared to placebo at CCI [redacted]
- The relationship between the CCI [redacted] of CIN-107 compared to placebo at CCI [redacted]

The CCI [redacted] of the study is to evaluate the CCI [redacted].

- Percentage change from baseline in CCI [redacted] in patients assigned to the CCI [redacted]
- Percentage change from baseline in CCI [redacted] in patients assigned to the CCI [redacted]
- Change from baseline in CCI [redacted]
- Change from baseline in CCI [redacted]

To protect the overall alpha level, the secondary efficacy endpoints will be tested in a hierarchical manner, each at a 2-sided 0.05 level of significance. Hypothesis testing of endpoints will proceed in the sequence shown above until a comparison is not statistically significant. At that point, all remaining sequential tests will be deemed not significant.

Secondary and CCI [redacted] analyses will compare the change in SBP, CCI [redacted] and CCI [redacted] from baseline to the EOT visit (Visit 11) between each dosing strategy of

CIN-107 and placebo. An MMRM will be used to perform these analyses. The analyses will include fixed effects for treatment, visit, stratification variables (SGLT2 inhibitor use and CKD category), and treatment-by-visit interaction, along with a covariate of the corresponding baseline value and the baseline by visit interaction. The restricted maximum likelihood estimation approach will be used with an unstructured covariance matrix. Least squares means, standard errors, and 2-sided 95% CIs for the true mean for each dosing strategy treatment group and for pairwise comparisons of each dosing strategy of CIN-107 to the placebo group will be provided.

Achieving CCI [redacted]

Sensitivity analyses may be carried out under secondary estimands and/or various assumptions for missing data. Full details will be provided in the SAP.

9.4.3 Safety

The safety population will be the primary population for the safety analysis. All safety endpoints will be summarized descriptively.

The assessment of safety will be based primarily on the frequency of AEs and SAEs, clinical laboratory assessments, vital signs, and 12-lead ECGs. Other safety data will be summarized as appropriate.

AEs and SAEs will be coded using the MedDRA. Treatment-emergent AEs, defined as those AEs and SAEs that newly occur or worsen in severity during the double-blind treatment period, will be summarized by system organ class and preferred term. A list of patients with SAEs, AE of special interest, and those who discontinue from the study due to an AE will be provided.

Summary statistics by treatment strategy group at baseline, at each visit, and of changes from baseline to each visit for laboratory parameters, vital signs, and other safety measurements will be provided. The occurrence of significant abnormalities in change from baseline of laboratory values will be summarized by treatment group. Physical examination data will be listed.

9.4.4 CCI [redacted]

All CCI [redacted] will be summarized descriptively. No adjustment for multiple comparisons will be made. Nominal p-values will be used to examine any trends in these endpoints.

CCI [redacted]

Individual CCI [redacted]

CCI [redacted]

An attempt will be made to correlate plasma CCI [redacted]

9.5 Interim Analysis

No formal interim analysis is planned. An independent DSMB will be formed in order to conduct data reviews to assess safety and tolerability. Details related to the DSMB responsibilities, authorities, and procedures will be documented in the DSMB Charter.

9.5.1 Missing Data

All efficacy analyses, as well as all safety analyses, will be conducted using available data with no imputation for missing values.

9.6 Data Monitoring Committees

9.6.1 Data Safety Monitoring Board

A DSMB will be formed to conduct data reviews to assess safety and tolerability of CIN-107 and to make recommendations to AstraZeneca regarding the study. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study. Details related to the DSMB responsibilities, authorities, and procedures will be documented in the DSMB Charter.

9.6.2 Unblinded Review Committee

The Sponsor may initiate an URC, whose members are not involved in the execution of the study and would be described in a separate URC Charter. The URC would assess the safety and efficacy of baxdrostat in a CKD population in preparation for the initiation of Phase III studies. Review by the URC is not intended to inform any decision making by the sponsor regarding the conduct of this ongoing Phase II trial d6972c00001. The sponsor will take every necessary step to maintain the scientific and data integrity of this study.

9.7 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

9.7.1 Ethical Conduct of the Study

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients

are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

9.7.2 Institutional Review Board/Independent Ethics Committee

The IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

Federal regulations and ICH guidelines require that approval be obtained from an IRB prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this clinical study to be provided to a patient or patient's legal guardian must be approved by the IRB.

No drug will be released to the clinical site for dosing until written IRB authorization has been received by the sponsor.

9.7.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the investigator and is subject to inspection by a representative of the sponsor, their representatives, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

9.7.4 Study Monitoring Requirements

It is the responsibility of the investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the investigator and, at the same time, the sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any patient in this clinical study, the sponsor or their designee

will review with the investigator and site staff the following documents: protocol, IB, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The investigator will permit the sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the clinical site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to investigators. The investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

9.7.5 Committees Structure

A DSMB will be formed to conduct data reviews to assess safety and tolerability of CIN-107. In addition, the sponsor may initiate an URC, whose members are not involved in the execution of the study and would be described in a separate URC Charter. Refer to Section 9.6 for additional information about these committees.

9.7.6 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-trial 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 http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov 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.**Disclosure of Data**

Data generated by this clinical study must be available for inspection by the FDA, the sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical staff responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

9.7.8 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The investigator must obtain written permission from the sponsor before disposing of any records, even if retention requirements have been met.

If the investigator relocates, retires, or for any reason withdraws from the study, the sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the sponsor.

9.7.9 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each investigator is obligated to keep data pertaining to the study confidential. The investigator must consult with the sponsor before any study data are submitted for publication. The sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

9.7.10 Financial Disclosure

Investigators are required to provide financial disclosure information to the sponsor to permit the sponsor to fulfill its obligations under 21 CFR Part 54. In addition, investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

9.8 DATA MANAGEMENT AND RECORD KEEPING

9.8.1 Data Quality Assurance

- All patient 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.
- 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 Parexel 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 Parexel Monitoring Plan.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

9.8.2 Data Management

9.8.2.1 Data Handling

Data will be recorded at the clinical site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

9.8.2.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

9.8.2.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site staff must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

9.8.2.4 Medical Information Coding

For medical information, the following thesauri will be used:

- MedDRA (latest) for medical history and AEs; and
- WHO Drug Dictionary for prior and concomitant medications.

9.8.2.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the investigator.

9.8.3 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other sponsor correspondence pertaining to the study must be kept in the appropriate study files at the clinical site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the sponsor must be notified in writing and be given the opportunity to further store such records.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A 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 patient or has the potential to cause harm to the patient.

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 patient.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognized 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 patient
- 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 patient received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to patient (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
- Patient accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient 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 DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study patient or if the drug abuse involves a person not enrolled in the study (such as a relative of the study patient).

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 patient 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 patient) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized 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 patient or if the drug misuse regards a person not enrolled in the study (such as a relative of the study patient).

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 patient 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 B ELECTROCARDIOGRAM ALERT CRITERIA GUIDANCE

Investigators should contact the sponsor or designee if any clinically meaningful changes from baseline ECGs, including, but not limited to, those listed below, are noted upon review:

- QTcF $\geq$ 450 msec (male)
- QTcF $\geq$ 470 msec (female)
- A > 60 msec increase in QTcF from baseline
- A $\geq$ 6% increase in QTcF from baseline
- New onset findings including, but not limited to, the following:
  - Second degree AV block (Mobitz II)
  - Third degree AV block (complete heart block)
  - Acute myocardial infarction
  - New left bundle branch block
  - Severe bradycardia (ventricular rate $\geq$ 40 bpm)
  - Supraventricular tachycardia (ventricular rate $\geq$ 150 bpm)
  - Torsades de pointes
  - Ventricular tachycardia ($\geq$ 3 beats regardless of rate)
  - Ventricular fibrillation
  - Atrial fibrillation/atrial flutter (ventricular rate $\geq$ 150 bpm).

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

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

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

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

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

[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

Note: An example of biological samples are genetic and biomarker samples.

Add the following when local requirements are such that samples should be legally returned to the source, eg, specific countries.

Add if applicable for the study:

[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 analyzed, 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 organization(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

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

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

Appendix D Protocol Version History

Protocol Amendments

Any amendments to the study protocol will be communicated to the investigators by the sponsor or designated CRO. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

Document	Date	Global/Country/Site Specific
Original Protocol (V1)	19 January 2022	Global
Protocol Amendment 1 (V2)	20 November 2022	**Global**
Protocol Amendment 2 (V3)	27 March 2023	**Global**

11 REFERENCES

Andersen et al 2001
Andersen M, Bjerre P, Schrøder HD, Edal A, Høilund-Carlsen PF, Pedersen PH, et al. In vivo secretory potential and the effect of combination therapy with octreotide and cabergoline in patients with clinically non-functioning pituitary adenomas. Clin Endocrinol (Oxf). 2001;54(1):23-30.

Calhoun et al 2011
Calhoun DA, White WB, Krum H, Weinong G, Georgina R, Trapani A, et al. Effects of a novel aldosterone synthase inhibitor for treatment of primary hypertension: results of a randomized, double-blind, placebo- and active-controlled phase 2 trial. Circulation. 2011;124(18):1945-55.

Coresh et al 2019
Coresh J, Heerspink HJL, Sang Y, Matsushita K, Arnlov J, Astor BC, et al. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. Lancet Diabetes Endocrinol. 2019;7(2):115-27.

Duprez 2007
Duprez DA. Aldosterone and the vasculature: mechanisms mediating resistant hypertension. J Clin Hypertens (Greenwich). 2007;9(1 Suppl 1):13-8.

Funder 2009
Funder JW. Reconsidering the roles of the mineralocorticoid receptor. Hypertens. 2009;53(2):286-90.

Gant et al 2017
Gant C, Laverman GD, Vogt L, Slagman MCJ, Heerspink H, Waanders F, Hemmelder MH, Navis G; Holland Nephrology Study (HONEST) Network. Renoprotective RAAS inhibition does not affect the association between worse renal function and higher plasma aldosterone levels. BMC Nephrol. 2017;18:370.

Heerspink et al 2019
Heerspink HJL, Greene T, Tighiouart H, Gansevoort RT, Coresh J, Simon AL, et al. Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. Lancet Diabetes Endocrinol. 2019;7(2):128-39.

Karns et al 2013
Karns AD, Bral JM, Hartman D, Peppard T, Schumacher C. Study of aldosterone synthase inhibition as an add-on therapy in resistant hypertension. J Clin Hypertens (Greenwich). 2013;15(3):186-92.

Levey et al 2015
Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA. 2015;313(8):837-46.

Levey et al 2020
Levey AS, Gansevoort RT, Coresh J, Inker LA, Heerspink HL, Grams ME, et al. Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. Am J Kidney Dis. 2020;75(1):84-104.

Marney and Brown 2007
Marney AM, Brown NJ. Aldosterone and end-organ damage. Clin Sci (Lond) Engl 2007;113(6):267-78.

Oelkers 1996
Oelkers W. Adrenal insufficiency. N Engl J Med. 1996;335(16):1206-12.

Riboulet 2015
Riboulet W. ZSF1 rat: a model of chronic cardiac and renal diseases in the context of metabolic syndrome. Characterization with anti-oxidant, mineralocorticoid receptor antagonist and aldosterone synthase inhibitor. Human health and pathology. Université de Lorraine. 2015.

Ritz and Tomaschitz 2014
Ritz E, Tomaschitz A. Aldosterone and the kidney: a rapidly moving frontier (an update). Nephrol Dial Transplant. 2014;29(11):2012-9.

Sato and Saruta 2004
Sato A, Saruta T. Aldosterone-induced organ damage: plasma aldosterone level and inappropriate salt status. Hypertens Res. 2004;27(5):303-310.

Wagner et al 1984
Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med. 1984;310(22):1415-21.

Wagner and White 1984
Wagner RL, White PF. Etomidate inhibits adrenocortical function in surgical patients. Anesthesiology. 1984;61(6):647-51.

Weldon and Brown 2019
Weldon SM, Brown NF. Inhibitors of aldosterone synthase. Vitam Horm. 2019;109:211-39.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: cin-107-123-csp-v4		
Document Title:	CIN-107-123 Clinical Study Protocol version 4	
Document ID:	Doc ID-005218000	
Version Label:	1.0 CURRENT LATEST APPROVED	
Server Date (dd-MMM-yyyy HH:mm 'UTC'Z)	**Signed by**	**Meaning of Signature**
18-Aug-2023 15:06 UTC	PPD	Author Approval
19-Aug-2023 01:12 UTC	PPD	Content Approval
18-Aug-2023 13:51 UTC	PPD	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.