STATISTICAL ANALYSIS PLAN

Protocol Title:	A Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, and Effectiveness of CIN-107 for the Management of Blood Pressure in Patients with Primary Aldosteronism
Protocol Number:	SPARK-PA CIN-107-122
Protocol D code:	D6970C00001
Protocol Version/Date:	7.0/31 March 2023
Investigational Product:	CIN-107 (generic name: baxdrostat)
Sponsor:	AstraZeneca AB Västra Mälarehamnen SE-151 85 Södertälje, Sweden
SAP Version/Date:	3.0/ 27 November 2024

SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
[redacted]	
[redacted]	
[redacted]	

VERSION HISTORY

Version	Version Date	Description
1.0	06-Oct-2023	Original signed version
2.0	27-Sep-2024	Updated following Dry Run
3.0	27-Nov-2024	Remove Visit 8 from analyses throughout Section 3.1.11 Update to antihypertensive medication list Section 3.2.2 PP Population finalization prior to database lock Section 3.4.2.3 Final medical review prior to database lock Section 3.4.3.1 Clarify which PD parameters to include in analyses. E.g. only 24-hour urine excretion results. Section 3.4.3.3 Clarify home blood pressure derivation

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
ADaM	Analysis Data Model
AE	Adverse event
ARR	Aldosterone-to-renin ratio
ATC	Anatomical therapeutic chemical
BP	Blood pressure
CDISC	Clinical Data Interchange Standards Consortium
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case report form
CSR	Clinical Study Report
DBP	Diastolic blood pressure
DRC	Data Review Committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ICF	Informed consent form
MBL	Medpace Bioanalytical Laboratories
MedDRA	Medical Dictionary for Regulatory Activities
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	NT-pro B-type natriuretic peptide
PA	Primary Aldosteronism
PAC	Plasma aldosterone concentration
PD	Pharmacodynamics
PK	Pharmacokinetics
PRA	Plasma renin activity
QD	Once daily
QOD	Every other day
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SDTM	Study Data Tabulation Model
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFL	Tables, figures, and listings
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number SPARK-PA CIN-107-122 (Protocol D code D6970C00001, which will be used throughout the remaining text). The data will be cleaned, database will be locked, and the analyses will be conducted upon study completion. Any deviations from the SAP after clinical data lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objectives of Study D6970C00001 are to evaluate:

- The safety and tolerability of CIN-107 in patients with Primary Aldosteronism (PA) at doses from 2 to 8 mg per day after 12 weeks of treatment
- The reduction in systolic blood pressure (SBP) with CIN-107 in patients with PA after 12 weeks of treatment

2.1.2 Secondary Objectives

The secondary objectives of Study D6970C00001 are to evaluate:

- The reduction in diastolic blood pressure (DBP) as a function of dose in patients with PA after 12 weeks of treatment
- The change in serum potassium and requirement for potassium supplementation as a function of CIN-107 dose
- The change in serum sodium and requirement for fluid or mineral replacement as a function of CIN-107 dose

2.1.3 Exploratory Objectives

Exploratory objectives are to evaluate:

- The correlation of serum aldosterone and plasma aldosterone-to-renin ratio (ARR) changes to drug dosage of CIN-107
- Relationship between blood pressure (BP) reduction and changes in aldosterone and renin levels with CIN-107 dosages
- The changes in concentration in pharmacodynamic (PD) markers, including but not limited to:
    - plasma aldosterone and its relevant precursors (18-OH corticosterone, corticosterone, and 11-deoxycorticosterone)
    - plasma cortisol (free and total) and its relevant precursor
    - NT-pro (B-type natriuretic peptide) (NT-proBNP)
    - plasma renin concentration and activity

- 24-hour urine analytes sodium, potassium, creatinine, albumin, protein, and aldosterone

2.1.4 Pharmacokinetic-Pharmacodynamic Objectives

The pharmacokinetic (PK) and PD objectives are to evaluate:

- The exposure-response relationships of CIN-107 in patients with PA using measures of safety, effectiveness, and/or PD
- The relationship between plasma renin, aldosterone, and ARR to the SBP response to CIN-107

2.1.5 Extension Part (Part 2) Additional Objective

To assess:

- The safety and tolerability of CIN-107 in patients with PA at doses from 2 to 8 mg per day for patients who elect to participate in the extension study for up to 74 weeks
- The management of blood pressure control for patients who elect to participate in the extension study for up to 74 weeks
- The CIN-107 long term treatment effects on PD markers

2.2 Study Design

2.2.1 Overview

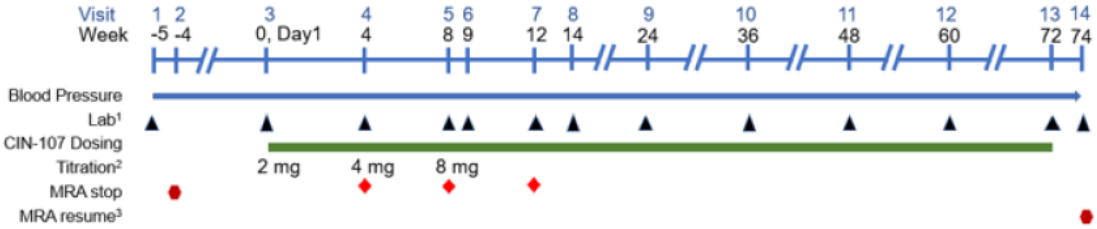
This is a multicenter, open-label clinical pharmacology study in adult patients with PA to evaluate the effectiveness and safety of CIN-107 after up to 12 weeks of treatment (Part 1), and then for eligible, consenting patients follow patients in Part 2 for up to 74 weeks for evidence of long-term safety and tolerability. Twelve to 18 patients with a confirmed diagnosis of PA will be enrolled at clinical sites in the United States. Patients will complete 14 visits over a period of approximately 74 weeks.

The safety of CIN-107 will be assessed from the time of informed consent until the end of the Extension Phase (end of Part 2). Patients will be followed for safety, effectiveness, and adherence throughout the study. PD variables analyzed during the study may include, but are not limited to, measures of aldosterone and its precursors, cortisol and its precursor, plasma renin activity (PRA), and calculation of ARR. PK variables analyzed during the study will include plasma concentrations of CIN-107 and any measured metabolite(s).

Figure 1 Schedule of Visits for Study D6970C00001

Top Panel (Part 1 only)

Bottom Panel Part 1 + Part 2 (Extension)



2.2.2 Study Visits

The study periods/visits are detailed in protocol section 3.1.1.

2.2.3 Randomization and Blinding

This is an open-label study. There is no blinding of study drug.

2.2.4 Study Drug

The CIN-107 doses to be tested in this study are 2, 4, and 8 mg.

2.2.5 Sample Size Determination

A total of 12 to 18 patients with a confirmed diagnosis of PA, who consent to participate in the study and meet the eligibility criteria, will be enrolled. The study sample size is chosen empirically for the purpose of this study without considering any formal hypothesis testing. The selected sample size is considered adequate to meet the study objectives and support decision-making for future clinical studies.

2.3 Study Endpoints

2.3.1 Primary Endpoints

The primary endpoints include the following:

- Safety parameters measured by adverse events (AEs), electrocardiograms (ECGs), hematology and chemistry laboratory values, vital signs, and physical examination
- Effectiveness measured by change in mean seated SBP after 12 weeks of treatment in patients with PA

2.3.2 Secondary Endpoints

The secondary efficacy endpoints include the following:

- Effectiveness measured by change in mean seated DBP, after 12 weeks of treatment in patients with PA
- The percentage of patients who achieve a seated BP response < 140/90 mmHg with CIN-107 after treatment at each dose
- The percentage of patients who achieve a seated BP response < 130/80 mmHg with CIN-107 after treatment at each dose
- Change from baseline in potassium levels and/or potassium supplementation requirements with CIN-107 after 12 weeks of treatment in patients with PA
- The change in serum sodium and requirement for fluid or mineral replacement with CIN-107 after 12 weeks of treatment in patients with PA
- The percentage of patients who, after 12 weeks of treatment with CIN-107 for PA, achieve either:
    - Serum aldosterone < 15 ng/dL and a PRA ≥ 0.5 ng/mL/h; or
    - an ARR < 15; or
    - unsuppressed PRA ≥ 1.0 ng/mL/h

2.3.3 Exploratory Endpoints

The exploratory endpoints include the following:

- Changes in the concentrations from baseline to Week 12 in PD markers, including but not limited to, serum aldosterone concentration, 11-deoxycorticosterone, PRA, direct renin concentration, calculated ARR, NT-proBNP, and 24-hour urinary aldosterone, urinary sodium, and urinary potassium with CIN-107 treatment
- Relationship between BP reduction and changes in aldosterone and renin levels with CIN-107 dosages

2.3.4 Exploratory endpoints in extension study

The exploratory endpoints include the following:

- The decline in SBP at end of study versus baseline for patients who elect to participate in the extension study
- The decline in DBP at end of study versus baseline for patients who elect to participate in the extension study
- Change in the concentrations from baseline to Week 72 in PD markers, including but not limited to, serum aldosterone, 11-deoxycorticosterone, PRA, direct renin concentration, calculated ARR, NT-proBNP, and 24-hour urinary aldosterone, urinary sodium, and urinary potassium with CIN-107 treatment
- Safety parameters measured by AEs, ECGs, hematology and chemistry laboratory values, vital signs, and physical examination throughout the extension study

2.3.5 Pharmacokinetic Endpoints

Pre- and post-dose PK samples will be collected within 15 minutes before study drug dosing at Visits 3, 4, 5, 7, and 13 and at approximately 2 hours ± 5 minutes after study drug dosing. The actual date and time of collection of each PK sample will be recorded.

Additional PK samples may also be collected in the event of a serious adverse event (SAE), an AE leading to withdrawal, or any other safety event at the discretion of the Investigator, Data Review Committee (DRC), and/or Sponsor, if needed for comparison with safety and tolerability data.

Samples will be analyzed to measure plasma concentrations of CIN-107 and any measured metabolites using validated liquid chromatography mass spectrometry methods.

2.3.6 Pharmacodynamic Endpoints

PD samplings, including blood at Visits 2, 3, 4, 5, 6, 7, 8, 10 and 13, and 24-h urine collections at Visits 2, 4, 6, 7, 10 and 13 will be performed. Site staff and patients will make every effort to time-match PD blood sampling at each visit. Variables analyzed will include measurement of aldosterone and relevant precursors, cortisol and relevant precursor, plasma renin activity, direct renin concentration, and calculated aldosterone to renin ratio (see Appendix C). The 24-h urine samples will be collected for measurements of aldosterone, electrolytes (potassium and sodium), creatinine, albumin and protein. Additional PD samples may also be collected in the event of an SAE, an AE leading to withdrawal, or any other safety event at the discretion of the Investigator, Sponsor and/or DRC. The actual date and time of collection of each PD sample will be recorded.

2.3.7 Pharmacogenomic Endpoint

A single, optional, pharmacogenomic blood sample may be collected at any time during the patient's participation in the Treatment Period of the study. The pharmacogenomic samples may be used for genetic research to explore the underlying causes of variability and/or differences in response in PK, PD, and/or safety data following administration of CIN-107.

2.3.8 Safety Endpoints

The safety of CIN-107 will be assessed from the time of informed consent until Visit 14 (Week 74). All safety endpoints will be summarized descriptively. The safety endpoints will include the following:

- Vital signs (heart rate, respiratory rate, body temperature), mean SBP, mean DBP, orthostatic vitals (standing BP and heart rate), physical examinations, electrocardiography, weight measurement, and clinical laboratory evaluations including standard safety chemistry panel, hematology, coagulation, and urinalysis
- Treatment-emergent adverse events (TEAEs)
- TEAEs of special interest
- Serious adverse events (SAEs)
- Treatment Emergent Serious adverse events (TESAEs)
- TEAEs leading to premature discontinuation of the study drug
- Treatment-emergent marked laboratory abnormalities
- Change in standing SBP and DBP (measured at the clinical site prior to administration of study drug)

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

Visits will be assigned to analysis visits according to the following visit windows:

Study Part	Analysis Visit	Target Analysis Day	Analysis Window Beginning	Analysis Window Ending
Part 1	Visit 3/Day 1/Week 0	1	1	1
	Visit 4/Week 4	28	2	41
	Visit 5/Week 8	56	42	59
	Visit 6/Week 9	63	60	76
	Visit 7/Week 12	89	77	94
	Visit 8/Week 14/Safety Follow-Up	98	95	160
Part 2	Visit 9/Week 24	168	161	209
	Visit 10/Week 36	252	210	293
	Visit 11/Week 48	336	294	377
	Visit 12/Week 60	420	378	461
	Visit 13/ Week 72	504	462	517
	Visit 14/Week 74/Safety Follow-Up	532	518	>518

For each analysis visit, if a scheduled visit occurs within the analysis day window, then the measurement from this scheduled visit will be used as the measurement for the analysis visit. Visits are determined to be scheduled or unscheduled based in visit labels. If no scheduled visit occurs within the analysis day window, the unscheduled measurement within window closest to the target day will be used. If measurements are equidistant to the target day, the latter will be used. If no visits occur within the analysis day window, the measurement for this analysis visit will be treated as missing.

3.1.3 Definition of Baseline

Measures recorded at Visit 3 will constitute baseline measurements. If missing, the last non-missing measurement prior to first dose of study drug will constitute baseline measurements.

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of patients. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

3.1.5 Hypothesis Testing

No formal hypothesis testing will be performed.

3.1.6 Evaluation of Site Effect

There is no planned analysis to evaluate site effect.

3.1.7 Handling of Dropouts and Missing Data

3.1.7.1 Missing efficacy or safety data

Only observed data will be used in the analyses with no imputation for missing efficacy or safety data.

3.1.7.2 Missing or incomplete start or stop dates for concomitant medications

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Missing date imputation will not exceed last date in the trial or death date, Incomplete start and stop dates will be listed as collected without imputation.

3.1.7.3 Missing or incomplete start or stop dates for adverse events (AEs)

If an adverse event (AE) has incomplete start or stop dates, dates will be imputed to determine whether an AE should be considered treatment emergent. Missing date imputation will not exceed last date in the trial or death date,

If the AE start month and day are missing and the year is the same as the year of first dose of study drug, then the month and day will be imputed as the month and day of the date of first dose.

If the AE start month and day are missing, and the year is before year of date of first dose, then the last day of the month will be imputed for the missing day and December will be imputed for the missing month.

If the AE start month and day are missing and the year is after year of date of first dose, then the first day of the month will be imputed for the missing day and January will be imputed for the missing month.

If the AE start day is missing and the starting month and year is the same as the first dose of study drug, then the starting day will be imputed as the day of first dose.

If the AE start day is missing and the month is before the month of first dose, then the last day of the month will be imputed for the missing day.

If the AE start day is missing and the month is after month of first dose, then the first day of the month will be imputed for the missing day.

If the AE start date is completely missing, then the AE start date will be imputed as the date of first dose unless the AE end date is prior to date of first dose. If the AE start date is completely missing, and the AE end date is prior to date of first dose, then the AE start date will be imputed as the AE end date.

If AE end date is incomplete, the last day of the month will be imputed for the missing day and December will be imputed for the missing month.

If the AE end date is completely missing, then AE end date will be left as missing, and the AE is considered ongoing.

3.1.7.4 Missing or incomplete start or stop dates for medical history

If a medical history event has incomplete start or stop dates, dates will be imputed to determine medical history duration or if medical event is ongoing. If a medical history start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medical history stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Missing date imputation will not exceed last date in the trial or death date, Incomplete start and stop dates will be listed as collected without imputation.

3.1.8 Clinical Laboratory Values

For continuous clinical laboratory values that are not able to be determined due to being less than the lower limit of quantification (LLOQ) or higher than the upper limit of quantification (ULOQ), the value will be assigned as half the LLOQ or the ULOQ, respectively, for any analyses performed.

Pharmacodynamic parameters may be analyzed by Quest or Medpace Bioanalytical Laboratories (MBL). PD parameters analyzed by MBL, deoxycorticosterone, 11-deoxycortisol, 18-hydroxycorticosterone serum aldosterone, corticosterone, and total cortisol, will be used in analyses. Both Quest and MBL PD measures will be listed.

3.1.9 Definition of Part 2 After Titration Start Date

The start of Part 1 After Titration period will be defined as the date of the day following Visit 4.

3.1.10 Definition of Part 2 Extension Study Start Date

For patients that opt to enter the Part 2 extension study, the start date of Part 2 will be defined as the date the day following Visit 7.

Descriptive summaries for Part 2 will be presented only for Visits 7, 9, 10, 11, 12, 13, and 14, and change from Visit 7 will be presented. For the purpose of descriptive statistics during Part 2, if Visit 7 measure is missing, the last non-missing measurement prior to Visit 7 will constitute the Visit 7 measure.

3.1.11 Background Antihypertensive Medications

Background antihypertensive medications are any antihypertensive medications with WHO Drug standardized medication name listed in the table below. Calcium channel blocker class medications will include any non-dihydropyridine calcium channel blockers or dihydropyridine calcium channel blockers. Diuretic class medications will include any loop diuretics, thiazide diuretics, or thiazide-like diuretics. General antihypertensive class medications will be any antihypertensive that is not an angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, beta-adrenergic blocker, calcium channel blocker, or diuretic.

Guidance for Industry Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims:

Pharmacologic Class	Standardized Medication Name
Mineralocorticoid (Aldosterone) Receptor Antagonists	Eplerenone, Spironolactone, Finerenone
Alpha-adrenergic blockers	Doxazosin, Phenoxybenzamine, Phentolamine, Prazosin, Terazosin
Angiotensin converting enzyme inhibitors	Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril
Angiotensin II receptor blockers	Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan
Arteriolar vasodilators	Hydralazine, Minoxidil
Autonomic ganglionic vasodilators	Mecamylamine
Beta-adrenergic blockers	Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carvedilol, Carteolol, Esmolol, Labetolol (Labetalol), Metoprolol, Nadolol, Penbuterol, Pindolol, Propranolol, Timolol
Catecholamine-depleting sympatholytics	Deserpidine, Reserpine
Central alpha-2 adrenergic agonists	Clonidine, Guanabenz, Guanfacine, Methyldopa
Non-dihydropyridine calcium channel blockers	Diltiazem, Verapamil
Dihydropyridine calcium channel blockers	Amlodipine, Felodipine, Isradipine, Nicardipine, Nifedipine, Nisoldipine
Loop diuretics	Bumetanide, Ethacrynic acid, Furosemide, Torsemide
Renin inhibitors	Aliskiren
Thiazide diuretics	Chlorothiazide , Hydrochlorothiazide, Hydroflumethiazide, Methyclothiazide, Polythiazide
Thiazide-like diuretics	Chlorthalidone (Chlortalidone), Indapamide, Metolazone
Potassium-sparing diuretics	Amiloride, Triamterene

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The ITT Population is defined as all patients enrolled in the study. Enrolled patients will include any patient that did not screen fail and intended to enter treatment period as determined by investigator. The ITT Population will be the primary population for efficacy analyses.

3.2.2 Per-Protocol (PP) Population

The PP Population is defined as all patients in the ITT population who have a baseline value for the SBP assessment, have at least one post-dose value for the SBP assessment, and have no major protocol deviations that could potentially impact the primary efficacy endpoint. PP Population will be finalized prior to database lock.

3.2.3 Safety Population

The Safety Population is defined as all enrolled patients who receive at least one dose of study drug. The Safety Population will be the primary population for the safety analyses.

3.2.3.1 Safety Population – Part 2

The Safety Population – Part 2 is defined as all subjects who entered Part 2 and received at least one dose of study drug.

3.2.4 Pharmacokinetic Population

The PK Population is defined as all patients in the ITT Population who have at least 1 quantifiable plasma concentration.

3.2.5 Pharmacodynamic Population

The PD Population is defined as all patients in the ITT Population who have at least 1 quantifiable concentration of a PD variable.

3.2.5.1 Pharmacodynamic Population – Part 2

The PD Population – Part 2 is defined as all patients in the ITT Population that entered Part 2 and have at least 1 quantifiable concentration of a PD variable.

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

Counts and percentages of patients who were screened (signed informed consent), discontinued early during screening (screen failures), enrolled in Part 1, and completed the study will be summarized in total based on all screened patients. Reasons for screen failure and early discontinuation will also be summarized.

Counts and percentages of patients who were enrolled in Part 1, discontinued early from Part 1, and completed Part 1 will be summarized in total based on all enrolled patients. Reasons for early discontinuation will also be summarized. A patient is a Part 1 completer if they did not permanently interrupt study treatment prior to Week 12 (Visit 7).

Counts and percentages of patients who were enrolled in Part 2, discontinued early from Part 2, and completed Part 2 will be summarized in total based on all patients enrolled in Part 2. Reasons for early discontinuation will also be summarized. A patient is a Part 2 completer if they did not permanently interrupt study treatment prior to Week 72 (Visit 13) or completed 504 (+/- 7 days) of treatment without permanent termination.

3.3.2 Protocol Deviations

Protocol deviations will be identified based on any change, divergence, or departure from the study design or procedures defined in the protocol as defined in the Protocol Deviation Plan. The Protocol Deviation Plan will define all protocol deviations as either CSR reportable or non-CSR reportable deviations. Counts and percentages of subjects with CSR reportable protocol deviations by deviation category will be summarized in total based on all enrolled subjects. A listing of CSR-reportable protocol deviations will be generated.

3.3.3 Analysis Populations

Counts and percentages of patients in each analysis population will be summarized in total based on all enrolled patients.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, 65-75 years, >75 years)
- Sex
- Childbearing potential
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) and BMI categories (<30 kg/m^2, ≥30 kg/m^2)
- Diabetes Type 1 or Type 2 on entry
- Mean seated SBP and SBP categories (<145mmHg, ≥145 mmHg)
- Mean seated DBP
- Serum aldosterone (ng/dL) and serum aldosterone categories (<6 ng/dL, ≥6 ng/dL)
- Plasma renin activity (PRA) (ng/mL/hr) and PRA categories (<1 ng/mL/hr, ≥1 ng/mL/hr)
- Aldosterone Renin Ratio and ARR categories (<15, 15-30, >30)
- Serum Direct Renin Concentration (ng/L)
- Estimated Glomerular Filtration Rate (eGFR) and eGFR categories (<60 mL/min/1.73m2, ≥60 mL/min/1.73m2)
- Use of Mineralocorticoid Receptor Antagonist (MRA)
- Hypokalemia (serum potassium <3.5 mmol/L) at baseline
- Use of potassium supplements at baseline
- Number of Background Antihypertensive Medications
- Background Antihypertensive Medication Class

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate in total based on the ITT, Safety, and PP Populations.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Counts and percentages of patients with medical history by system organ class and preferred term will be summarized in total based on ITT Population

PA related history including time since PA diagnosis, method of diagnosis, and confirmatory categorization will be summarized with descriptive statistics or counts and percentages of patients as appropriate in total based on ITT Population.

3.3.6 Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the World Health Organization (WHO) Drug Dictionary version B3 Global, Mar 2020G. As of May 2023, dictionary updates will be applied bi-annually. For summary

purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time on or after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing/ended or started on or after the first dose of study drug).

Counts and percentages of patients taking prior and concomitant medications by ATC class and standardized drug name will be summarized in total based on the Safety Population separately for Part 1 and for the whole study (Part 1 and Part 2).

Descriptive summaries for the number of background antihypertensive medications, as specified in Section 3.1.11, taken concomitantly at baseline, during part 1, and during Part 2 will be presented in total based on the Safety Population. Additional descriptive summaries of number and percent of subjects requiring at least one antihypertensive within each medication class will be summarized in total at baseline, during Part 1, and during Part 2 based on the Safety Population.

3.3.7 Study Drug Exposure and Compliance

Study drug exposure and compliance will be summarized for Part 1 and for the whole study (Part 1 and Part 2) separately. Within study part, days of exposure to study drug will be calculated as date of last dose of study drug – date of first dose of study drug + 1. Note that the exposure calculation is intended to describe the length of time a patient was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarized in total based on the Safety Population with descriptive statistics and with counts and percentages of patients with exposure in the following categories:

Part 1:

- <7 weeks (<49 days)
- 7 - <11 weeks (49 – 76 days)
- 11 - <14 weeks (77 – 97 days)
- ≥14 weeks (≥ 98 days)

Part 1 and Part 2:

- 14 - <36 weeks (<252 days)
- 36 - <68 weeks (252 – 475 days)
- 68 - <73 weeks (476 – 510 days)
- ≥73 weeks (≥511 days)

Percent compliance to the study drug regimen will be calculated as 100 x number of tablets taken / number of expected tablets taken. The number of tablets taken will be calculated as number of tablets dispensed – number of tablets returned – number of tablets destroyed/lost. If study drug is not returned, the number of tablets taken will be the minimum of the number of tablets dispensed or the number of expected tablets taken after dispensation. One tablet is expected to be taken per 2 mg dose of CIN-107. While subjects are on every day (QD) dosing, the number of tablets expected will be calculated as the sum at each dose level of (date of last dose – date of first dose+1) x number of tablets expected per dose. While subjects are on every other day (QOD) dosing, the number of tablets expected will be calculated as the sum at each

dose level of floor((date of last dose – date of first dose +1) / 2) x number of tables expected per dose (i.e., the sum of the number of days study drug was expected to be taken at each dose level x 1 tablet per 2 mg CIN-107 per day). Percent compliance to the study drug regimen will be summarized in total based on the Safety Population separated by Part 1 and whole study (Part 1 and Part 2) with descriptive statistics and with counts and percentages of patients with compliance in the following categories:

- <70%
- 70 – 120%
- >120%

3.4 Efficacy Assessment

Efficacy data will be summarized based on the ITT Population. The primary efficacy endpoint will also be summarized based on the PP Population.

Unless specified, summary by dose level will be conducted as follows.

For endpoints related to Part 1 of the study using

1a) final Part 1 dose the subject was on prior to or on the date of Visit 7;

1b) IP dose the subject stayed on the longest in Part 1 of the study.

For endpoints related to Part 2 of the study, using the IP dose the subject stayed on longest in Part 2 of the study.

In case of a tie of dose the subject stayed on longest in Part 1 or Part 2, use the highest of the doses.

3.4.1 Primary Efficacy Endpoints

The primary efficacy analysis will compare the change in mean SBP after 12 weeks of treatment in patients with PA. Descriptive statistics will summarize mean SBP, and mean change and percent change from baseline in SBP at each post-baseline visit up until Visit 7 in total based on the ITT and PP Population, summarized by dose level using both 1a) final Part 1 dose and 1b) Part 1 dose with longest treatment duration. Spaghetti plots of SBP by analysis day up until Visit 7 will be provided for both summary level and individual level. In the individual Spaghetti plot, IP up-titration and down-titration timing will be highlighted with different symbols and the individual Spaghetti plot presented for ITT population and PP population.

3.4.2 Secondary Efficacy Endpoints

3.4.2.1 Diastolic Blood Pressure

Efficacy measured by mean change in mean DBP after 12 weeks of treatment in patients with PA will be assessed by descriptive statistics that will summarize mean DBP, and mean change and percent change from baseline in DBP at each post-baseline visit up until Visit 7 in total based on the ITT Population. Spaghetti plots of DBP by analysis day up until Visit 7 will be provided for both summary level and individual level. In the individual Spaghetti plot, up-titration and down-titration timing will be highlighted with different symbols and the individual Spaghetti plot presents only for ITT population.

3.4.2.2 BP Response

The percent of patients who achieved a seated BP response <140/90 mmHg after CIN-107 treatment will be evaluated at each dose level at Week 12. Counts and percentages of patients who achieved SBP<140, DBP <90, and BP<140/90 will be summarized by dose level using both 1a) final Part 1 dose and 1b) Part 1 dose with longest treatment duration and in total based on the ITT Population.

The percent of patients who achieved a seated BP response <130/80 mmHg after CIN-107 treatment will be evaluated at each dose level at Week 12. Counts and percentages of patients who achieved SBP<130, DBP <80, and BP<130/80 will be summarized by dose level using both 1a) final Part 1 dose and 1b) Part 1 dose with longest treatment duration and in total based on the ITT Population.

3.4.2.3 Potassium Supplementation and Fluid or Mineral Replacement

The count and percent of patients that required potassium supplementation or fluid or mineral replacement during the study will be presented by dose level using both 1a) final Part 1 dose and 1b) Part 1 dose with longest treatment duration and in total based on the Safety Population. In addition, the count and percent of patients that required potassium supplementation or fluid or mineral replacement by each visit will be summarized. The requirement for potassium supplementation and for fluid or mineral replace will also be listed in a listing including change in supplementation (up- or down- titration of potassium supplements and fluid or mineral replacement medications).

Medical review will be conducted by Medpace to identify potassium supplements and fluid or mineral replacements. The concomitant medication records will be coded using WHO Drug Dictionary. After coding, the medical monitors will review the records and indicate medications as a potassium supplement, or fluid or mineral replacement based on WHO Drug coding and other relevant data collected within the case report form (CRF). These medical flags will be imported and used in analysis. Final medical review will occur prior to database lock.

3.4.2.4 PD Response

The percentage of patients who, after 12 weeks of treatment with CIN-107 for PA, achieve either a serum aldosterone < 15 ng/dL and a PRA ≥ 0.5 ng/mL/h; an ARR < 15; or unsuppressed PRA ≥ 1.0 ng/mL/h will be summarized. Counts and percentages of patients who achieved PD response at Week 12 will be summarized by dose level using both 1a) final Part 1 dose and 1b) Part 1 dose with longest treatment duration and in total based on PD Population.

3.4.3 Exploratory Efficacy Endpoints

3.4.3.1 PD Markers

Changes in the concentrations from baseline in PD plasma markers including serum aldosterone and its relevant precursors (18-OH corticosterone, corticosterone, and 11-deoxycorticosterone), plasma cortisol (free and total) and its relevant precursor 11-deoxycortisol, PRA, direct renin concentration, calculated ARR, NT-proBNP; 24-hour urinary markers aldosterone excretion, sodium excretion, potassium excretion, creatinine excretion, albumin excretion, and protein excretion; and 24-hour normalized urinary markers by dose level using both 1a) final Part 1 dose and 1b) Part 1 dose with longest treatment duration will be assessed. The normalized analytes will be calculated as follows

$$\text{Normalized Aldosterone (ng/g)} = 1{,}000{,}000 \times \frac{\text{Aldosterone Excretion(ug/day)}}{\text{Creatinine Excretion (mg/day)}}$$

$$\text{Normalized Albumin (mg/g)} = 1{,}000 \times \frac{\text{Albumin (mg/day)}}{\text{Creatinine (mg/day)}}$$

$$\text{Normalized Potassium (mmol/g)} = 1{,}000 \times \frac{\text{Potassium (mmol/day)}}{\text{Creatinine (mg/day)}}$$

$$\text{Normalized Protein (mg/g)} = 1{,}000 \times \frac{\text{Protein (mg/day)}}{\text{Creatinine (mg/day)}}$$

$$\text{Normalized Sodium (mmol/g)} = 1{,}000 \times \frac{\text{Sodium (mmol/day)}}{\text{Creatinine (mg/day)}}$$

Descriptive statistics for each PD marker will be given at each visit (at Visits 2, 3, 4, 5, 6, 7) based on PD population. Spaghetti plots of each PD marker by analysis day up until Visit 7 will be provided for both summary level and individual level. In the individual Spaghetti plot, up-titration and down-titration timing will be highlighted with different symbols and the individual Spaghetti plot presents only for ITT population.

The relationship between change in serum aldosterone and change in plasma aldosterone-to-renin ratio (ARR) from baseline to Week 12 will be explored using a scatter plot and an arrow plot.

The relationship between BP reduction and changes in aldosterone, renin levels, and ARR with CIN-107 will be explored. Scatterplots of change from baseline to Week 12 in SBP vs change from baseline to Week 12 in each PD marker and corresponding arrow plot will be presented. Scatterplots of change from baseline to Week 12 in DBP vs change from baseline to Week 12 in each PD marker will be presented.

3.4.3.2 Extension Study

The change in SBP at end of study versus baseline for patients who elect to participate in the extension study will be assessed. Descriptive statistics will summarize mean SBP, and mean and percent change from Visit 7 in SBP at each Part 2 visit by dose level with longest treatment duration in Part 2. Spaghetti plots of SBP by analysis day will be provided for both summary level and individual level. In the individual Spaghetti plot, up-titration and down-titration timing will be highlighted with different symbols.

The change in DBP at end of study versus baseline for patients who elect to participate in the extension study will be assessed. Descriptive statistics will summarize mean DBP, and mean change and percent change from Visit 7 in DBP at each Part 2 visit by dose level with longest treatment duration in Part 2. Spaghetti plots of SBP by analysis day will be provided for both summary level and individual level. In the individual Spaghetti plot, up-titration and down-titration timing will be highlighted with different symbols.

Change in the concentrations from baseline to end of the extension study participation in PD plasma markers including serum aldosterone and its relevant precursors (18-OH corticosterone, corticosterone, and 11-deoxycorticosterone), plasma cortisol (free and total) and its relevant precursor, PRA, direct renin concentration, calculated ARR, NT-proBNP, and 24-hour urinary markers aldosterone excretion, sodium excretion, potassium excretion, creatinine excretion, albumin excretion and protein excretion will be summarized by dose level using Part 2 dose with

longest treatment duration. Descriptive statistics for each PD marker will be given at each Part 2 visit. Spaghetti Plots of each PD marker by analysis day will be provided.

3.4.3.3 Home BP Monitoring

Morning and evening home BP measurements will be recorded in a daily diary by the patient. Triplicate measures will be averaged prior to summarization. The last 2 of the multiple measures during same timepoint (e.g. multiple morning measures) will be averaged prior to summarization. Spaghetti plots of morning and evening home SBP and DBP will be provided on the individual level for the ITT Population including Part 1 and Part 2. Up-titration and down-titration timing will be highlighted with different symbols.

3.4.4 Subgroups

Descriptive statistics will summarize mean SBP, and mean change and percent change from baseline in SBP at each post-baseline visit in total based on the ITT Population for the following subgroups:

1. Sex
2. Background MRA Use
3. Age (<65 years, ≥65 years)
4. Baseline SBP (<145 mmHg, ≥145 mmHg)
5. Baseline Serum Aldosterone (<6 ng/dL, ≥6 ng/dL)
6. Baseline PRA (<1 ug/L/h, ≥1 ug/L/h)
7. Baseline eGFR (<60 mL/min/1.73m^2, ≥60 mL/min/1.73m^2)

3.5 Pharmacokinetic Assessment

Pre- and post-dose PK samples will be collected within 15 minutes before study drug dosing at Visits 3, 4, 5, 7, and 13 and at approximately 2 hours ± 5 minutes after study drug dosing. The actual date and time of collection of each PK sample will be recorded. The plasma concentrations of CIN-107 and any measured metabolite will be listed and presented separately in tabular and graphical form by visit, timepoint (pre- vs post-dose), and actual dose (dose administered before respective PK sample) for each sample, that includes applicable descriptive statistics, as well as final TFL shells that define handling of individual concentrations below the lower limit of quantification for listings, descriptive statistics and figures, and precision and rounding rules for concentrations. The analysis will be based on the Pharmacokinetic population.

3.5.1 Pharmacokinetic Concentrations

Concentration Listings:

Plasma pharmacokinetic concentration data for CIN-107 and any measured metabolite will be listed separately by visit, timepoint (pre- vs post-dose), actual dose (dose administered before respective PK sample) for each sample and participant. Concentration listings will include nominal PK sampling time, actual sampling times relative to dose administration and concentrations. Plasma concentrations below the lower limit of quantification (LLOQ) will be

presented as below the limit of quantification (BLQ) in the listings and the LLOQ value presented as a footnote.

Concentration Summary Tables:

Source data as reported from the laboratory will be used for calculation of concentration summary statistics. Tabular summaries for concentration-time data will report N (number of participants who received treatment), n (number of participants with non-missing values), and n(BLQ) (the number of participants with BLQ samples).

Plasma concentration will be summarized by visit, timepoint (pre- vs post-dose), and actual dose (dose administered before respective PK sample) for the PK Population. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: N, n, n(BLQ), arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (calculated as: gCV% =SQRT(exp(s²)-1)*100; where s is the SD of the log transformed values), median, minimum, and maximum values.

For summary tables, all BLQs will be considered zero (except for geometric mean in which BLQ will be substituted with ½ the LLOQ), and the number of BLQs and non-BLQs at each scheduled time point will be reported.

Concentration Figures:

Plasma concentrations will be displayed in boxplots by visit, timepoint (pre- vs post-dose), and actual dose for the Pharmacokinetic population. All BLQ values will be substituted with ½ the LLOQ. Boxplots will be displayed on a semi-logarithmic scale.

3.6 Pharmacodynamic Assessment

Please refer to Section 3.4.3.1 for details.

3.7 Pharmacogenomic Assessments

Details of pharmacogenomic sample and data analyses will be provided in a separate analysis plan if applicable.

3.8 Safety Assessment

Safety data will be summarized in total based on the Safety Population.

3.8.1 Adverse Events

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class and preferred term using MedDRA version 23.0. As of May 2023, dictionary updates will be applied bi-annually. Part 1 Pre-Titration treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug during the Part 1 treatment period prior to Visit 4. Part 1 After Titration TEAEs are defined as AEs that start after the first dose of study drug during the period starting with Visit 4 until the end of part 1. Part 2 TEAEs are defined as AEs that start after first dose of study drug and after Visit 7.

Dose level will be determined by the last dose prior to AE start. If an AE started before first dose of study drug, then ‘Pre-Dose’ will be specified. If an AE started on the same day as a dose titration, the pre-titration dose will be used. If an AE started while off study drug, the dose level will be determined by the last dose prior to AE start.

Adverse events of special interest 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

An overview of AEs will be provided including counts and percentages of patients (and event counts) with the following:

- Any AEs (overall and by maximum severity)
- Any TEAEs (overall and by maximum severity)
- Any study drug related TEAEs (overall and by maximum severity)
- Any TEAEs of special interest (overall and by maximum severity)
- Any serious AEs (SAEs)
- Any serious TEAEs (TESAEs)
- Any TEAEs leading to discontinuation of study drug
- Any TEAEs leading to dose interruption
- Any TEAEs leading to dose reduction
- Any TEAEs leading to dose increase
- Any TEAEs leading to discontinuation of study
- Any TEAEs leading to death

Counts and percentages of patients (and event counts) will also be presented by dose level and in total based on the Safety Population, by system organ class and preferred term for each of the categories in the overview.

AEs will be summarized by the following study periods and dose level:)

Part 1 Before titration (before Visit 4): period prior to up-titration with all patients on 2mg. Summaries will be separated by Pre-Dose, 2 mg and overall.

Part 1 After titration (From Visit 4): period starting with Visit 4 after titration until the end of part 1 (visit 7). Summaries will be separated by 2 mg, 4 mg, 8 mg and overall.

Part 2: separated by 2mg, 4mg, 8mg dose groups.

Listings will be presented specifically for SAEs, and AEs leading to discontinuation of study drug.

3.8.2 Clinical Laboratory Tests

Blood and urine samples for clinical laboratory tests will be collected at Visits 1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 and processed by a central laboratory. A list of laboratory tests to be performed is included in Appendix B.

Estimated GFR will be calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:

$$\text{eGFR} = 142 \times min\left(\frac{\text{Scr}}{\kappa}, 1\right)^{\alpha} \times max\left(\frac{\text{Scr}}{\kappa}, 1\right)^{-1.2} \times 0.9938^{\text{Age}} \times 1.012[\text{if female}]$$

where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Values and changes from baseline will be presented at each scheduled visit and baseline by laboratory test. Counts and percentages of the incidence of treatment-emergent abnormalities will be summarized. Shift from baseline category (e.g. normal, low, high) at each post-baseline visit will be provided for select laboratory parameters. The table will be provided for Part 1 and Part 2 separately.

The change from baseline in serum potassium, serum sodium, and eGFR after 12 weeks of treatment will be summarized at each post-baseline visit up until Visit 7 by dose level using both 1a) final Part 1 dose and 1b) Part 1 dose with longest treatment duration and in total based on the Safety Population. Spaghetti plots of serum potassium, serum sodium, and eGFR by analysis day will be provided for both summary level and individual level. In the individual Spaghetti plot, up-titration and down-titration timing will be highlighted with different symbols.

Spaghetti plot of potassium level by analysis day will be presented for patients that had potassium measure ≥5.5 mmol/L at any post-baseline visit. Additionally, spaghetti plots of potassium level by analysis day will be presented for patients that had a potassium measure of ≥5.0 mmol/L and ≥6.0 mmol/L. Summary of potassium categories <3.5, ≥3.5 and <5.0, ≥5.0 and <5.5 mmol/L, ≥5.5 and <6.0 mmol/L, and ≥6.0 mmol/L will be presented.

Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plots will be provided.

3.8.3 Vital Signs

Vital signs will include heart rate (beats/min), respiratory rate (breaths/min), body temperature (C), and height (cm) and weight (kg) measurements. Orthostatic vitals will include change from seated to standing BP and change from seated to standing heart rate. Vital signs and BP will be measured at all visits as indicated in Appendix A. Height will be measured at Screening visit only. The table will be provided for Part 1 and Part 2 separately.

Orthostatic blood pressure findings will be presented as the change from mean seated blood pressure to mean standing blood pressure at a given visit by subtracting the mean seated SBP from the mean standing SBP. A similar approach will be employed for the diastolic blood pressure assessments at a given visit.

Descriptive statistics will be presented at baseline and each scheduled post-baseline visit. The change from baseline to post-baseline visit will also be presented.

3.8.4 Electrocardiograms

Standard 12-lead ECGs will be performed at Visits 1, 3, 4, 5, 6, 7, 8, 9, 13, and 14 as indicated in Appendix A.

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

- Heart rate (beats/min)
- QRS duration (msec)

- PR interval (msec)
- RR interval (msec)
- QT interval (msec)
- QTc (QTcF) (msec)

Descriptive statistics will be presented at baseline and each scheduled post-baseline visit. The change from baseline to post-baseline visits will also be presented. The overall interpretation will be summarized by visit. The table will be provided for Part 1 up until Visit 7 and Part 2 separately.

A summary table for categorical QTcF e.g. those above 450,480 and 500 msec as well as those who exceed a change from baseline of 30 /60 msec, and combination of the above will be presented for Part 1 and Part 2 separately.

3.8.5 Physical Examinations

A complete physical examination will be performed at Visit 2 and 13. A limited physical examination will be performed at Visits 1, 3, 7, 9, 10, 11,12, and 14.

Physical examination data will be listed.

4 DATA REVIEW COMMITTEE

A Data Review Committee (DRC) will monitor the safety of patients over the course of the study. The DRC will meet once or more during the patient enrollment period to examine the unblinded accumulated safety data.

Details related to the DRC responsibilities, authorities, and procedures will be documented in a DRC charter which will be finalized prior the first patient being enrolled in the study.

5 ANALYSIS TIMING

5.1 Interim Analysis

No formal interim analysis is planned.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

There are no changes from the protocol-specified statistical analyses.

APPENDIX A: SCHEDULE OF EVENTS

SCHEDULE OF EVENTS WEEKS -5 TO 14 NOTE: VISIT 8/WEEK 14 IS FOR PATIENTS ONLY IN PART 1, NOT IN THE EXTENSION PHASE (SEE FOLLOWING PAGES FOR THAT SCHEDULE)

	Screening		**Treatment**					**Follow-up [n]**
***Visit**	**1**	**2**	**3**	**4 [l]**	**5 [m]**	**6**	**7**	**8 [o]**
Study Day (visit window)	**up to Day -35 (+/- 3)**	**up to Day -28 (+/- 3)**	**1 (+/- 3)**	**28 (+/- 3)**	**56 (+/- 3)**	**63 (+/- 3)**	**89 (+/- 3)**	**98 (+/- 3)**
Week	**-5**	**-4**	**0**	**4**	**8**	**9**	**12**	**14**
Mineralocorticoid Receptor Antagonist (MRA)[a]								
MRA washout		X						
MRA treatment								X
CIN-107 **								
Dispense study drug			X	X	X			
CIN-107 treatment [b]			X	X	X	X	X	
Dose titration assessment				X	X			
Unused study drug collection							X	
Assess treatment adherence				X	X	X	X	
Administrative								
Informed consent	X							
Eligibility	X							
Demographics	X							
Medical/surgical history	X							
BP monitor dispensation and instructions [c]	X							
Review of home BP monitoring		X	X	X	X	X	X	X
Assessments								
Vital Signs [e]	X	X	X	X	X	X	X	X
Weight and Height (screening only)	X	X	X	X	X	X	X	X
Complete Physical Examination		X						
Limited Physical Examination	X		X				X	
12-Lead ECG	X		X	X	X	X	X	X

	Screening		Treatment					Follow-up [n]
***Visit**	**1**	**2**	**3**	**4 [l]**	**5 [m]**	**6**	**7**	**8 [o]**
Study Day (visit window)	**up to Day -35 (+/- 3)**	**up to Day -28 (+/- 3)**	**1 (+/- 3)**	**28 (+/- 3)**	**56 (+/- 3)**	**63 (+/- 3)**	**89 (+/- 3)**	**98 (+/- 3)**
Week	**-5**	**-4**	**0**	**4**	**8**	**9**	**12**	**14**
Safety laboratory testing including urinalysis [f, g]	X		X	X	X	X	X	X
PD blood sampling [h]		X	X	X	X	X	X	X
Provide 24-hour urine collection kit	X		X		X	X		
PD urine sampling [i]		X		X		X	X	
PK blood sampling [j]			X	X	X		X	
HIV, HbsAg, HCV screen	X							
Pregnancy test (WOCBP)	X							
Follicle-stimulating hormone [k]	X							
PGx sample (optional, once V3 to V7)			X					
Safety								
Adverse event monitoring	X	X	X					X
Prior/concomitant medications	X	X	X					X

Abbreviations: BP: blood pressure; ECG: electrocardiogram; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; PD: pharmacodynamic; PGx: pharmacogenomic; PK: pharmacokinetic; SBP: systolic blood pressure; WOCBP: women of childbearing potential.

* Note: Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical study site visit. Additional unscheduled visits may occur at Investigator's discretion to manage BP and electrolyte balance.

** Note: If a patient is taking more than 1 anti-hypertensive agent, the other non-MRA agents should be taken continuously.

[a] Eligible patients that take an MRA to manage BP will discontinue MRA and monitor BP daily with provided BP monitor for up to 4 weeks before CIN-107 dosing starts. After the treatment period is complete, patients will resume the MRA after a 2-week Follow-Up Period is complete so that the BP, safety data, and biomarker changes can be assessed. The Follow-Up Period may be shortened and MRA may be prescribed, if necessary, due to safety concern per Investigator's discretion.

[b] Dosing with CIN-107 (2 mg once daily) will start after 4 weeks of MRA washout or when SBP is ≥ 160 mmHg or the SBP increases by ≥ 20 mmHg, whichever is sooner. For patients who are newly diagnosed with PA, have never taken MRA for managing hypertension, and have SBP ≥ 150 mmHg, dosing with CIN-107 may start after all eligibility criteria are confirmed. Visit 2 is not required for these patients.

[c] Patients will be instructed to measure BP daily and to contact the Investigator if BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or if BP is < 90/60 mmHg.

[d] 24-hour urine collection will be analyzed for aldosterone, electrolytes (including but not limited to sodium and potassium), and albumin, protein, and creatinine.

[e] Vital signs include heart rate (seated and standing), respiratory rate, body temperature, and BP (seated and standing).

[f] Safety laboratory tests include standard hematology, coagulation, chemistry panel and urinalysis. Full listing of laboratory analytes can be found in Appendix B.

[g] Safety laboratory testing may take place at local laboratory.

[h] PD blood sample variables analyzed will include measurement of aldosterone and relevant precursors, cortisol and relevant precursor, plasma renin activity, direct renin concentration, calculated aldosterone to renin ratio and NT-proBNP. PD samples should be drawn prior to taking CIN-107.
[i] PD 24-hour urine samples will be collected for measurements of aldosterone, electrolytes (potassium and sodium), creatinine, albumin and protein.
[j] PK variables analyzed will include plasma concentration of CIN-107 and any additional metabolites. Pre- and post-dose PK samples will be collected within 15 minutes before study drug dosing at Visits 3, 4, 5, and 7 and 12 and at approximately 2 hours ± 5 minutes after study drug dosing.
[k] Follicle-stimulating hormone levels will be measured only for female patients ≤ 60 years of age who are postmenopausal for at least 1 year at Screening and are not surgically sterile
[l] At Visit 4 (Week 4), CIN-107 dose may be increased to 4 mg if the patient tolerates dosing of CIN-107 at 2 mg. The Investigator will contact the patient by phone approximately 7 days after the dose is up-titrated and the laboratory results are available. CIN-107 dose may be down-titrated to 2 mg if the safety laboratory results indicate hyperkalemia, hyponatremia, or other abnormal safety laboratory findings suggest that the patient does not tolerate CIN-107 4 mg dosing.
[m] At Visit 5 (Week 8), CIN-107 dose may be up-titrated to 8 mg QD if the patient tolerates dosing of CIN-107 at 4 mg. CIN-107 dose may be down-titrated to the 2 mg initial dose or continued with 4 mg if the patient experiences hyperkalemia, hyponatremia, or signs and symptoms of hypotension or un-suppressed renin activity (plasma renin activity [PRA] ≥ 1.0 ng/mL/h). The final CIN-107 dose level will be determined by the Investigator based on the BP and safety laboratory values.
[n] During the safety follow-up period (approximately 2 weeks after the last dose of CIN-107), patients will continue taking the non-MRA agents but will not start the MRA so that the BP, safety data, and biomarker changes can be assessed after CIN-107 dosing. MRA may be prescribed, if necessary, per Investigator's discretion. Patients will receive a telephone call from the clinical site 1-week (± 3 days) following the last dose of CIN-107 to assess adverse events and concomitant medications.
[o] At Visit 8 (Week 14) [Visit 13 (week 74) in the extension phase)], patients will complete the last clinical visit and data for BP, samples for safety, and biomarker assessment samples will be collected. Patients will be counseled to maintain a healthy diet and lifestyle and resume MRA if clinically indicated.

SCHEDULE OF EVENTS WEEKS 12-74 FOR PATIENTS IN THE PART 2 EXTENSION

	Extension Phase				Follow-up [n]	
***Visit**	**9**	**10**	**11**	**12**	**13**	**14**
Study Day (visit window)	**168 (+/- 7)**	**252(+/- 7)**	**336(+/-7)**	**420(+/-7)**	**504(+/-7)**	**532(+/-7)**
Week	**24**	**36**	**48**	**60**	**72**	**74**
Dispense study drug	X	X	X	X	X	
CIN-107 treatment [b]	X	X	X	X	X	
Dose titration assessment	X	X	X	X		
Unused study drug collection	X	X	X	X	X	
Assess treatment adherence	X	X	X	X	X	
Eligibility [p]	X					
Review of home BP monitoring	X	X	X	X	X	X
Vital Signs [e]	X	X	X	X	X	X
Weight	X	X	X	X	X	X
Complete Physical Examination					X	
Limited Physical Examination	X	X	X	X		X
12-Lead ECG	X				X	X
Safety laboratory testing including urinalysis [f, g]	X	X	X	X	X	X
PD blood sampling [h]		X			X	
Provide 24-hour urine collection kit	X			X		
PD urine sampling [i]		X			X	
PK blood sampling [j]					X	
Pregnancy test (WOCBP)						X
Safety						
Adverse event monitoring	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X
MRA treatment						X

Abbreviations: BP: blood pressure; ECG: electrocardiogram; HbsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; PD: pharmacodynamic; PGx: pharmacogenomic; PK: pharmacokinetic; SBP: systolic blood pressure; WOCBP: women of childbearing potential.

* Note: Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical study site visit. Additional unscheduled visits may occur at Investigator's discretion to manage BP and electrolyte balance.

** Note: If a patient is taking more than 1 anti-hypertensive agent, the other non-MRA agents should be taken continuously.

[a] Eligible patients that take an MRA to manage BP will discontinue MRA and monitor BP daily with provided BP monitor for up to 4 weeks before CIN-107 dosing starts. After the treatment period is complete, patients will resume the MRA after a 2-week Follow-Up Period is complete so that the BP, safety data, and biomarker changes can be assessed. The Follow-Up Period may be shortened and MRA may be prescribed, if necessary, due to safety concerns per Investigator's discretion.
[b] Dosing with CIN-107 (2 mg once daily) will start after 4 weeks of MRA washout or when SBP is ≥ 160 mmHg or the SBP increases by ≥ 20 mmHg, whichever is sooner. For patients who are newly diagnosed with PA, have never taken MRA for managing hypertension, and have SBP ≥ 150 mmHg, dosing with CIN-107 may start after all eligibility criteria are confirmed. Visit 2 is not required for these patients.
[c] Patients will be instructed to measure BP daily and to contact the Investigator if BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or if BP is < 90/60 mmHg.
[d] 24-hour urine collection will be analyzed for aldosterone, electrolytes (including but not limited to sodium and potassium), and albumin, protein, and creatinine.
[e] Vital signs include heart rate (seated and standing), respiratory rate, body temperature, and BP (seated and standing).
[f] Safety laboratory tests include standard hematology, coagulation, chemistry panel and urinalysis. Full listing of laboratory analytes can be found in Appendix B.
g Safety laboratory testing may take place at local laboratory.
[h] PD blood sample variables analyzed will include measurement of aldosterone and relevant precursors, cortisol and relevant precursor, plasma renin activity, direct renin concentration, calculated aldosterone to renin ratio and NT-proBNP. PD samples should be drawn prior to taking CIN-107.
[i] PD 24-hour urine samples will be collected for measurements of aldosterone, electrolytes (potassium and sodium), creatinine, albumin and protein.
[j] PK variables analyzed will include plasma concentration of CIN-107 and any additional metabolites. Pre- and post-dose PK samples will be collected within 15 minutes before study drug dosing at Visits 3, 4, 5, and 7 and 12 and at approximately 2 hours ± 5 minutes after study drug dosing.
[k] Follicle-stimulating hormone levels will be measured only for female patients ≤ 60 years of age who are postmenopausal for at least 1 year at Screening and are not surgically sterile
[l] At Visit 4 (Week 4), CIN-107 dose may be increased to 4 mg if the patient tolerates dosing of CIN-107 at 2 mg. The Investigator will contact the patient by phone approximately 7 days after the dose is up-titrated and the laboratory results are available. CIN-107 dose may be down-titrated to 2 mg if the safety laboratory results indicate hyperkalemia, hyponatremia, or other abnormal safety laboratory findings suggest that the patient does not tolerate CIN-107 4 mg dosing.
[m] At Visit 5 (Week 8), CIN-107 dose may be up-titrated to 8 mg QD if the patient tolerates dosing of CIN-107 at 4 mg. CIN-107 dose may be down-titrated to the 2 mg initial dose or continued with 4 mg if the patient experiences hyperkalemia, hyponatremia, or signs and symptoms of hypotension or un-suppressed renin activity (plasma renin activity [PRA] ≥ 1.0 ng/mL/h). The final CIN-107 dose level will be determined by the Investigator based on the BP and safety laboratory values.
[n] During the safety follow-up period (approximately 2 weeks after the last dose of CIN-107), patients will continue taking the non-MRA agents but will not start the MRA so that the BP, safety data, and biomarker changes can be assessed after CIN-107 dosing. MRA may be prescribed, if necessary, per Investigator's discretion. Patients will receive a telephone call from the clinical site 1-week (± 3 days) following the last dose of CIN-107 to assess adverse events and concomitant medications.
[o] At Visit 8 (Week 14) [Visit 13 (week 74) in the extension phase)], patients will complete the last clinical visit and data for BP, samples for safety, and biomarker assessment samples will be collected. Patients will be counseled to maintain a healthy diet and lifestyle and resume MRA if clinically indicated.
[p] Eligibility for Part 2 will be determined based on the patient achieving at least comparable BP control to historical treatment and requiring potassium replacement while on baxdrostat that is less than or comparable to historical replacement in patients with a history of hypokalemia.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel	
Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate [a]
Blood urea nitrogen [a]	Calcium
Chloride [a]	Creatine kinase
Creatinine [a]	Estimated glomerular filtration rate [a]
Gamma-glutamyl transferase	Glucose [a]
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium [a]
Sodium [a]	Total bilirubin
Total protein	Uric acid
Additional Chemistry Parameters	
Glycosylated hemoglobin	
Hematology	
Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential [b]	
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	
Endocrinology	
β-human chorionic gonadotropin [c]	Follicle-stimulating hormone [d]

[a] Values typically measured/reported at a minimum for unscheduled electrolyte determinations.
[b] Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.
[c] Serum or point-of-care pregnancy tests will be performed only for female patients of childbearing potential (i.e., ovulating, pre-menopausal, and not surgically sterile).
[d] Follicle-stimulating hormone levels will be measured only for female patients ≤ 60 years of age who are postmenopausal for at least 1 year at Screening and are not surgically sterile.

APPENDIX C: LIST OF PHARMACODYNAMIC ASSESSMENTS

Blood Analytes	
Aldosterone and its relevant precursors (18 OH corticosterone, corticosterone, and 11-deoxycorticosterone)	Cortisol (free and total) and its relevant precursor, 11 deoxycortisol
Direct renin concentration	Plasma renin activity
NT-proBNP	ARR
24-hour Urine Collection Analytes	
Aldosterone	Potassium
Sodium	Creatinine
Albumin	Protein