MEDPACE

STATISTICAL ANALYSIS PLAN

Protocol Title:	An Open-Label Extension Study of Patients Previously Enrolled in Study CIN-107-124 to Evaluate the Long-Term Safety and Effectiveness of CIN-107
Protocol Number:	D6971C00001
Protocol Version/Date:	2.0/31 March 2023
Investigational Product:	CIN-107 (Generic Name: Baxdrostat)
Sponsor:	AstraZeneca AB Västra Mälarehamnen, SE-151 85 Södertälje, Sweden
SAP Version/Date:	2.0/15 December 2023

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SIGNATURE PAGE

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

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

VERSION HISTORY

Version	Version Date	Description
1.0	17 May 2023	Original signed version
2.0	15 December 2023	Second version

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical therapeutic chemical
BMI	Body Mass Index
BP	Blood Pressure
CDISC	Clinical Data Interchange Standards Consortium
CIN-107	Baxdrostat
CRF	Case report form
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
ECG	Electrocardiograms
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
PD	Pharmacodynamics
PK	Pharmacokinetics
PK-PD	Pharmacokinetic-Pharmacodynamic
PRA	Plasma renin activity
QD	Once daily
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	Table, figure, 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 CIN-107-130 Version 2.0. The SAP will be finalized prior to database lock. Any deviations from the SAP after database 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 objective is to evaluate the long-term safety and tolerability of CIN-107 over an extended treatment period of up to 52 weeks.

2.1.2 Effectiveness Objectives

The effectiveness objectives are to evaluate the following relative to baseline (Visit 1) in

Study CIN-107-130 over 52 weeks:

- The mean SBP change;
- The mean DBP change;
- The percentage of patients achieving a seated SBP <130 mmHg;
- The percentage of non-responders in Study CIN-107-124 achieving a seated SBP response <130 mmHg with CIN-107 (with/without a single background antihypertensive agent and/or rescue medication), irrespective of Study CIN-107-124 dose strength; and
- The percentage of responders in Study CIN-107-124 maintaining a seated SBP response <130 mmHg with CIN-107 (with/without a single background antihypertensive agent and/or rescue medication), irrespective of Study CIN-107-124 dose strength.

2.1.3 Safety and Tolerability Objectives

The safety and tolerability objectives are the following:

- To evaluate treatment-emergent adverse events (TEAEs);
- To evaluate treatment-emergent serious AEs (SAEs);
- To evaluate TEAEs of special interest;
- To evaluate TEAEs leading to premature discontinuation of study drug;
- To evaluate treatment-emergent marked laboratory abnormalities;
- To evaluate the change on standing systolic blood pressure (SBP) and diastolic blood pressure (DBP), measured pre-dose at the clinical site, from baseline (Visit 1) of Study CIN-107-130 to End of Treatment (EOT);
- To evaluate vital signs, standing blood pressure (BP) and heart rate, physical examinations, electrocardiograms (ECGs), body weight, and clinical laboratory evaluations, including standard safety chemistry panel, hematology, coagulation, and urinalysis;
- To determine the extent of electrolyte imbalance in the study population;
- To determine the percentage of patients requiring down-titration of CIN-107 from the maximal dose strength of 2 mg to a lower dose strength of 1 mg or 0.5 mg;

- To determine the percentage of patients resuming a single background antihypertensive agent at 3, 6, 9, and 12 months; and
- To determine the percentage of patients requiring rescue medication (with/without a single background antihypertensive agent) during study participation.

2.1.4 Pharmacokinetic-Pharmacodynamic (PK-PD) Objectives

The PK-PD objective is to evaluate exposure-response relationships of CIN-107 using measures of safety, PD, and/or effectiveness.

2.2 Study Design

2.2.1 Overview

This is a Phase 2, multicenter, open-label extension (OLE) study to evaluate the long-term safety, tolerability, and effectiveness of CIN-107 for up to 52 weeks in patients with hypertension who have completed Part 1 or Part 2 of Study CIN-107-124. The study will be conducted at clinical sites that have participated in the double-blind, Phase 2 Study CIN-107-124. Patients will be assigned the same unique subject ID they have had in Study CIN-107-124.

Eligible patients from Study CIN-107-124 who elect to participate in the OLE will be enrolled directly following the EOT assessments at the end of Part 1 or Part 2 of Study CIN-107-124. The EOT assessments at the end of Part 1 or Part 2 of Study CIN-107-124 will serve as the Day 1 pre-dose assessments for those enrolling in Study CIN-107-130.

Enrolled patients will continue treatment with 2 mg CIN-107 tablets. The guiding principle for medical decision making with regard to BP management in the OLE study is to try to maintain patients on the highest dose of CIN-107 that is safe and medically reasonable. Investigators will be allowed to determine whether the patient should start the OLE study with an additional single background antihypertensive (non-CIN-107) agent based on the patient's BP control in Study CIN-107-124 (i.e., whether the patient in addition to the CIN-107 study drug would start the OLE study with an additional single background antihypertensive agent from another or same class as during Part 1 of Study CIN-107-124).

The single background antihypertensive agent chosen at Visits 1 or 2 should remain stable until Visit 3 of the OLE study, after which the Investigator is permitted to use his/her medical judgment to up/down titrate or discontinue the background antihypertensive (non-CIN-107) agent.

Rescue medication use is permitted and recommended if the SBP shows an acute and sustained increase of 30 mmHg (or greater) from Visit 1 and/or is ≥170 mmHg and/or the DBP is ≥105 mmHg in office measurement. Investigators should use their best clinical judgment when determining the need for rescue medications and are encouraged to discuss selection of rescue medication with the study Medical Monitors.

The Investigator is to document the clinical rationale for adding, changing dose, or discontinuing either the single background antihypertensive agent or rescue medication. The range of antihypertensive classes that may be used during this study is left to the Investigator's discretion, but potassium-sparing diuretics and MRAs are not allowed.

To manage persistent or symptomatic hypotension, the Investigator should first reduce or discontinue any rescue medication, and then reduce or discontinue use of the single background antihypertensive (non-CIN-107) agent if medically sound. If the symptoms continue, the dose strength of CIN-107 may be down-titrated from 2 mg to 1 mg. The CIN-107 dose may be further down-titrated to 0.5 mg if the SBP remains ≤100 mmHg for 3 consecutive days or if symptoms persist. CIN-107 may be temporarily discontinued if the SBP remains <90 mmHg for 3 consecutive days or if symptoms persist. Study drug dosing may be resumed or up-titrated after reassessments.

Patients will complete approximately 8 study visits during the OLE study, including enrollment (Visit 1) and follow-up (Visit 8) visits. During the treatment period, patients will return to the clinical site for visits. Unscheduled visits may be scheduled at any time during the study period based on the Investigator's discretion. Every effort should be made to secure the continued participation of patients.

The safety and tolerability of CIN-107 will be assessed from the day of the first dose of study drug in Study CIN-107-130 until the end of the follow-up visit. Patients will be followed for effectiveness and adherence throughout the treatment period. PD variables analyzed during the study may include, but are not limited to, measures of aldosterone and its precursors, cortisol and its precursor, and plasma renin activity (PRA), and calculation of aldosterone/PRA ratio. PK variables analyzed during the study will include plasma concentrations of CIN-107 and any measured metabolite(s).

Clinical sites will provide patients with a 24-hour urine collection kit at Visit 6. Patients will be instructed to start the collection up to 3 days prior to Visit 7, refrigerate the collected sample, and bring the entire sample to the clinical site at Visit 7. A 24-hour urine collection will commence after the first morning void on the first day and will include the first morning void on the second day for a total duration of 24 (±2) hours. Patients must be instructed to keep the sample refrigerated at all times except during their transit to the clinical site. A 24-hour urine collection may be repeated if the Investigator suspects that the sampling is insufficient, and the patient is within the visit window. Clinical sites will aliquot urine into a transfer tube and send it to the Central Laboratory.

On clinical site visit days, patients will self-administer the morning dose of any other concomitant medications (if applicable) at home. CIN-107 should be withheld as it will be self-administered at the clinical site and witnessed by site staff, after completion of pre-dose evaluations and laboratory sampling. Between clinical site visits, patients will continue to self-administer study drug once daily (QD) by mouth at approximately the same time each morning. Patients will be instructed to bring their antihypertensive medication(s) and study drug to all clinical site visits for pill counts. Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical site visit. All scheduled clinical site visits should occur between 6:00 a.m. and 11:00 a.m.

2.2.2 Randomization and Blinding

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

2.2.3 Study Drug

CIN-107 tablets will be provided in 0.5, 1, and 2 mg dose strengths. Eligible patients from Study CIN-107-124 who elect to participate in this study will continue treatment with 2 mg CIN-107 tablets QD after enrollment, starting at Visit 1 and concluding at EOT (Visit 7).

2.2.4 Sample Size Determination

The study sample size is predicated on the overall size of the parent Study CIN-107-124. It is estimated that about 200 patients will enroll in this study.

2.3 Study Endpoints

2.3.1 Primary Effectiveness Endpoints

The effectiveness endpoints include the following:

- Change from baseline in mean seated SBP with CIN-107 over the 52-week treatment period. Baseline mean seated SBP is the value at Visit 1 of Study CIN-107-130;
- Change from baseline in mean seated DBP with CIN-107 over the 52-week treatment period. Baseline mean seated DBP is the value at Visit 1 of Study CIN-107-130;
- The percentage of patients achieving a seated SBP response <130 mmHg with CIN-107 monotherapy without a single background antihypertensive agent over the 52-week treatment period;
- The percentage of non-responders in Study CIN-107-124 achieving a seated SBP response <130 mmHg with CIN-107 (with/without a single background antihypertensive agent and/or rescue medication), irrespective of Study CIN-107-124 dose strength;
- The percentage of responders in Study CIN-107-124 maintaining a seated SBP response <130 mmHg with CIN-107 (with/without a single background antihypertensive agent and/or rescue medication), irrespective of Study CIN-107-124 dose strength;
- Measures over time of PD variables analyzed during the study, including aldosterone and its precursors, cortisol and its precursor, and PRA, and calculated aldosterone/PRA ratio; and measures over time of PK variables analyzed during the study, including plasma concentrations of CIN-107 and any measured metabolite(s).

2.3.2 Pharmacodynamic-Pharmacokinetic Assessments

The PK-PD objective is to evaluate exposure-response relationships of CIN-107 using measures of safety, PD, and/or effectiveness.

2.3.2.1 Pharmacodynamic Blood Sampling

Pre-dose blood samples for PD analysis will be collected at the visits specified in Appendix A. The actual date and time of collection of each PD sample will be recorded. PD blood samples will be collected in the morning at the clinical site, after the patient has been out of bed for approximately 2 hours and has been seated for 5 to 15 minutes.

2.3.2.2 Twenty-Four-Hour Urine Collection

Kits for 24-hour urine collection will be provided, and 24-hour urine samples will be obtained as

specified in Appendix A. A 24-hour urine collection will commence after the first morning void on the first day and will include the first morning void on the second day for a total duration of 24 ±2 hours.

2.3.3 Pharmacokinetic Assessments

PK variables to be analyzed during the study will include plasma concentrations of CIN-107 and any measured metabolite(s). Pre-dose blood samples for PK analysis will be collected within approximately 15 minutes prior to dosing at the visits specified in Appendix A. The actual date and time of collection of each PK sample will be recorded.

2.3.4 Safety and Tolerability Endpoints

The safety and tolerability endpoints will include the following:

- TEAEs;
- Treatment-emergent SAEs;
- TEAEs of special interest;
- TEAEs leading to premature discontinuation of study drug;
- Treatment-emergent marked laboratory abnormalities;
- Change on standing SBP and DBP, measured pre-dose at the clinical site, from baseline (Visit 1) of Study CIN-107-130 to EOT (Visit 7);
- Vital signs, standing BP and heart rate, physical examinations, ECGs, body weight, and clinical laboratory evaluations, including standard safety chemistry panel, hematology, coagulation, and urinalysis;
- The percentage of patients with electrolyte imbalance;
- The percentage of laboratory results with electrolyte imbalance;
- The percentage of patients requiring down-titration of CIN-107 from the maximal dose strength of 2 mg to a lower dose strength of 1 mg or 0.5 mg;
- The percentage of patients resuming a single background antihypertensive agent at Day 1, and 3, 6, 9, and 12 months; and
- The percentage of patients requiring rescue medication (with/without a single background antihypertensive agent) during study participation.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of CIN-107-130 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:

Analysis Visit	Target Analysis Day	Analysis Window Beginning	Analysis Window Ending
Week 1/Visit 1[1]	1	1	1
Week 2/Visit 2	7	2	25

Analysis Visit	Target Analysis Day	Analysis Window Beginning	Analysis Window Ending
Week 6/Visit 3	42	26	63
Week 12/Visit 4	84	64	126
Week 24/Visit 5	168	127	217
Week 38/Visit 6	266	218	315
Week 52/Visit 7	364	316	378
Week 56/Follow up	392	379	>379

1. The EOT assessments at the end of Part 1 (Visit 6) or Part 2 (Visit 9) of Study CIN-107-124 will serve as the Day 1 pre-dose assessments for those enrolling in Study CIN-107-130.

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. If no scheduled visit occurs within the analysis day window, the unscheduled measurement 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

Baseline is defined as the last value prior to the first dose in Study CIN-107-130.

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. 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 is planned.

3.1.6 Evaluation of Site Effect

Sites may be pooled for subgroup analysis to assess the heterogeneity of treatment effects among pooled sites. The final pooling algorithm, if needed, will be provided as an addendum to the SAP.

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. Missing date imputation will not exceed last date in the trial or death date.

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. Incomplete start and stop dates will be listed as collected without imputation.

3.1.7.3 Missing or incomplete start or stop dates for AEs

If an 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 start month and year is the same as the first dose of study drug, then the start 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 imputed date is after AE end date, then the AE start date will be imputed as the AE end date.

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.

If the imputed AE start date is after AE end date, then the AE start date will be imputed as the AE end date.

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), the value as half of the LLOQ will be assigned. In case where values that are not able to be determined due to being higher than the upper limit of quantification (ULOQ), the ULOQ value will be assigned. This will be done for any analyses performed.

3.2 Analysis Populations

3.2.1 Safety Population

The Safety Population includes any patients enrolled in Study CIN-107-130 who have taken at least 1 dose of any study drug. The Safety Population will be the primary population used for analyses.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of subjects who were enrolled, discontinued early from the study, and completed the study (defined as the date the last protocol-specified visits/assessment was completed) will be summarized in total. Reasons for early discontinuation of study drug will also be summarized.

3.3.2 Protocol Deviations

Counts and percentages of subjects with protocol deviations by deviation category will be summarized by treatment and in total based on all enrolled subjects.

3.3.3 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (≤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/m2, ≥30 kg/m2)
- Mean seated SBP
- Mean seated DBP
- Estimated Glomerular Filtration Rate (eGFR)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate in total for all enrolled subjects in the Safety Population.

3.3.4 Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Dictionary version B3 Global, September 2021. WHO Drug Dictionary version will be updated as available. For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of CIN-107-130 study drug and concomitant medications if they were taken at any time on or after the first dose of CIN-107-130 study drug (i.e., started prior to the first dose of study drug and were ongoing or started at or after the first dose of study drug).

Counts and percentages of subjects taking prior and concomitant medications by ATC class and standardized medication name will be summarized by treatment and in total based on the Safety Population.

3.3.5 Study Drug Exposure and Compliance

Days of exposure to study drug will be calculated as date of last dose of study drug – date of first dose of CIN-107-130 study drug + 1. Note that the exposure calculation is intended to describe the length of time a subject was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarized by treatment based on the Safety Population with descriptive statistics and with counts and percentages of subjects with exposure in the following categories:

- <14 weeks (<98 days)
- 14 - <22 weeks (98 – 153 days)
- 22 - <58 weeks (154 – 405 days)
- ≥58 weeks (≥406 days)

Percent compliance to the study drug regimen will be calculated as 100 x number of actual tablets taken / number of expected tablets taken. The number of actual tablets taken will be calculated as number of tablets dispensed – number of tablets returned – number of tablets lost. If study drug is not returned, the number of tablets returned is calculated as actual number of tablets returned+ min {number of tablets not returned, max {0, number of tablets dispensed – number of actual tablets returned – number of tablets lost – number of expected tablets taken}} (i.e., the number of expected tablets returned assuming that those not returned were taken as expected). The number of tablets expected will be calculated as (date of last dose – date of first dose +1) (i.e., the number of days study drug was expected to be taken x 1 tablet). Percent compliance to the study drug regimen will be summarized by treatment based on the Safety Population with descriptive statistics and with counts and percentages of subjects with compliance in the following categories:

- <70%
- 70-120%
- >120%.

3.3.6 Background Antihypertensives Identification

Medical review will be conducted by Medpace to identify background antihypertensives. The concomitant medication records will be coded using WHO Drug Dictionary. After coding, the medical monitors will review each record and indicate medication as a background antihypertensive based on WHO Drug coding and other relevant data collected within the CRF. The provided classifications will be used in analysis.

3.4 Effectiveness Assessment

Efficacy data will be summarized based on the Safety Population.

3.4.1 Systolic Blood Pressure

Descriptive statistics will summarize mean seated SBP and mean change from baseline in SBP at baseline and each post-baseline visit in total. Mean seated SBP and ± SD will be graphed with week on the x-axis and mean change in mean seated SBP on the y-axis. Mean change

from baseline SBP and ± SD will be graphed with week on the x-axis and mean change from baseline in mean seated SBP on the y-axis.

The count and percentage of patients achieving a seated SBP response <130 mm Hg with CIN-107 monotherapy without a single background antihypertensive agent over the 52-week treatment period will be summarized in total. Any patient without a Week 52 SBP measure will be considered a non-responder.

The count and percentage of non-responders in CIN-107-124 achieving a mean seated SBP response <130 mmHg with CIN-107 without a single background antihypertensive agent and/or rescue medication will be summarized in total. The count and percentage of non-responders in CIN-107-124 achieving a mean seated SBP response <130 mmHg with CIN-107 with background antihypertensive agent and/or rescue medication will be summarized in total. Any patient without Week 52 SBP measure will be considered a non-responder.

The count and percentage of responders in CIN-107-124 maintaining a mean seated SBP response <130 mmHg with CIN-107 without a single background antihypertensive agent and/or rescue medication will be summarized in total. The count and percentage of responders in CIN-107-124 maintaining a mean seated SBP response <130 mmHg with CIN-107 with background antihypertensive agent and/or rescue medication will be summarized in total. Any patient without Week 52 SBP measure will be considered a non-responder.

Scatter plots of systolic blood pressure versus plasma concentration at Week 38 and Week 52 will be provided.

3.4.2 Diastolic Blood Pressure

Descriptive statistics will summarize mean seated DBP and mean change from baseline in DBP at baseline and each post-baseline visit in total. Mean seated DBP and ± SD will be graphed with week on the x-axis and mean change in mean seated DBP on the y-axis. Mean change from baseline in mean seated DBP and ± SD will be graphed with week on the x-axis and mean change from baseline in mean seated DBP on the y-axis. Scatter plots of diastolic blood pressure versus plasma concentration at Week 38 and Week 52 will be provided.

3.5 Pharmacodynamic Assessment

PD samplings, including blood sampling at Visits 2, 3, 4, 5, 6, and 7; and 24-hour urine collections at Visit 7 will be performed for PD parameters given in Appendix A. Blood analytes aldosterone, 18 OH corticosterone, corticosterone, 11 deoxycortisol, cortisol, 11 deoxycortisol, plasma renin activity, and NT-proB-type natriuretic peptide will be summarized in total at each post baseline visit. 24-hour urine parameters albumin excretion, aldosterone excretion, creatinine excretion, potassium excretion, protein excretion, renin excretion, and sodium excretion will be summarized.

3.6 Pharmacokinetic Assessment

Pre-dose blood samples for PK analysis will be collected at Visits 6 and 7. Concentration of CIN-107 and any measured metabolite(s) will be summarized in total at each post-baseline visit.

3.7 Safety Assessment

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

3.7.1 Adverse Events (AEs)

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 Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. MedDRA version will be updated as available. TEAEs are defined as AEs that start after the first dose of study drug.
Adverse events of special interest (AESIs) include the following:

- Events of hypotension that require clinical intervention;
- Abnormal potassium laboratory values that require clinical intervention; and
- Abnormal sodium laboratory values that require clinical intervention.

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

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

- 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 treatment-emergent serious AEs (TESAEs)
- Any TEAEs leading to discontinuation of study drug
- Any TEAEs leading to discontinuation of study
- Any AEs leading to death.

Counts and percentages of subjects and event counts will also be presented by system organ class and preferred term for each of the categories in the overview.
Summary tables including key subject information (age, sex, and race) for any serious adverse events (SAE), any SAE leading to death and any AEs leading to discontinuation of study drug will be presented.

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

3.7.2 Clinical Laboratory Tests

Blood samples for clinical laboratory tests will be collected at Weeks 1, 2, 6, 12, 24, 38, 52, and 56. Urine samples for clinical laboratory tests will be collected at Weeks 1, 2, 6, 12, 24, 38, and 52. Blood and urine samples will be processed by a central laboratory. A list of laboratory tests to be performed is included in Appendix B. Units of laboratory parameters is resented in Appendix C.

Values and changes from baseline will be presented at each scheduled visit and baseline by laboratory test.

The counts and percentages of subjects and event counts of electrolyte imbalance will be presented. Electrolyte imbalance will be defined as any abnormal value in serum chloride, potassium, sodium, or bicarbonate.

Summary of potassium categories will be presented as follow:

- <3.5 mmol/L,
- ≥3.5 - <=5.0 mmol /L,

- >5.0 - <=5.5 mmol /L,
- >5.5 - <=6.0 mmol /L,
- >6.0 - <=6.5 mmol /L,
- and >6.5 mmol/L.

Summary of potassium by visit and baseline eGFR categories (<30, >=30-<=45, >45-<=60, and >60) will be presented. Summary of sodium categories (<125mmol/L, >=125-<130 mmol/L, >=130-<135 mmol/L, >=130) by visit and baseline eGFR categories (<30, >=30-<=45, >45-<=60, and >60) will be presented. Treatment emergent laboratory parameters will be presented to describe the change in laboratory parameter values at post-baseline visits using normal range categories (low, normal, and high) where appropriate.

Box plots of potassium and sodium concentrations, and eGFR will be presented at each visit. 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, a spaghetti plot of potassium level by analysis day will be presented for patients that had a potassium measure of ≥6.0 mmol/L.
Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plots will be provided. Scatter plots of serum potassium and serum aldosterone versus plasma concentration at Week 38 and Week 52 will be provided.

3.7.3 Vital Signs

Vital signs will include height, weight, BMI, heart rate, respiratory rate, upper arm circumference and body temperature. Height will be collected at Week 1 only and will be used to calculate BMI. Orthostatic vitals will include standing BP and standing heart rate. Vital signs and BP will be measured pre-dose at Weeks 1, 2, 6, 12, 24, 38, and 52.

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.

3.7.4 Electrocardiograms

Standard 12-lead ECGs will be performed at Weeks 1 and 52.

ECGs will be performed after the patient has been resting in the supine position for at least 10 minutes and after measuring vital signs and BP. Twelve-lead ECGs will be printed and will be interpreted as soon as possible by a qualified Investigator (or Sub-Investigator) for the presence of abnormalities.

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

- QRS interval (msec);
- Heart rate (beats/min);
- PR interval (msec);
- RR interval (msec);
- QT interval (msec); and
- QTc (QTcF) (msec), where QTcF is the QT interval corrected for heart rate using Fridericia's cube root correction.

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.

A treatment emergent QTcF measurements will be summarized by the following predefined criteria:

- >450 msec,
- Change from Baseline >30 msec,
- >450 msec and change from Baseline >30 msec.

3.7.5 Physical Examinations

A complete physical examination will consist of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system at the Week 1. A limited physical examination will consist of a minimum of general appearance, skin, heart, lungs, and abdomen at Weeks 2, 6, 12, 24, 38, and 52.

Physical examination data will be listed.

3.7.6 Additional Safety Assessments

The counts and percentage of patients requiring down-titration of CIN-107 from the maximal dose of 2mg to 1mg and 0.5 mg will be presented for visit and by any visit.

The count and percentage of patients resuming a single background antihypertensive agent at Day 1, and by 3, 6, 9, and 12 months will be presented.

The count and percent of patients requiring rescue medication at Day 1, and by 3, 6, 9, and 12 months will be presented.

4 ANALYSIS TIMING

4.1 Interim Analysis

No interim analysis is planned.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

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

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: SCHEDULE OF PROCEDURES

Table 1. Schedule of Procedures – Open-Label Extension

	Treatment Period							Follow-Up
Visit[a]	1[b] (Visits 6 or 9 of Study CIN-107-124)	2	3	4	5	6	7 (EOT)/ET	8
Week	1	2	6	12	24	38	52	56
Day (±Visit Window)	1 (-)	7 (±2 days)	42 (±7 days)	84 (±7 days)	168 (±14 days)	266 (±14 days)	364 (±14 days)	392 (±14 days)
Informed consent[c]	X							
Inclusion/exclusion criteria	X[d]							
Adverse events	←----------X----------→							
Prior/concomitant medications	←----------X----------→							
Weight, height, and BMI[e]	X[d]	X	X	X	X	X	X	
Upper arm circumference	X[d]							
Vital signs, including seated BP[f]	X	X	X	X	X	X	X	X
Standing BP and heart rate[g]	X	X	X	X	X	X	X	
Complete physical examination[h]	X							
Limited physical examination[i]		X	X	X	X	X	X	
12-lead ECG[j]	X						X	
Urinalysis	X	X	X	X	X	X	X	
Standard safety chemistry panel, hematology, coagulation	X	X	X	X	X	X	X	X
Pregnancy test[k]	X						X	
PD blood sampling[l]		X	X	X	X	X	X	
PK blood sampling[m]						X	X	
Dispense/collect study drug[n]	X[d]	←----------X----------→						
Administer study drug[o]	X[d]	X	X	X	X	X	X	
Assess treatment adherence[p]		X	X	X	X	X	X	
Adherence counseling[q]	X[d]	X	X	X	X	X	X	
Provide instructions for next visit[r]	X[d]	X	X	X	X	X	X	
Provide materials for next 24-hour urine collection[s]						X		
Obtain sample from 24-hour urine collection[t]							X	

a. All clinical site visits should occur between 6:00 a.m. and 11:00 a.m. Unscheduled visits may be scheduled at any time during the study period based on the Investigator's discretion.
b. The EOT assessments at the end of Part 1 or Part 2 of Study CIN-107-124 will serve as the Day 1 pre-dose assessments for those enrolling in Study CIN-107-130.
c. Written informed consent must be obtained before any Protocol-specific procedures are performed.
d. Procedure to be completed pre-dose on Day 1 of Study CIN-107-130.
e. Height will be collected at enrollment (Visit 1) only and will be used to calculate BMI at subsequent visits. See Section 8.12 for details on body measurements.
f. The patient should be seated for at least 5 minutes in the examination room before measurement of vital signs and BP. Vital signs and BP will be measured pre-dose using the standardized procedures listed in Section 8.9.
g. 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 (orthostatic vital signs) measurement will be obtained.
h. A complete physical examination will consist of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system.
i. A limited physical examination will consist of a minimum of general appearance, skin, heart, lungs, and abdomen.
j. Perform 12-lead ECG after the patient has been resting in the supine position for at least 10 minutes and after measuring vital signs and BP.
k. For female patients of childbearing potential (ie, ovulating, pre-menopausal, and not surgically sterile), perform serum pregnancy tests at enrollment (Visit 1) and EOT (Visit 7)/ET.
l. Pre-dose blood samples for PD analysis will be collected at specified visits. See Section 7.2.1 for details of blood sample collection for PD analysis.
m. Pre-dose blood samples for PK analysis will be collected within approximately 15 minutes prior to dosing. See Section 7.3 for details of blood sample collection for PK analysis.
n. Study drug dispensation may occur at any time starting at enrollment (Visit 1) and before EOT (Visit 7). A Study Reference Manual with details of study drug dispensation and collection of unused study drug will be provided to clinical sites.
o. On clinical site visit days, patients will self-administer the morning dose of any other concomitant medications (if applicable) at home. CIN-107 should be withheld as it will be self-administered at the clinical site and witnessed by site staff, after completion of pre-dose evaluations and laboratory sampling. Between clinical site visits, patients will continue to self-administer CIN-107 QD by mouth at approximately the same time each morning.
p. Site staff will calculate treatment adherence based on pill counts.
q. Site staff will counsel patients about the importance of adhering to the following: study drug, background antihypertensive regimen (if applicable).
r. Instruct patients to take their scheduled morning doses of the antihypertensive medication(s) at home and to hold their dose of CIN-107 on the morning of their next visit. Instruct patients to bring their antihypertensive medication(s) and study drug to all clinical site visits for pill counts. Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical site visit.
s. Clinical sites will provide patients with a 24-hour urine collection kit at Visit 6. Patients will be instructed to start the collection up to 3 days prior to Visit 7, refrigerate the collected sample, and bring the entire sample to the clinical site at Visit 7. A 24-hour urine collection will commence after the first morning void on the first day and will include the first morning void on the second day for a total duration of 24 (±2) hours. Patients must be instructed to keep the sample refrigerated at all times except during their transit to the clinical site.
t. A 24-hour urine collection may be repeated if the Investigator suspects that the sampling is insufficient and the patient is within the visit window. Clinical sites will aliquot urine into a transfer tube and send it to the Central Laboratory.

BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; EOT = End of Treatment; ET = Early Termination; PD = pharmacodynamic(s); PK = pharmacokinetic(s); QD = once daily.

APPENDIX B: CLINICAL LABORATORY ANALYTES

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 [1]
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid

1. Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation:
   Estimated glomerular filtration rate (mL/min/1.73 m^2) = $141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) × 1.159 (if Black), where, min indicates the minimum of SCr/κ or 1, SCr is standardized serum creatinine in mg/dL, κ is 0.7 (females) or 0.9 (males); α is -0.329 (females) or -0.411 (males); and max indicates the maximum of SCr/κ or 1.
   Source: Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate [published correction appears in Ann Intern Med. 2011;155(6):408]. *Ann Intern Med.* 2009;150(9):604-612.

Endocrinology

β-human chorionic gonadotropin [1]

1. Serum pregnancy tests will be performed only for female patients of childbearing potential (ie, ovulating, pre-menopausal, and not surgically sterile).

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count

White blood cell count and differential [1]

1. Manual microscopic review will be performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

1. Microscopy will be performed only as needed based on positive dipstick test results.

Coagulation

Activated partial thromboplastin time	International normalized ratio
Prothrombin time	

Pharmacodynamic Analytes

Aldosterone and its precursors [1] (18-hydroxycorticosterone, corticosterone, and 11-deoxycorticosterone)	Cortisol [2] and its precursor 11-deoxycortisol
NT-proB-type natriuretic peptide	Plasma renin activity [1]

1. Analyte will be used to calculate aldosterone/plasma renin activity ratio.
2. Total cortisol will be measured. Measurement of free cortisol will be performed if changes are noted in total cortisol.

Pharmacokinetic Analytes

CIN-107	Any measured metabolite(s) of CIN-107

Twenty-Four-Hour Urine Collection Analytes

Albumin	Aldosterone
Creatinine	Potassium
Protein	Renin
Sodium	

APPENDIX C: CLINICAL LABAROTARY PARAMETER UNITS

Parameter	**Unit**
Activated Partial Thromboplastin Time	Sec
Alanine Aminotransferase	U/L
Albumin	g/L
Alkaline Phosphatase	U/L
Amylase	U/L
Aspartate Aminotransferase	U/L
Bacteria	per HPF
Basophils	10^9/L
Basophils/Leukocytes	%
Bicarbonate	mmol/L
Bilirubin	µmol/L
Calcium	mmol/L
Chloride	mmol/L
Choriogonadotropin Beta	IU/L
Creatine Kinase	U/L
Creatinine	µmol/L
Eosinophils	10^9/L
Eosinophils/Leukocytes	%
Ery. Mean Corpuscular HGB Concentration	g/L
Ery. Mean Corpuscular Hemoglobin	pg
Ery. Mean Corpuscular Volume	fL
Erythrocytes	10^12/L
Gamma Glutamyl Transferase	U/L
Glomerular Filtration Rate	mL/min/1.73m²

Glucose	mmol/L
Granular Casts	per LPF
Hematocrit	1
Hemoglobin	g/L
Hyaline Casts	per LPF
Ketones	mmol/L
Lactate Dehydrogenase	U/L
Leukocyte Esterase	Leu/µL
Leukocytes	per HPF
Lipase, Pancreatic	U/L
Lymphocytes	10^9/L
Lymphocytes/Leukocytes	%
Monocytes	10^9/L
Monocytes/Leukocytes	%
Mucous Threads	per HPF
Neutrophils	10^9/L
Neutrophils/Leukocytes	%
Occult Blood	µmol/L
Phosphate	mmol/L
Platelets	10^9/L
Potassium	mmol/L
Protein	g/L
Prothrombin Time	Sec
Sodium	mmol/L
Squamous Epithelial Cells	per HPF

Transitional Epithelial Cells	per HPF
Urate	µmol/L
Urea Nitrogen	mmol/L
Urobilinogen	µmol/L
Yeast Cells	per HPF
Amorphous Crystals	Sec
Amylase	U/L