MEDPACE

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Multiple Dose Strengths of CIN-107 as Compared to Placebo After 8 Weeks of Treatment in Patients with Uncontrolled Hypertension
Protocol Number:	CIN-107-124
Protocol Version/Date:	V3.0 / 25 February 2022
Investigational Product:	CIN-107
Sponsor:	CinCor Pharma, Inc. 230 Third Avenue, 6th Floor Waltham, MA 02451 United States Telephone: [redacted]
SAP Version/Date:	V1.0 / 07 Oct 2022

SIGNATURE PAGE

Protocol Title:	A Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Multiple Dose Strengths of CIN-107 as Compared to Placebo After 8 Weeks of Treatment in Patients with Uncontrolled Hypertension
Protocol Number:	CIN-107-124
SAP Version/Date:	V1.0 / 07 Oct 2022

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

Signature		**Date**
[redacted]		07-Oct-2022
Medpace, Inc.		
[redacted]		07-Oct-2022
CinCor Pharma, Inc		
[redacted]		07-Oct-2022
CinCor Pharma, Inc.		

VERSION HISTORY

Version	Version Date	Description
1.0	07-Oct-2022	Original signed version

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACEi	Angiotensin converting enzyme inhibitor
ACEi/ARB	Angiotensin converting enzyme inhibitor or angiotensin II receptor blocker
ADaM	Analysis Data Model
AE	Adverse event
ANCOVA	Analysis of covariance
ARB	Angiotensin II receptor blocker
ARR	Aldosterone-to-renin ratio
ATC	Anatomical therapeutic chemical
BP	Blood Pressure
CCB	Calcium channel blocker
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRF	Case report form
CSR	Clinical Study Report
DBP	Diastolic blood pressure
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
EGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
HTN	Hypertension
IRT	Interactive response technology
ITT	Intent-to-Treat
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
MTD	Maximum tolerated dose
OLE	Open label extension
PD	Pharmacodynamics
PGx	Pharmacogenomic
PK	Pharmacokinetics
PP	Per-protocol
PRA	Plasma renin activity
QD	Once daily
REML	Restricted maximum likelihood
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard deviation
SDTM	Study Data Tabulation Model
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event

Abbreviation	Definition
TFL	Table, figure, and listing
ULOQ	Upper limit of quantification
WHO	World Health Organization
WHR	Waist-to-hip ratio

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-107-124 entitled "A double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of multiple dose strengths of CIN-107 as compared to placebo after 8 weeks of treatment in patients with uncontrolled hypertension". 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 demonstrate that at least 1 dose strength of CIN-107 is superior to placebo for the change from baseline in mean seated systolic blood pressure (SBP) after 8 weeks of treatment (Part 1) in patients with uncontrolled hypertension (HTN) receiving background antihypertensive agent(s) that are either an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker (ACEi/ARB), an ACEi/ARB plus a thiazide diuretic, or an ACEi/ARB plus a calcium channel blocker (CCB).

2.1.2 Secondary Objectives

The secondary objectives are to evaluate the following parameters in the study population of individuals with uncontrolled hypertension:

- The change from baseline in mean seated diastolic blood pressure (DBP) with each of the selected dose strengths of CIN-107 compared to placebo after 8 weeks of treatment (Part 1);
- The change from baseline in 24-hour urine aldosterone and serum aldosterone levels with each of the selected dose strengths of CIN-107 compared to placebo after 8 weeks of treatment (Part 1);
- The percentage of patients achieving a mean seated SBP <130 mmHg ("responders") with each of the selected dose strengths of CIN-107 compared to placebo after 8 weeks of treatment (Part 1); and
- The change from baseline in 24-hour urine renin and serum renin levels with CIN-107 compared to placebo after 8 weeks of treatment (Part 1).

2.1.3 Exploratory Objectives

The exploratory objectives are to evaluate the following:

- The relation between baseline plasma renin, aldosterone, and the aldosterone-to-renin ratio (ARR) and the SBP response to CIN-107;

- The change in 24-hour urine aldosterone and serum aldosterone levels from values measured at the end of Part 1 to those measured following 4 weeks of treatment with CIN-107 2 mg dose strength and no background antihypertensive agent(s) at the end of Part 2; and
- The percentage of patients maintaining a mean seated SBP <130 mmHg ("responders") when treated with CIN-107 2 mg dose strength alone and no background antihypertensive agent(s) for 4 weeks during Part 2.

2.1.4 Safety Objectives

The safety objectives are the following:

- Vital signs, standing blood pressure (BP) and heart rate, physical examinations, electrocardiogram (ECG), body weight, and clinical laboratory assessments, including standard safety chemistry panel, hematology, coagulation, and urinalysis;
- Treatment-emergent adverse events (TEAEs);
- Treatment-emergent serious adverse events (TESAEs);
- TEAEs leading to premature discontinuation of study drug;
- Treatment-emergent marked laboratory abnormalities; and
- Change from seated to standing (ie, orthostatic) SBP (measured pre-dose at the clinical site) from baseline to End of Treatment (EOT) (Visit 9).

2.1.5 Pharmacokinetic-Pharmacodynamic Objectives

The pharmacokinetic (PK)-pharmacodynamic (PD) objectives for both Parts 1 and 2 are to evaluate the exposure-response relationships of CIN-107 using measures of safety, PD, and/or efficacy.

2.2 Study Design

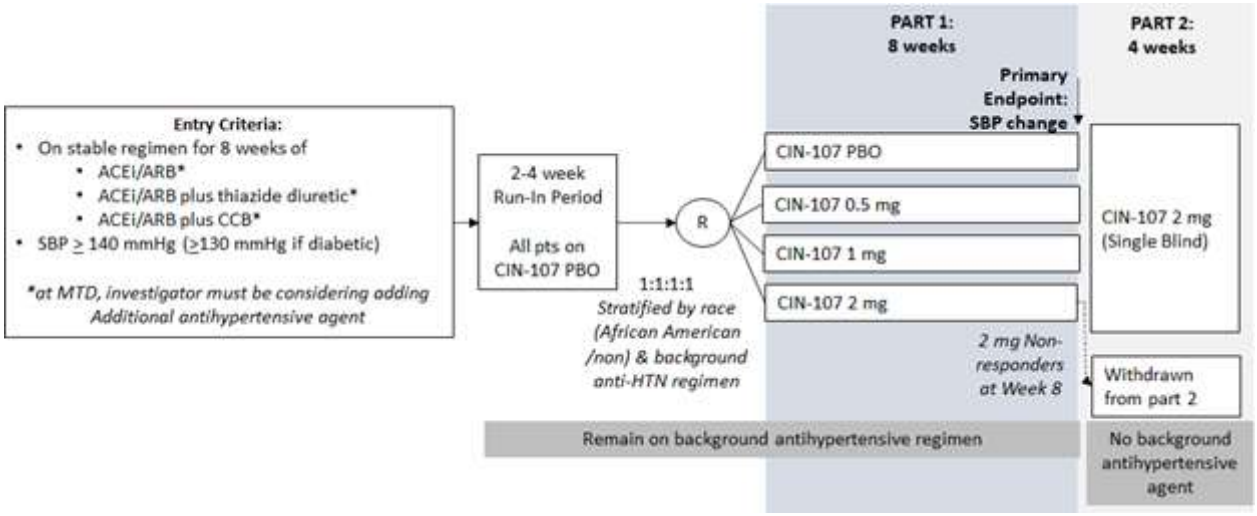
2.2.1 Overview

This is a Phase 2, randomized, multicenter study to evaluate the efficacy and safety of multiple dose strengths of CIN-107 in the treatment of patients with HTN. To be considered for study participation, patients must have uncontrolled HTN (mean seated SBP ≥ 140 mmHg [or ≥130 mmHg if diabetic]) despite being on a stable regimen of an ACEi/ARB inhibitor or a combination drug of an ACEi/ARB plus a thiazide diuretic or an ACEi/ARB plus a CCB background antihypertensive agents at the maximum tolerated dose (MTD) (in the opinion of the Investigator) for at least 8 weeks and would be considered a candidate for addition of a second or third antihypertensive agent at the time of Screening. At least 212 patients are expected to complete the study across approximately 75 clinical sites in the United States.

Patients that were enrolled under version 1.0 or 2.0 of the protocol were required to have uncontrolled HTN, a higher serum aldosterone and were receiving 1 background antihypertensive agent (Part 1), where acceptable classes of antihypertensive agents being used as primary treatment for systemic HTN included ACEis/ARBs, CCBs, and diuretics (other than mineralocorticoid receptor antagonists or potassium sparing diuretics).

During the study, patients will complete between 8 to 10 scheduled visits, including 7 to 9 clinical site visits and 1 telephone visit. Unscheduled visits may be scheduled at any time during the study based on Investigator's discretion. The study will consist of the following periods/visits:

- A Screening Period of at least 4 weeks consisting of:
  - A Screening Visit (Visit 1);
  - A Telephone Visit to convey patient eligibility for the study; and
  - A Run-In Period up to 4 weeks before randomization (Visit 2), to confirm the patient's adherence to their background antihypertensive medication(s) and placebo.
- A 2-part Treatment Period consisting of:
  - Part 1: A double-blind Treatment Period of 8 weeks (Weeks 1 to 8; Visits 2 to 6); and
  - Part 2: A Treatment Period of 4 weeks (Weeks 9 to 12; Starting the day after Visit 6 through Visit 9).
- A Safety Follow-Up Period (Visit 10) of approximately 2 weeks after the last dose of study drug.



Note: The primary endpoint (change in mean seated SBP from baseline compared to placebo) will be obtained at the end of Part 1 (Week 8).
Note: Patients who complete the study through the end of Part 2 or who were considered withdrawn at the end of Part 1 may be eligible to enter a separate open label extension (OLE) study (Study CIN-107-130).
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; MTD = maximum tolerated dose; PBO = placebo; R = randomization; SBP = systolic blood pressure.

Eligible patients will be instructed to begin the Run-In Period where they will take a placebo tablet once daily (QD) in addition to their background antihypertensive agent(s) until Visit 2. A patient who demonstrates treatment adherence (see protocol Section 4.1; Inclusion Criterion 4) and continues to satisfy all inclusion criteria and none of the exclusion criteria at Visit 2 will be randomized and enter the Part 1 Treatment Period.

During the double-blind Part 1 Treatment Period (Weeks 1 to 8; Visits 2 to 6), patients will be randomized (1:1:1:1) to 1 of 4 treatment arms: 0.5 mg CIN-107, 1 mg CIN-107, 2 mg CIN-107, or placebo, as add-on medications to their background antihypertensive agent(s).

During the Part 2 Treatment Period (Weeks 9 to 12; starting the day after Visit 6 and running through Visit 9), all responders (defined as achieving a mean seated SBP < 130 mmHg) at the end of Part 1 will move into Part 2. They will receive CIN-107 2 mg tablets (maximum in this study) and discontinue their background antihypertensive regimen. Non-responders who

received any study drug except 2 mg CIN-107 in Part 1 will move into Part 2, receive the 2 mg dose of CIN-107, and discontinue their background antihypertensive agent(s). A non-responder who decides not to participate in Part 2, or has already received the maximum dose strength (2 mg) of CIN-107 in Part 1, will be considered withdrawn from the study drug and should complete their EOT (Visit 9) procedures at the end of Part 1 (Visit 6) and the 2-week Safety Follow-Up. The subject may be offered to participate in the open-labeled extension (OLE) study CIN-107-130 if the investigator determines that it is safe for the patient.

During Safety Follow-Up (Visit 10), patients will be evaluated for vital signs, clinical laboratory assessments, adverse events (AEs), and concomitant medication use including antihypertensive regimen since study completion.

Patients who complete the study through Visit 9 or who were considered withdrawn at the end of Part 1 (Visit 6) may be eligible to enter a separate open label extension (OLE) study (Study CIN-107-130). These patients will not need to complete the Safety Follow-Up Period/Visit 10.

2.2.2 Randomization and Blinding

Patients who continue to be eligible during Visit 2 will be randomized 1:1:1:1, using an automated Interactive Response Technology (IRT) system, to 1 of the 4 treatment arms: 0.5 mg CIN-107, 1 mg CIN-107, 2 mg CIN-107, or placebo. Patient randomization will be stratified according to their race (African American versus non-African American) and the type of background antihypertensive regimen. A total of 50 to 100 patients are allowed in each of the three antihypertensive groups so that the population taking these antihypertensive agents will be adequately represented. The IRT will not allow any new screening to be registered if a patient is in the background antihypertensive agent group that has been fully enrolled. Because the study will be conducted in multiple investigative sites and will involve variable numbers of patients at different stages of enrollment, eligible patients who have started taking run-in drug will be allowed to continue even if the background antihypertensive agent group they belong to has been fully enrolled, and, if qualified, be randomized at visit 2.

Patients will receive either their assigned dose strength of CIN-107 or matching placebo as oral tablets in a double-blind manner during the Part 1 Treatment Period. During the Part 2 Treatment Period (Weeks 9 to 12; starting the day after Visit 6 and running through Visit 9), all responders (defined as achieving a mean seated SBP < 130 mmHg) at the end of Part 1 will move into Part 2. They will receive CIN-107 2 mg tablets (maximum in this study) and discontinue their background antihypertensive agent(s). Non-responders who received any study drug except 2 mg CIN-107 in Part 1 will move into Part 2, receive the 2 mg dose of CIN-107, and discontinue their background antihypertensive agent(s). A non-responder who decides not to participate in Part 2 or has already received the maximum dose strength (2 mg) of CIN-107 in Part 1, will be considered withdrawn from the study drug, and should complete their EOT (Visit 9) procedures at the end of Part 1 (Visit 6) and the 2-week Safety Follow-Up. The subject may be offered to participate in the open-labeled extension (OLE) study CIN-107-130 if the investigator determines that it is safe for the patient.

The Sponsor, Investigators, and study team will be blinded to the treatment group of each patient, and patients will also be blinded to the treatment they receive during Part 1. The randomization information will be concealed until at least the end of Part 1 or during an emergency situation involving a patient that requires unblinding of the treatment assignment

(see protocol Section 5.4). Management of unblinded information will be described in a separate Blinding Plan and DSMB Charter.

2.2.3 Study Drug

For the Run-In Period, all patients will self-administer 1 tablet of single-blind placebo QD by mouth at approximately the same time each morning.

During clinical site visits for the Treatment Period (Parts 1 and 2), patients will self-administer 1 tablet of study drug in the clinic to be witnessed by site staff, after completion of pre-dose evaluations and laboratory sampling.

Between clinical site visits, patients will continue to self-administer 1 tablet of study drug QD by mouth at approximately the same time each morning.

2.2.4 Sample Size Determination

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the change from baseline in mean seated SBP after 8 weeks of treatment in patients with uncontrolled HTN (Part 1).

2.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study in the same population as that described for the primary endpoint are as follows:

- The change from baseline in mean seated DBP with CIN-107 compared to placebo after 8 weeks of treatment (Part 1); and
- The change from baseline in 24-hour urine aldosterone and serum aldosterone levels with CIN-107 compared to placebo after 8 weeks of treatment (Part 1); and
- The percentage of patients achieving a mean seated SBP <130 mmHg (“responders”) with CIN-107 compared to placebo after 8 weeks of treatment (Part 1; Weeks 1 to 8); and
- The change from baseline in 24-hour urine renin and serum renin levels with CIN-107 compared to placebo after 8 weeks of treatment (Part 1).

2.3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints of this study are as follows:

- The changes from baseline on mean seated SBP with CIN-107 over time by baseline plasma renin, aldosterone, and ARR
- The change in 24-hour urine aldosterone and serum aldosterone levels from values measured at the end of Part 1 to those measured following 4 weeks of treatment with CIN-107 2 mg dose strength and no background antihypertensive agent(s) at the end of Part 2; and
- The percentage of patients maintaining a mean seated SBP <130 mmHg ("responders") when treated with CIN-107 2 mg alone and no background antihypertensive agent(s) for 4 weeks during Part 2.

2.3.4 Pharmacodynamic Assessments

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 aldosterone/PRA ratio (Appendix B).

2.3.4.1 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. Samples will be analyzed using validated methods, as appropriate. Samples will be obtained after vital signs have been measured and prior to dosing of Study Drug.

2.3.4.2 24-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. The analytes that will be measured in the 24-hour urine collection samples are provided Appendix B.

2.3.5 Pharmacokinetic Assessments

Pre-dose blood samples for PK analysis will be collected within approximately 30 minutes prior to dosing at the visits specified in Appendix A. PK variables analyzed during the study will include plasma concentrations of CIN-107 and any measured metabolite(s) (Appendix B).

2.3.6 Pharmacogenomic Assessments

A single, optional, pharmacogenomic (PGx) blood sample may be collected at any time during the Treatment Period. The PGx 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. The PGx 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. If analysis of the PGx samples is undertaken, details of sample and data analyses will be provided in a separate protocol and/or analysis plan.

2.3.7 Safety Assessments

The safety endpoints of the study are as follows:

- Vital signs, standing BP and heart rate, physical examinations, ECG, body weight, and clinical laboratory assessments, including standard safety chemistry panel, hematology, coagulation, and urinalysis;
- TEAEs
- TESAEs
- TEAEs leading to premature discontinuation of study drug
- Treatment-emergent marked laboratory abnormalities; and
- Change from seated to standing (ie, orthostatic) SBP (measured pre-dose at the clinical site) from baseline to EOT (Visit 9).

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of double-blind study drug. The day of the first dose of double-blind 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

Scheduled visits will be assigned to analysis visits as recorded on the case report form (CRF). Unscheduled visits recorded on the CRF will not be re-assigned and will remain labeled as unscheduled. Unscheduled visits will be presented in by-patient listings. Early termination visits will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 1	1	1	1
Week 2	14	2	18
Week 4	28	19	35
Week 6	42	36	49
Week 8	56	50	60
Week 9	63	61	67
Week 10	70	68	77
Week 12	84	78	>78

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.

3.1.3 Definition of Baseline

Measurements recorded at randomization (Visit 2) will constitute Part 1 baseline measurements. If missing, the last non-missing assessment prior to first dose of study drug will constitute Part 1 baseline measurements.

Measurements recorded at Week 8 (Visit 6) will constitute Part 2 baseline measurements.

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

A significance level of 0.05 will be used for hypothesis tests. To protect the overall alpha level on the primary endpoint, the hypothesis testing will be performed sequentially. The first comparison will be between the highest active dose group and placebo at a 2-sided alpha = 0.05 level; if significant, the next highest active dose group will be compared to placebo at the 2-sided alpha = 0.05 level. Hypothesis testing will proceed in this step-down fashion until a comparison is not significant. At that point, all remaining sequential tests will be deemed not significant. No adjustment will be made for multiplicity in testing the secondary and exploratory efficacy endpoints.

3.1.6 Evaluation of Site Effect

Sites will not be pooled for any planned inferential analysis but may be pooled for subgroup analysis to assess the heterogeneity of treatment effects among pooled sites. The final pooling algorithm, if needed, will be specified before treatment unblinding and will be provided as an addendum to the SAP. Additionally, a review of by-site effects will be performed in the context of data listing review.

3.1.7 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 for any analyses performed.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The ITT Population will include all patients randomized into the study. Treatment classification will be based on the randomized treatment.

3.2.2 Modified ITT (mITT) Population

The mITT Population will include all patients in the ITT Population who receive at least 1 dose of any study drug and have a baseline value for the SBP assessment. Treatment classification will be based on the randomized treatment. The mITT Population will be used for the primary analysis of all efficacy endpoints.

3.2.3 Per-Protocol (PP) Population

The PP Population will include all patients in the mITT Population who have a baseline value for the SBP assessment, have a Week 8 (Visit 6) value for the SBP assessment, and who do not experience a major protocol deviation that could potentially impact the primary efficacy endpoint. The PP Population, along with the reason for exclusion, will be finalized prior to study unblinding.

3.2.4 Safety Population

3.2.4.1 Safety Population Part 1

The Safety Population Part 1 will include all patients who receive at least 1 dose of any study drug in Part 1. Treatment classification will be based on the actual treatment received.

3.2.4.2 Safety Population Part 2

The Safety Population Part 2 will include all patients who receive at least 1 dose of study drug in Part 2. Treatment classification will be based on the actual treatment received. PK Population

3.2.5 Pharmacokinetic Population

3.2.5.1 PK Population Part 1

The PK Population Part 1 will include all patients in the mITT Population who have at least 1 quantifiable post-randomization plasma concentration in Part 1.

3.2.5.2 PK Population Part 2

The PK Part 2 Population will include all patients in the mITT Population who have at least 1 quantifiable post-randomization concentration in Part 2.

3.2.6 PD Population

3.2.6.1 PD Population Part 1

The PD Population Part 1 will include all patients in the mITT Population who have at least 1 quantifiable concentration of any PD variable in Part 1.

3.2.6.2 PD Population Part 2

The PD Population Part 2 will include all patients in the mITT Population who have at least 1 quantifiable concentration of any PD variable in Part 2.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of subjects who were screened (signed informed consent) and discontinued early during screening (screen failures)will be summarized in total based on all screened subjects. Reasons for screen failure will also be summarized.

Counts and percentages of subjects who were randomized (entered Part 1), completed Part 1, entered Part 2, and completed Part 2 will be summarized by treatment and in total based on all randomized subjects. Reasons for early discontinuation will also be summarized for Part 1 and Part 2, separately.

3.3.2 Protocol Deviations

Protocol deviations will be identified based on the clinical data 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 by treatment and in total based on all randomized subjects. A listing of CSR-reportable protocol deviations will be generated.

3.3.3 Analysis Populations

Counts and percentages of subjects in each analysis population will be summarized by treatment and in total based on all randomized subjects. Reasons for exclusion from each analysis population will also be summarized.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, ≥65 years; and ≤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)
- Background antihypertensive regimen (ACEi/ARB and CCB, ACEi/ARB and thiazide diuretic, monotherapy with either ACEi/ARB, CCB, or a thiazide diuretic, Other)
- Diabetes on entry
- Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73m^2) and eGFR categories (<45 mL/min/1.73m^2, ≥45 mL/min/1.73m^2)
- 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)
- Mean seated SBP (<145 mm Hg, ≥145 mm Hg)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment and in total for all randomized subjects and each defined analysis population.

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 24.0. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment and in total based on all randomized subjects.

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 B3 Global, March 2021. 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 after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

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

Counts and percentages of subjects taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment and in total 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 Part 2 separately. Within treatment 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 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 categories.

Part 1 categories:

- <4 weeks (<28 days)
- 4 - <8 weeks (28 - 55 days)
- 8 - <12 weeks (56 – 83 days)
- ≥12 weeks (≥84 days)

Part 2 categories:

- <2 weeks (<14 days)
- 2 - <4 weeks (14 - 27 days)
- 4 - <6 weeks (28 – 41 days)
- ≥6 weeks (≥42 days)

Percent compliance to the study drug regimen will be calculated as

$$100 \times \frac{\textit{number of actual tablets taken}}{\textit{number of expected tablets taken}}$$

If study drug kit is not returned, the number of tablets taken will be considered as the minimum of either the number of tablets dispensed, or the expected number of tablets taken from the time tablets were dispensed to the end of treatment part. The number of tablets returned will be calculated as:

number of tablets dispensed - min{*number of tablets dispensed*, *end of treatment part date* – *date dispensed* +1}

The number of analysis tablets taken will be calculated as:

number of tablets dispensed – number of tablets returned – number of tablets lost

Within treatment part, the number of capsules 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 per day).

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%

3.4 Efficacy Assessment

Efficacy data will be summarized by randomized treatment based on the mITT Population. The primary efficacy endpoint will also be summarized based on the ITT Population and the PP Population.

3.4.1 Primary Efficacy Endpoints

Primary Analysis

The primary efficacy analysis will compare the change in mean seated SBP from baseline (Visit 2) to the end of Part 1, Week 8 (Visit 6), between each dose strength of CIN-107 and placebo. Mean seated SBP is measured at the randomization visit (Visit 2) and 4 post-baseline visits in Part 1: Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), and Week 8 (Visit 6). The primary analysis will be based on the mITT Population.

A mixed model for repeated measures (MMRM) will be used to perform this analysis. The analysis will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with covariates of the baseline value, race (African American versus non-African American), and the type of background antihypertensive regimen. The restricted maximum likelihood estimation (REML) approach will be used with the degrees of freedom approximated using the Kenward Rogers approach. The model will be fit with an unstructured covariance matrix. If the model fails to converge, a simpler covariance structure with fewer parameters will be used according to the following order: Toeplitz (TOEPH), first-order autoregressive [AR(1)], heterogeneous compound symmetry (CSH), and compound symmetry (CS).

The primary estimand will correspond to a treatment policy estimand. The target population will comprise participants who are randomized into the study, receive at least 1 dose of any study drug, and have a baseline value for the SBP assessment. The primary summary measure to access the treatment effect will be the LS mean difference for the primary endpoint between CIN-107 and placebo based on the mixed model for repeated measures methodology. The primary estimand will be addressed using the in-study observation period (ie, including data collected post-treatment discontinuation or post-prohibited medication use). Missing data for the primary efficacy analysis will be based on the assumption the data are missing at random and will not be imputed.

The least squares (LS) means, standard errors, and 2-sided 95% confidence intervals (CIs) for each treatment group and for pairwise comparisons of each dose strength of CIN-107 to the placebo group will be provided.

Example SAS® code for performing this analysis as follows:

[redacted]

To protect the overall alpha level on the primary endpoint, a fixed-sequence testing procedure will be implemented. The hypothesis testing will be performed sequentially. The first comparison will be between the highest active dose group and placebo at the 2-sided alpha=0.05 level; if significant, the next highest active dose group will be compared to placebo at the same 2-sided significance level. Hypothesis testing will proceed in this step-down fashion until a comparison is not significant. At that point, all remaining tests will be deemed not significant.

Secondary Analyses

The primary analysis model will also be used to estimate the difference between treatment groups at each of the other 4 post-baseline visits in Part 1: Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), and Week 8 (Visit 6). The estimated difference between each dose strength of CIN-107 and placebo, its 95% CI, and its associated p-value will be presented for each visit. No adjustments will be made for multiplicity.

Descriptive statistics will summarize mean seated SBP at each post-baseline visit by treatment group. Statistics will be calculated for all patients who had a measurement at the visit. Mean change from baseline in mean seated SBP and ± SD for each treatment group will be graphed with week on the x-axis and mean change from baseline in mean seated SBP on the y-axis.

Sensitivity Analyses

To assess the robustness of the primary analysis results, the following sensitivity analyses will be performed:

1. The primary analysis will be repeated on the ITT Population and PP Population. These analyses will use a modification of the primary efficacy SAS code.
2. Missing data will be imputed based on a pattern mixture model that uses a multiple imputation technique analyzed with analysis of covariance (ANCOVA). If appropriate, based on the number of retrieved dropouts, missing measurements of non-retrieved dropouts will be modeled by known measurements from retrieved dropouts (ie, participants who remain in the trial after treatment discontinuation) in the same treatment group. If the number of retrieved dropouts is insufficient then control (placebo) based reference will be implemented.

   The outcome variable will be imputed at consecutive visits in a sequential (chain) manner. Initially, 25 data sets will be imputed for non-monotone missing values in the original data set. Then, a monotone imputation method will be used to impute the remaining missing

data. Upon completion of the trial, if the percentage of cases with incomplete data is larger than initially anticipated then the number of imputations will be increased for the final analysis.

Example SAS® code for performing the non-monotone analysis is as follows:

[redacted]

For the monotone imputation method, at the first post-baseline visit (Week 2), the data will be split into two groups as follows: (1) all retrieved dropout patients and active treatment patients that had missing Week 2 mean SBP values; and (2) all active treatment patients who did not have missing Week 2 mean SBP values. The variables for the imputation model for the first group of patients will consist of baseline mean seated SBP, race, and background antihypertension regimen values from baseline and Week 2. The imputation will make no direct use of observed data from the active treatment arms and the imputation model will be based solely on the observed data from the retrieved dropouts. In this manner, missing data at the first time point for all patients without a Week 2 value will be estimated from the retrieved dropout patients.

[redacted]

The data sets from the two patient groups at the first time point will be combined and then the data will be split into two groups as follows: (1) all retrieved dropout patients and active treatment patients that had missing Week 4 mean SBP values; and (2) all active treatment patients who did not have missing Week 4 mean SBP values. The variables for the imputation model for the first group of patients will consist of race, background antihypertension regimen, baseline SBP, Week 2, and Week 4. Once again, the imputation will make no direct use of observed data from the active treatment arms and the imputation model will be based solely on the observed data from the retrieved dropouts.

The data sets from the two patient groups will be combined as before. The process will be repeated as described previously such that missing data will be imputed and the data sets combined for the Week 6 and Week 8 time points, respectively. The final database will contain 25 imputed data sets with no missing values. For each imputation data set, the change from baseline in mean seated SBP will be analyzed using ANCOVA with fixed effects of treatment group and covariates of baseline value, race and background antihypertensive regimen.

The results will be combined using Rubin's method to construct the treatment estimates using the parameter estimates and associated standard errors.

3. The primary efficacy endpoint will be analyzed using an ANCOVA model with fixed effects of treatment group and covariates of baseline value, race and background antihypertensive regimen. Only observed data will be used in the analysis model with no imputation for missing data.

   The LS means for change in mean seated SBP, standard errors, 2-sided p-values, and 2-sided 95% CIs will be presented for each treatment group and for pairwise comparisons of each dose strength of CIN-107 to the placebo group.

   Example SAS® code for performing this analysis as follows:

[redacted]

4. The primary efficacy endpoint will be analyzed using an ANCOVA model with fixed effects of treatment group and covariates of baseline value, race and background antihypertensive regimen. Missing data will be imputed using last observation carried forward (LOCF) method.

   The LS means for change in mean seated SBP, standard errors, 2-sided p-values, and 2-sided 95% CIs will be presented for each treatment group and for pairwise comparisons of each dose strength of CIN-107 to the placebo group.

3.4.2 Secondary Efficacy Endpoints

3.4.2.1 Diastolic Blood Pressure

The difference in mean seated DBP from baseline to Week 8 (Visit 6) will be analyzed using an MMRM model similar to the primary efficacy analysis. Mean seated DBP is measured at the randomization visit (Visit 2) and 4 post-baseline visits in Part 1: Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), and Week 8 (Visit 6).

The analysis will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with covariates of the baseline value, race, and background antihypertensive regimen. The restricted maximum likelihood estimation (REML) approach will be used with the degrees of freedom approximated using the Kenward Rogers approach. The model will be fit with an unstructured covariance matrix. If the model fails to converge, a simpler covariance structure with fewer parameters will be used according to the following order: Toeplitz (TOEPH), first-order autoregressive [AR(1)], heterogeneous compound symmetry (CSH), and compound symmetry (CS). Missing observations will be considered missing at random and will not be imputed.

The LS means, standard errors, and 2-sided 95% CIs for change in mean seated DBP for each treatment group and for pairwise comparisons of each dose strength of CIN-107 to the placebo group will be provided. No adjustment will be made for multiplicity.

Descriptive statistics will summarize mean seated DBP at each visit by treatment group at each post-baseline visit. Statistics will be calculated for all patients who had a measurement at the visit. Mean change in mean seated DBP and ± SD for each treatment group will be graphed with week on the x-axis and mean change in mean seated DBP on the y-axis.

3.4.2.2 Serum Aldosterone and Renin

The difference in mean serum aldosterone levels from baseline (Visit 2) to Week 8 (Visit 6) between each dose strength of CIN-107 and placebo will be evaluated. The difference in mean serum renin levels from baseline (Visit 2) to Week 8 (Visit 6) between each dose strength of CIN-107 and placebo will be similarly evaluated. Serum Aldosterone and serum renin are measured at the randomization visit (Visit 2), Week 4 (Visit 4), and Week 8 (Visit 6).

MMRM will be used to perform these analyses. The analyses will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with covariates of the baseline value, race, and background antihypertensive regimen. The restricted maximum likelihood estimation (REML) approach will be used with the degrees of freedom approximated using the Kenward Rogers approach. The model will be fit with an unstructured covariance matrix. If the model fails to converge, a simpler covariance structure with fewer parameters will be used according to the following order: Toeplitz (TOEPH), first-order autoregressive [AR(1)], heterogeneous compound symmetry (CSH), and compound symmetry (CS). Missing observations will be considered missing at random and will not be imputed.

LS means for change in mean serum aldosterone, standard errors, and 2-sided 95% CIs for each treatment group and for pairwise comparisons of each dose strength of CIN-107 to the placebo group will be provided. No adjustment will be made for multiplicity. Descriptive statistics will summarize mean serum aldosterone at each visit by treatment group at each post-baseline visit. Statistics will be calculated for all patients who had a measurement at the visit.

LS means for change in mean serum renin, standard errors, and 2-sided 95% CIs for each treatment group and for pairwise comparisons of each dose strength of CIN-107 to the placebo group will be provided. No adjustment will be made for multiplicity. Descriptive statistics will summarize mean serum renin at each visit by treatment group at each post-baseline visit. Statistics will be calculated for all patients who had a measurement at the visit.

3.4.2.3 Responders: SBP <130 mmHg

The percentage of responders, defined as patients achieving a mean SBP<130 mmHg at Week 8 (Visit 6), will be evaluated between placebo and each dose CIN-107. Comparisons between the percent of responders will be based on a logistic regression model with covariates of baseline SBP, race, and background antihypertensive regimen.

Odds ratios, 95% Wald CIs, and p-values will be presented. The number and percentage of responders will be summarized for each treatment group.

Example SAS® code for performing this analysis as follows:

[redacted]

3.4.2.4 24-Hour Urine Aldosterone and Renin

The excreted urinary aldosterone and renin in 24 hr will be calculated as the total amount of aldosterone in the 24-hour urine collection sample and as aldosterone normalized with urinary creatinine. Only by subject listing will be presented if there are not sufficient number of samples for analysis (i.e. 50 baseline samples or more).

$$\text{Normalized Aldosterone (ng/g)} = 1000 \times \frac{\text{Aldoserone (ng/dL)}}{\text{Creatinine (mg/dL)}}$$

The difference in mean 24-hour urine aldosterone levels from baseline (Visit 2) to Week 8 (Visit 6) between each dose strength of CIN-107 and placebo will be evaluated. The difference in mean 24-hour urine renin levels from baseline (Visit 2) to Week 8 (Visit 6) between each dose strength of CIN-107 and placebo will be similarly evaluated. 24-hour urine aldosterone and 24-hour urine renin levels are measured at the randomization visit (Visit 2), and Week 8 (Visit 6).

ANCOVA models with fixed effects of treatment group and covariates of baseline value, race and background antihypertensive regimen will be used in these analyses. Only observed data will be used in the analysis model with no imputation for missing data.

The LS means for change in mean 24-hour urine aldosterone, standard errors, 2-sided p-values, and 2-sided 95% CIs will be presented for each treatment group and for pairwise comparisons of each dose strength of CIN-107 to the placebo group.

The LS means for change in mean 24-hour urine renin, standard errors, 2-sided p-values, and 2-sided 95% CIs will be presented for each treatment group and for pairwise comparisons of each dose strength of CIN-107 to the placebo group.

3.4.3 Exploratory Efficacy Endpoints

3.4.3.1 SBP Response to CIN-107 in relation to Baseline Plasma Renin, Aldosterone, and ARR

The difference in mean seated SBP from baseline (Visit 2) to Week 8 (Visit 6) between each dose strength of CIN-107 and placebo will be evaluated in relation to baseline plasma renin (pg/mL), aldosterone (ng/dL) and ARR (ng/dL per ng/mL/hr).

$$\text{Aldosterone to Renin Ratio (ng/dL per ng/mL/hr)} = \frac{\text{Aldoserone (ng/dL)}}{\text{Plasma Renin Activity (ng/mL/hr)}}$$

MMRM will be used to perform these three analyses. The analyses will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with covariates of the baseline value, baseline SBP, race, and background antihypertensive regimen. The restricted maximum likelihood estimation (REML) approach will be used with the degrees of freedom approximated using the Kenward Rogers approach. The model will be fit with an unstructured covariance matrix. If the model fails to converge, a simpler covariance structure with fewer parameters will be used according to the following order: Toeplitz (TOEPH), first-order autoregressive [AR(1)],

heterogeneous compound symmetry (CSH), and compound symmetry (CS). Missing observations will be considered missing at random and will not be imputed.

LS means for change in mean seated SBP, standard errors, and 2-sided 95% CIs for each treatment group and for pairwise comparisons of each dose strength of CIN-107 to the placebo group will be provided. No adjustment will be made for multiplicity. Descriptive statistics will summarize mean serum aldosterone at each visit by treatment group at each post-baseline visit. Statistics will be calculated for all patients who had a measurement at the visit.

3.4.3.2 Change in Aldosterone Levels from Part 1 to Part 2

The difference in 24-hour urine aldosterone levels from end of Part 1 (Week 8) to levels measured following 4 weeks of treatment with CIN-107 2 mg dose strength and no background antihypertensive agent(s) at the end of Part 2 (Week 12) will be evaluated. Similarly, the difference in serum aldosterone levels from end of Part 1 (Week 8) to the end of Part 2 (Week 12) will be evaluated.

These analyses will be done using an ANCOVA model with fixed effects of Part 1 treatment group and covariates of race and background antihypertensive regimen. Only observed data will be used in the analysis model with no imputation for missing data.

The LS means for change in mean 24-hour urine aldosterone, standard errors, 2-sided p-values, and 2-sided 95% CIs will be presented for each Part 1 treatment group.

The LS means for change in mean serum aldosterone, standard errors, 2-sided p-values, and 2-sided 95% CIs will be presented for each Part 1 treatment group.

3.4.3.3 Maintaining SBP <130 mmHg

The percentage of patients maintaining a mean seated SBP<130 mmHg at Week 12 (Visit 9), will be evaluated between placebo and each dose CIN-107. Comparisons between the percent of patients maintaining SBP<130 mmHg will be based on a logistic regression model with covariates of Part 1 treatment, baseline SBP, race, and background antihypertensive regimen in Part 1.

Odds ratios, 95% Wald CIs, and p-values will be presented. The number and percentage of patients maintaining SBP<130 mmHg will be summarized for each Part 1 treatment group.

3.4.4 Subgroups

The primary analysis model will be used to compare the change in mean seated SBP from baseline (Visit 2) to Week 8 (Visit 6) between each dose strength of CIN-107 and placebo by subgroup. Subgroup analyses will be performed for the following:

1. Background antihypertensive regimen in which patients will be grouped based on taking ACEi/ARB (Yes or No)
2. Background antihypertensive regimen in which patients will be grouped based on taking ACEi (Yes or No)
3. Background antihypertensive in which patients will be grouped based on taking ARB (Yes or No)
4. Background antihypertensive in which patients will be grouped based on taking CCB (Yes or No)

5. Background antihypertensive in which patients will be grouped based on taking thiazide diuretic (Yes or No)
6. Background antihypertensive in which patients will be grouped based on the number of background medications being taken (monotherapy or combination therapy)
7. Baseline eGFR (<45 mL/min/1.73m^2, ≥45 mL/min/1.73m^2)
8. Baseline serum aldosterone
9. Baseline PRA (<1 ng/mL/hr, ≥1 ng/mL/hr)
10. Baseline SBP (<145 mm Hg, ≥145 mm Hg)
11. Race (White, Black or African American, Other)
12. Gender (Male, Female)
13. Baseline BMI (<30 kg/m^2, ≥30 kg/m^2)
14. Ethnicity (Hispanic/Latino vs. Not Hispanic/Latino)

The LS means for change in mean seated SBP, standard errors, 2-sided p-values, and 2-sided 95% CIs will be presented for each treatment group and subgroup. The estimated difference in mean seated SBP from baseline between each dose strength of CIN-107 and the placebo group, its 95% CI, and its associated p-value will be presented. No adjustments will be made for multiplicity.

3.5 Pharmacokinetic Analysis

Individual plasma concentration data for CIN-107 and any measured metabolite(s) will be listed and summarized by visit, and treatment group for the PK Population.

For patients participating in Part 2, relevant parameters for CIN-107 and any measured metabolite(s) will be listed by individual patient and summarized in tabular format using descriptive statistics. Geometric mean and individual plasma concentrations of CIN-107 and any measured metabolite(s) will be plotted against time points for patients in Part 2.

3.6 Pharmacodynamic Analysis

The PD Population will be the primary population for the PD analysis. All PD variables will be summarized at each visit by treatment group.

3.6.1 Plasma PD Analysis

PD parameters include B type Natriuretic Peptide (pg/mL), free cortisol (µg/dL), cortisol (µg/dL), deoxycortisol (ng/dL), deoxycorticosterone (ng/dL), hydroxycorticosterone (ng/dL), and plasma renin activity (ng/mL/hr). PD parameters will be collected according to Appendix B at Baseline (Visit 2), Week 4 (Visit 4), Week 8 (Visit 6), and Week 12 (Visit 9) .

The effect of dose on plasma PD analytes from baseline to Week 8 (Visit 6) will be investigated using an MMRM model on change in concentration from baseline. The analysis will include fixed effects for Part 1 treatment, visit, and treatment-by-visit interaction, along with covariates of the baseline value, race (African American versus non-African American), and the type of background antihypertensive regimen.

The difference in plasma PD analytes concentration from the end of Part 1 (Week 8) to levels measured following 4 weeks of treatment with CIN-107 2 mg dose strength and no background antihypertensive agent(s) at the end of Part 2 (Week 12) will be evaluated using an ANCOVA model. The analysis will include fixed effects for Part 1 treatment with covariates of the Week 8

value, race (African American versus non-African American), and the type of background antihypertensive regimen.

The effect of dose on plasma PD analytes by sex (Male or Female) from baseline to Week 8 (Visit 6) will be investigated using an MMRM model on change in concentration from baseline. The analysis will include fixed effects for Part 1 treatment, visit, treatment-by-visit interaction, and sex along with covariates of the baseline value, race (African American versus non-African American), and the type of background antihypertensive regimen.

The difference in plasma PD analytes concentration by sex (Male or female) from the end of Part 1 (Week 8) to levels measured following 4 weeks of treatment with CIN-107 2 mg dose strength and no background antihypertensive agent(s) at the end of Part 2 (Week 12) will be evaluated using an ANCOVA model. The analysis will include fixed effects for Part 1 treatment and sex with covariates of the Week 8 value, race (African American versus non-African American), and the type of background antihypertensive regimen.

Least squares mean for change in concentration compared to placebo, standard errors, 2-sided p-values and two-sided 95% confidence interval will be presented. No adjustments will be made for multiplicity.

3.6.2 24-Hour Urine PD Analysis

Urine PD measures will include analytes of albumin, creatinine, potassium, protein, and sodium. The total excreted albumin (mg/24h), normalized albumin (mg/g), total excreted creatinine (mg/24h), total excreted potassium (mmol/24h), normalized potassium (mmol/g), total excreted protein (mg/24h), normalized protein (mg/g), total excreted sodium (mmol/24h), and normalized sodium (mmol/g) will be investigated. The normalized analytes will be calculated as follows

$$\text{Normalized Albumin (mg/g)} = 1000 \times \frac{\text{Albumin (mg/dL)}}{\text{Creatinine (mg/dL)}}$$

$$\text{Normalized Potassium (mmol/g)} = 100{,}000 \times \frac{\text{Potassium (mmol/mL)}}{\text{Creatinine (mg/dL)}}$$

$$\text{Normalized Protein (mg/g)} = 1000 \times \frac{\text{Protein (mg/dL)}}{\text{Creatinine (mg/dL)}}$$

$$\text{Normalized Sodium (mmol/g)} = 100{,}000 \times \frac{\text{Sodium (mmol/mL)}}{\text{Creatinine (mg/dL)}}$$

24-hour urine samples will be collected at Baseline (Visit 2), Week 8 (Visit 6), and Week 12 (Visit 9).

The effect of dose on 24-hour urine PD analytes will be investigated using an ANCOVA model on change from baseline to Week 8 (Visit 6). Total excreted albumin, normalized albumin, total excreted protein, and normalized protein will be log-transformed for analysis. The analysis will include fixed effects for Part 1 treatment, visit, and treatment-by-visit interaction, along with covariates of the baseline value, race (African American versus non-African American), and the type of background antihypertensive regimen.

The effect of dose on 24-hour urine PD analytes will be investigated using an ANCOVA model on change from Week 8 (Visit 6) to Week 12 (Visit 9). Total excreted albumin, normalized

albumin, total excreted protein, and normalized protein will be log-transformed for analysis. The analysis will include fixed effects for Part 1 treatment, visit, and treatment-by-visit interaction, along with covariates of the baseline value, race (African American versus non-African American), and the type of background antihypertensive regimen.

Least squares means, standard errors, 2-sided p-values, and two-sided 95% confidence intervals will be presented. No adjustments will be made for multiplicity.

3.7 Pharmacokinetic-Pharmacodynamic Analysis

An attempt will be made to correlate plasma concentrations and parameters with measures of safety, PD, and/or efficacy, if the data permit.

3.8 Safety Assessment

Safety data will be summarized by actual treatment received during Part 1 (and in total for selected analyses) based on the Safety Population. All safety endpoints will be summarized descriptively for records collected in Part 1. Additional safety endpoint analyses will be conducted including records collected in Part 2 and the post-dose follow up/end of study.

3.8.1 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 MedDRA version 24.0. Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug in Part 1. Part 2 TEAEs are defined as AEs that start the day after Week 8 (Visit 6).

If an AE has incomplete start or stop dates, the dates will be imputed using the most conservative assumption. If an AE stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. If an AE start date is missing, then the following rules will be applied:

- If both Month and Day are missing and Year = Year of treatment start date, then set to treatment start date.
- If both Month and Day are missing and Year ≠ Year of treatment start date, then set to January 1.
- If Day is missing and Month and Year = Month and Year of treatment start date, then set to treatment start date.
- If Day is missing and Month and Year ≠ Month and Year of treatment start date, then set to first of the month.
- If start date is completely missing, set to treatment start date as long as AE end date is not prior to treatment start date.

Adverse events of special interest 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

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 serious AEs (SAEs)
- 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.

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

3.8.2 Clinical Laboratory Tests

Blood samples for standard safety chemistry panel, hematology, and coagulation will be obtained as indicated in Appendix A and assessed at the Central Laboratory per institutional guidelines. The complete list of analytes is available in Appendix B.

Descriptive statistics will be presented at baseline and each scheduled post-baseline visit by laboratory test. The change from baseline to post-baseline visits will also be presented. Clinical laboratory data will be included in by-patient data listings. 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.

Box plots of potassium, sodium, and eGFR concentrations by each treatment group 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 mEq/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 mEq/L. Summary of potassium categories <5.5 mEq/L, ≥5.5 and <6.0 mEq/L, and >6.0 mEq/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, respiratory rate, and body temperature.
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 pre-dose at visits indicated in Appendix A. Seated BP will be measured in triplicate and single orthostatic vital measurements will be obtained. Triplicate measures will be averaged before summarization.
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. Additionally, the change in orthostatic blood pressure and heart rate findings from baseline will be presented..

3.8.4 Electrocardiograms

Standard 12-lead ECGs will be performed at visits indicated in Appendix A. Standard ECG parameters will be measured, and the following ECG parameters will be recorded:

- QRS interval;
- Heart rate;
- RR interval;
- QT interval; and
- QTc (QTcF).

3.8.5 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 and will be performed at visits indicated in Appendix A.

A limited physical examination will consist of general appearance, skin, heart, lungs, and abdomen at a minimum and will be performed at the other clinical site visits.

3.8.6 Body Measurements

Body measurements to be collected include weight, height, waist and hip circumference, and upper arm circumference. Weight will be measured at the visits indicated in Appendix A. Height will be measured at Screening only. Waist and hip circumference will be collected at visits specified in Appendix A and be used to calculate waist-to-hip ratio (WHR). Three consecutive measurements will be recorded for waist and hip circumference. Measures will be averaged prior to summarization.

4 DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) will monitor the safety of subjects over the course of the study. The DSMB will meet once or more during the subject enrollment period to examine the unblinded accumulated safety data. Subjects, investigators, site staff and in general all personnel directly involved in the conduct of the study will remain blinded to the subjects' treatment assignment until the completion of the study.

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

5 ANALYSIS TIMING

5.1 Draft Analysis/Blinded Data Reviews

Draft analysis tables, figures, and listings (TFLs) for blinded data reviews will be provided to assess data quality and assist in study monitoring.

5.2 Interim Analysis

No interim analysis is planned.

5.3 Pre-Final Analysis

After the database is locked and exclusions from analysis populations have been finalized, the randomized treatment assignments will be unblinded and the pre-final analysis will be generated. Pre-final TFLs will be provided approximately 3 weeks after database lock.

5.4 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. Final TFLs will be provided approximately 1 week after the study database is declared final. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final. In addition to TFLs, Study Data Tabulation Model (SDTM) data and Analysis Data Model (ADaM) data along with associated files will be provided. Associated files may include annotated CRFs, SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, reviewer's guides, and Clinical Data Interchange Standards Consortium (CDISC) Define packages for both SDTM and ADaM data.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The incorporation of the stratification variables corresponding to race and background antihypertensive regimen was not described in the protocol. Therefore, the categorical covariates of race and antihypertensive regimen were included in the efficacy analysis models.

Change from baseline in 24-hour urine renin secondary analysis to be performed only if sufficient number of samples are collected.

7 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

	Screening Period			Treatment Period								Safety FU Period
Study Period	Screening	Telephone	Run-In	Part 1					Part 2			
Visit[a]	1	Visit[b]	-[c]	2	3	4	5	6	7	8	9/EOT/ET	10
Week	-4 to -2	-4 to -2	-4 to -1	1	2	4	6	8	9	10	12	14
Day (±Visit Window, Days)	-28 to -14 (±2)	-28 to -14 (-)	-28 to -1 (-)	1 (-)	14 (±2)	28 (±2)	42 (±2)	56 (±2)	63 (±2)	70 (±3)	84 (±3)	(±3)
Informed consent[d]	X										X[e]	
Inclusion/exclusion criteria[f]	X			X[g]								
Demographic information	X											
Medical/surgical history	X											
Adverse events[h]	←----------X----------→											
Prior/concomitant medications[i]	←----------X----------→											
Weight, waist and hip circumference[j]	X			X	X	X	X	X		X	X	
Height[k]	X											
Upper arm circumference	X											
Vital signs (including seated BP)[l]	X[m]			X[n]	X	X	X	X	X	X	X	X
Standing BP and heart rate[o]	X			X	X	X	X	X	X	X	X	
Complete physical examination[p]	X							X			X	
Limited physical examination[q]				X	X	X	X		X	X		
12-lead ECG[r]	X							X			X	
Urinalysis	X			X	X	X	X	X		X	X	
Pregnancy test[s]	X			X							X	
FSH[t]	X											
Clinical laboratory assessments[u]	X			X	X	X	X	X	X	X	X	X
HbA1c	X											
HIV, HBsAg, HCV screen	X											
PD blood sampling[v]	X			X		X		X			X	
PK blood sampling[w]								X			X	
Randomization				X								
Dispense study drug[x]	X			←----------X----------→								
Administer study drug[y]			X[z]	←----------X----------→					←----------X----------→			

Study Period	Screening Period			Treatment Period								Safety FU Period
	Screening	Telephone	Run-In	Part 1					Part 2			
Visit[a]	1	Visit[b]	-[c]	2	3	4	5	6	7	8	9/EOT/ET	10
Week	-4 to -2	-4 to -2	-4 to -1	1	2	4	6	8	9	10	12	14
Day (±Visit Window, Days)	-28 to -14 (±2)	-28 to -14 (-)	-28 to -1 (-)	1 (-)	14 (±2)	28 (±2)	42 (±2)	56 (±2)	63 (±2)	70 (±3)	84 (±3)	(±3)
Continue background antihypertensive agents[aa]	←----------X----------→											X
Collect unused study drug[bb]				X				X			X	
Calculate adherence by pill counts[bb]				X	X	X	X	X	X	X	X	
Provide kits for 24-hour urine collection[cc,dd]	X						X			X		
Obtain 24-hour urine sample[cc,dd]				X				X			X	
Optional PGx sample[ee]				←----------X----------→								

a. All clinical site visits should occur at approximately the same time (intra-patient) and efforts should be made to have the visits occur between 6:00 AM and 11:00 AM. Unscheduled visits may be scheduled at any time during the study based on Investigator's discretion.
b. Upon return of the screening eligibility laboratory results including serum aldosterone, patients will be contacted via telephone (Telephone Visit) to inform them of their eligibility, and if eligible, to begin the Run-In Period and schedule their next visit.
c. For patients with serum sodium <130 mEq/L and/or serum potassium >5 mEq/L at Screening that the Investigator elects to correct or manage, 1 retest (at an Unscheduled Visit) is allowed at least 1 week prior to Visit 2 (see Section 4.2; Exclusion Criterion 21).
d. Written informed consent must be obtained before any protocol-specific procedures are performed.
e. Patients who complete the study through Visit 9 or who were considered withdrawn at the end of Part 1 (Visit 6) may be eligible to enter a separate open label extension study (Study CIN-107-130). These patients will not need to complete the Safety Follow-Up Period/Visit 10.
f. Screening laboratory evaluations, if abnormal, may be repeated once for eligibility purposes before excluding the patient; see Section 4.4.1 for details. Screen failures may be rescreened no less than 5 days after the last study visit, with Sponsor and/or Medical Monitor consultation and approval.
g. Patients must continue to satisfy all inclusion criteria and none of the exclusion criteria.
h. Clinical sites will record the time of event (hour, minute) for AEs that start and/or end on the first randomized study drug administration visit (Visit 2) or at EOT/ET (Visit 9).
i. Clinical sites will record the time of concomitant medication administration (hour, minute) if the medication is initiated and/or stopped on the first randomized study drug administration visit (Visit 2) or at EOT/ET (Visit 9).
j. Procedures for measuring weight and waist and hip circumference are detailed in Section 8.12. Waist and hip circumference will be collected and used to calculate waist-to-hip ratio.
k. Height will be collected at Screening only and will be used to calculate BMI at subsequent visits when weight is collected.
l. 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.
m. Laterality and cuff size should be determined first before taking the Screening measurements. BP will be measured in both upper arms (3 times/arm) using an appropriately sized cuff to detect possible laterality differences. The arm with the higher mean value from the laterality assessment will then be used to take the Screening BP measurements (at least 5 minutes after determining laterality) and for all subsequent measurements. The standardized procedures for measuring BP are listed in Section 8.9.
n. To assess BP for randomization eligibility, the last 3 consecutive, consistent SBP measurements will be averaged to determine the final value. The standardized procedures for measuring BP are listed in Section 8.9.
o. Once the seated BP has been determined, the patient will be asked to stand and within approximately 1 minute after the patient's feet touch the ground, a single standing BP and heart rate (orthostatic vitals) measurement will be obtained.

p. A complete physical examination will consist of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system.
q. A limited physical examination will consist of general appearance, skin, heart, lungs, and abdomen at a minimum.
r. 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.
s. For female patients of childbearing potential (ie, ovulating, pre-menopausal, and not surgically sterile), serum pregnancy tests will be performed at Screening, EOT, and ET Visits. A POC (urine) pregnancy test will be performed at Visit 2 to assess eligibility.
t. FSH levels will be measured only for female patients who are ≤60 years, postmenopausal for at least 1 year at Screening, and are not surgically sterile.
u. Includes standard safety chemistry panel, hematology, and coagulation. All blood samples will be obtained after vital signs have been measured and prior to dosing of Study Drug. See Appendix B for the complete list of analytes.
v. Pre-dose blood samples for PD analysis will be collected at the specified visits. See Section 7.4.1 for details of blood sample collection for PD analysis.
w. Pre-dose blood samples for PK analysis will be collected within approximately 30 minutes prior to dosing at the specified visits. See Section 7.5 for details of blood sample collection for PK analysis.
x. For the Run-In Period, placebo dispensation will occur at Visit 1 following initial eligibility confirmation. The randomized study drug (CIN-107 or placebo) dispensation may occur at any time during the Treatment Period. A Study Reference Manual with details of study drug dispensation will be provided to the clinical sites.
y. During clinical site visits for the Treatment Periods (Parts 1 and 2), patients will self-administer 1 tablet of study drug in the clinic to be witnessed by site staff, after completion of pre-dose evaluations and laboratory sampling. Between clinical site visits, patients will continue to self-administer 1 tablet of study drug QD by mouth at approximately the same time each morning.
z. For the Run-In Period, all patients will self-administer 1 tablet of placebo QD by mouth at approximately the same time each morning.
aa. All patients will receive their background antihypertensive medications, unless requested otherwise, through a Central Pharmacy starting at Visit 2. Clinical sites will send prescriptions for background antihypertensive medications to the Central Pharmacy at least 1 week before the planned dispensation.
bb. Patients will be instructed to bring their study drug and background antihypertensive medication to all clinical site visits. After calculating treatment adherence (by pill counts), site staff will collect any remaining study drug from the patient at the specified visits.
cc. Clinical sites will provide patients with a 24-hour urine collection kit at Visits 1, 5, and 8. Patients will be instructed to start the collection up to 3 days prior to Visits 2 (after confirmation of their eligibility during the Telephone Visit), 6, and 9, refrigerate the collected sample, and bring the entire sample to the clinical site at that visit. A 24-hour urine collection will commence after the morning void on the first day and will include the morning void on the second day for a total duration of 24 ±2 hours.
dd. 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.
ee. For patients who provide written informed consent to participate in the optional PGx assessment, a blood sample will be collected at any time after randomization during the Treatment Period.

ACEi = angiotensin-converting enzyme inhibitor; AE = adverse event; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; EOT = End of Treatment; ET = Early Termination; FSH = follicle-stimulating hormone; FU = Follow-Up; HbA1c = glycated hemoglobin; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PD = pharmacodynamic(s); PGx = pharmacogenomic(s); PK = pharmacokinetic(s); POC = point-of-care; QD = once daily; SBP = systolic blood pressure.

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) $\times$ 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.

Additional Chemistry Parameters

Glycated hemoglobin

Endocrinology

β-human chorionic gonadotropin [1]	Follicle-stimulating hormone [2]

Serum aldosterone

1. Serum or point-of-care (urine) pregnancy tests will be performed only for female patients of childbearing potential (ie, ovulating, pre-menopausal, and not surgically sterile).
2. Follicle-stimulating hormone levels will be measured only for female patients who are ≤60 years, postmenopausal for at least 1 year at Screening, and are 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.

Coagulation

Activated partial thromboplastin time	International normalized ratio
Prothrombin time	

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.

Viral Testing and Serology

Hepatitis B surface antigen	Hepatitis C virus RNA
HIV antibody	

HIV = human immunodeficiency virus; RNA = ribonucleic acid.

Pharmacodynamic Analytes

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

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

24-Hour Urine Collection Analytes

Albumin	Aldosterone
Creatinine	Potassium
Protein	Sodium
	Renin