STATISTICAL ANALYSIS PLAN

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group, Dose-Ranging Study to Evaluate the Efficacy and Safety of Multiple Dose Strengths of CIN-107 as Compared to Placebo After 12 Weeks of Treatment in Patients with Treatment-Resistant Hypertension (rHTN)
Protocol Number:	CIN-107-121
Protocol Version/Date:	8.0/07 Dec 2021
Investigational Product:	CIN-107
Sponsor:	CinCor Pharma 5375 Medpace Way Cincinnati, OH 45227 United States Telephone: [redacted] Fax: [redacted]
SAP Version/Date:	2.0/12 Jul 2022

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SIGNATURE PAGE

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

Signature		**Date**
[redacted]		12-Jul-2022
Medpace, Inc.		
[redacted]		12-Jul-2022
Medpace, Inc.		
[redacted]		12-Jul-2022
CinCor Pharma, Inc.		
[redacted]		12-Jul-2022
CinCor Pharma, Inc.		

VERSION HISTORY

Version	Version Date	Description
1.0	09 Mar 2022	Original signed version
2.0	12 Jul 2022	Sections 2.2.2 and 6 GFR randomization strata clarified as from Visit 3, while baseline GFR used in analyses is Visit 4. Section 3.1.2 Analysis window updated for Visit 11 Section 3.2.2 updated mITT population language regarding the removal of efficacy measures after receiving restricted medication. Section 3.3.4 Demographic and baseline characteristics updated to summarize diabetes, and background antihypertensives. Section 3.3.7 exposure categories, compliance calculation, and compliance categories updated Section 3.4.1 Subgroup and supplementary analyses added, and updated to use SDG to define background antihypertensive subgroups 3.5 PK Assessment language updated Section 3.6 PD analysis updated Section 3.7 PK-PD Assessment language updated Section 3.8.2 Plots of safety parameters: potassium, sodium, GFR added, and updated to investigate patients with high potassium at post-baseline visits.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AUC_{0-8h}	Area Under the Curve from time 0 to time 8 hours post-dose
BMI	Body Mass Index
BP	Blood Pressure
BLQ	Below Limit of Quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL/F	Apparent total plasma clearance after oral administration
C_{max}	Maximum plasma concentration
CRF	Case report form
CSR	Clinical Study Report
C_{trough}	Concentration associated with the pre-dose sample
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DRC	Data Review Committee
EOT	End of Treatment
GFR	Glomerular Filtration Rate
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMRM	Mixed model for repeated measures
MTD	Maximum Tolerated Dose
PD	Pharmacodynamic
PK	Pharmacokinetic
PK-PD	Pharmacokinetic-pharmacodynamic
PP	Per-Protocol
PRA	Plasma Renin Activity
QD	Once Daily
REML	Restricted Maximum Likelihood Estimation
rHTN	Treatment-Resistant Hypertension
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SB-RI	Single Blind-Run In
SD	Standard Deviation
SDG	Standardized Drug Groupings

Abbreviation	Definition
SDTM	Study Data Tabulation Model
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFL	Table, Listing, Figure
T_{max}	Time to C_{max}
Vz/F	Apparent volume of distribution during terminal elimination phase after oral administration
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-107-121. 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 one dose strength of CIN-107 is superior to placebo in mean change from baseline in seated systolic blood pressure (SBP) after 12 weeks of treatment in patients with treatment-resistant hypertension (rHTN).

2.1.2 Secondary Objectives

The secondary objectives are the following:

- To evaluate 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 12 weeks of treatment in patients with rHTN; and
- To evaluate the percentage of patients achieving a seated blood pressure (BP) response <130/80 mmHg with each of the selected dose strengths of CIN-107 compared to placebo after 12 weeks of treatment for rHTN.

2.1.3 Safety Objectives

The safety objectives are the following:

- To evaluate vital signs, standing BP and heart rate, physical examinations, electrocardiography, weight measurement, and clinical laboratory evaluations, including standard safety chemistry panel, hematology, coagulation, and urinalysis;
- To evaluate treatment-emergent adverse events (TEAEs);
- To evaluate TEAEs leading to premature discontinuation of study drug;
- To evaluate treatment-emergent marked laboratory abnormalities; and
- To evaluate the change in standing SBP and DBP (measured pre-dose at the clinical site) from baseline to End of Treatment (EOT) (Day 85/Visit 11).

2.1.4 Pharmacokinetic-Pharmacodynamic Objective

The pharmacokinetic-pharmacodynamic (PK-PD) objective is to evaluate 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, 2-part, randomized, double-blind, placebo-controlled, multicenter, parallel-group, dose-ranging study to evaluate the efficacy and safety of the selected dose strengths of CIN-107 as compared to placebo after 12 weeks of treatment in patients with rHTN.

Patients with rHTN will be defined as being on a stable regimen of ≥3 antihypertensive agents, 1 of which is a diuretic, at maximum tolerated dose (MTD) based on Investigator judgment, with a mean seated BP ≥130/80 mmHg.

The safety of CIN-107 will be assessed from the time of informed consent until the end of the Follow-up Period. Patients will be followed for efficacy and adherence throughout the Double-Blind Treatment Period. Pharmacodynamic 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. Pharmacokinetic variables analyzed during the study will include plasma concentrations of CIN-107 and any measured metabolite(s).

2.2.1.1 Part A

Part A is a Phase 2, randomized, double-blind, placebo-controlled, multicenter, parallel-group, dose-ranging study to evaluate the efficacy and safety of the selected dose strengths of CIN-107 as compared to placebo after 12 weeks of treatment in patients with rHTN.

2.2.1.1.1 Adaptive design

During the Double-Blind Treatment Period, eligible patients will be randomized 1:1:1 into 1 of the 3 treatment groups (2 active [1 mg and 2 mg CIN-107] and 1 placebo). After approximately the first 25 randomized patients per group reach approximately 4 weeks of study drug dosing, a data review committee (DRC) will evaluate emerging data and reports on cumulative serious adverse events (SAEs). Based on their assessments, the DRC will determine the next dose level(s) (not to exceed 4 mg once daily [QD]) of CIN-107 to be studied. Patient enrollment in the study will not stop during the first DRC review. Following DRC review, Part A will enroll patients using a randomization ratio to allow for approximately equal distribution between the treatment groups at the conclusion of the study.

2.2.1.1.2 Study Visits

Part A of the study will consist of 4 periods:

- A Screening Period (Screening Visit [Visit 1/Day -70 to -14] and Telephone Call 1 [Visit 2/Day -28 to -14]) of up to 8 weeks;
- A Single Blind-Run In (SB-RI) Period (Visit 3/Day -14 to -1) of 2 weeks;
- A Double-Blind Treatment Period (Visits 4 to 11/ Day 1 to 85) of 12 weeks; and
- A Follow-up Period (Telephone Call 2 [Visit 12/Day 92]) of up to 1 week.

Patients will complete at least 12 total visits over a period of approximately 6 months, including 10 clinic visits and 2 Telephone Visits. Additional Unscheduled Visits may occur at any time during the study period.

2.2.1.2 Part B

After taking part in the prior visits and procedures of Part A, approximately 10-15% of the patients are expected to participate in the optional Part B sub-study at EOT (Visit 11/Day 85).

Patients participating in Part B will present to the clinical site at Visit 11 in a fasted state for 8 hours relative to study drug administration and will remain so for 4 hours after study drug administration. Additional post-dose PK sampling will be performed at the following timepoints at Visit 11: 1, 2, 3, 4, 6, and 8 hours.

2.2.2 Randomization and Blinding

Patients will be randomized in a 1:1:1 ratio into 1 of the 3 treatment groups (2 active [1 mg and 2 mg CIN-107] and 1 placebo) for Part A. After approximately the first 25 randomized patients per group reach approximately 4 weeks of study drug dosing in the Double-Blind Treatment Period, a DRC will evaluate emerging data and reports on cumulative SAEs collected during the study. Based on their assessments, the DRC will determine the next dose level(s) of CIN-107 to be studied. Following DRC review, Part A will enroll patients using a randomization ratio to allow for approximately equal distribution between the treatment groups at the conclusion of the study.

Patients will be stratified according to their baseline SBP (<145 or ≥145 mmHg) and their estimated glomerular filtration rate (GFR) (<60 or ≥60 mL/min/1.73m^2). GFR used for stratification is based on Single Blind Run-In period (Visit 3) laboratory results.

Following randomization, study drug will be dispensed in a double-blind manner. The Sponsor and Investigators will be blinded to the treatment group for each patient. Patients will also be blinded to the treatment they receive. Randomization information will be concealed from the Investigators, the patients, and the study team until the end of the study unless considered necessary by the Investigator for emergency situations for reasons of patient safety or as determined by the DRC or Sponsor.

For further details, please refer to the Randomization Plan within the Randomization and Study Product Management Requirements Specification.

2.2.3 Data Review Committee (DRC) Decision

Based on the first data review meeting of the DRC, after approximately the first 25 randomized patients per group (1 mg CIN-107, 2 mg CIN-107, and placebo) reached approximately 4 weeks of study drug dosing in the Double-Blind Treatment Period, it was determined to add a 0.5 mg treatment group to the study design.

The randomization scheme corresponding to this adaptation in the study design was performed to allow for approximately equal distribution between the selected treatment groups at the conclusion of the study. Meaning, overall patients will be randomized 1:1:1:1 into 1 of the 4 treatment groups (3 active [0.5 mg, 1 mg, and 2 mg] and 1 placebo). For further details, please refer to the Randomization Plan within the Randomization and Study Product Management Requirements Specification.

2.2.4 Study Drug

CIN-107 tablets will be provided in the following strengths: 0.5 mg, 1 mg, and 2 mg. Patients will receive two tablets QD, based on treatment group, of either their assigned dose strength or

matching placebo tablets during the Double-Blind Treatment Period, starting at Visit 4 and concluding at Visit 11.

2.2.5 Sample Size Determination

2.2.5.1 Part A

[redacted]

2.2.5.2 Part B

[redacted]

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in mean seated SBP after 12 weeks of treatment in patients with rHTN.

2.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- Change from baseline in mean seated DBP of CIN-107 compared to placebo after 12 weeks of treatment in patients with rHTN;
- Percentage of patients achieving a seated BP response <130/80 mmHg of CIN-107 compared to placebo after 12 weeks of treatment for rHTN.

2.3.3 Pharmacokinetic Assessments

Pharmacokinetic variables C_{max}, T_{max}, and AUC from time 0 to the time of last measured plasma concentration will be determined for CIN-107 and any measured metabolite(s) using plasma concentration data from EOT Visit (Visit11/Day85).

2.3.4 Pharmacodynamic Assessments

Plasma PD variables analyzed during the study may include, but are not limited to, measures of aldosterone and its precursors (18-hydroxycorticosterone, corticosterone, and 11-deoxycorticosterone), plasma renin activity (PRA), and cortisol (total) and its precursor (11-deoxycortisol). Levels of plasma electrolytes will be used in the PD analysis. Urinary aldosterone and urine electrolyte levels will also be assessed from the 24-hour urine collections prior to Visits 4 and 11. Urine electrolyte levels may include, but not limited to, urinary sodium and potassium.

2.3.5 Pharmacogenomic Assessments

Pharmacogenomic assessments and analysis methods will be described in a separate analysis plan.

2.3.6 Safety Endpoints

The safety endpoints will include the following:

- Vital signs, standing BP and heart rate, physical examinations, electrocardiography, weight measurement, and clinical laboratory evaluations, including standard safety chemistry panel, hematology, coagulation, and urinalysis;
- TEAEs;
- Treatment-emergent serious adverse events (TESAEs);
- TEAEs leading to premature discontinuation of study drug;
- Treatment-emergent marked laboratory abnormalities; and
- Change in standing SBP and DBP (measured pre-dose at the clinical site) from baseline to EOT (Visit 11/Day 85).

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). 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
Visit 4	1	1	1
Visit 5	3	2	4
Visit 6	8	5	11
Visit 7	15	12	18
Visit 8	22	19	32
Visit 9	43	33	53
Visit 10	64	54	74
Visit 11	85	75	>75

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.

3.1.3 Definition of Baseline

Measurements of efficacy and safety variables at Randomization (Visit 4/Day 1) will constitute baseline measurements. If the baseline measurement is missing, then the last non-missing assessment prior to the first dose of double-blind study drug will be used as baseline.

3.1.4 Summary Statistics

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

3.1.5 Evaluation of Site Effect

With a sample size of approximately 348 patients and approximately 90 clinical sites in the United States, the number of patients at each site is expected to be too small to evaluate site effect.

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. Any efficacy measurement obtained after a patient received a restricted BP altering therapy, outside of the current study design, will be removed from the mITT analysis. If a patient entered the study while on a stable regimen of a restricted therapy and then discontinued this medication during the double-blind treatment period, then all efficacy measures after the date of discontinuation of this medication will be removed from the mITT analysis. 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 an EOT (Visit 11) value for the SBP assessment and who did not experience a major protocol deviation that potentially impacted the primary efficacy endpoint. Major protocol deviations will be defined as CSR reportable protocol deviations as described in the Protocol Deviation Plan. The PP Population, along with the reason for exclusion, will be finalized prior to study unblinding.

3.2.4 Safety Population

The Safety Population will include all patients who receive at least 1 dose of any randomized study drug. Treatment classification will be based on the actual treatment received. The Safety Population will be the primary population used for the safety analyses.

3.2.5 Pharmacokinetic Population

3.2.5.1 PK Part A Population

The PK Part A Population will include all patients in the mITT Population who have at least 1 quantifiable pre-dose plasma concentration and enrolled in Part A.

3.2.5.2 PK Part B Population

The PK Part B Population will include all patients in the mITT Population who have at least 1 quantifiable post-dose concentration and enrolled in Part B.

3.2.6 Pharmacodynamic Population

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

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

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

Counts and percentages of patients who received single-blind study drug and discontinued prior to randomization will be summarized based on all patients that entered the SB-RI period. Reasons for early discontinuation will also be summarized.

Counts and percentages of patients who were randomized, discontinued early from the study, and completed the study will be summarized by treatment and in total based on all randomized patients. Reasons for early discontinuation will also be summarized.

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 patients with CSR reportable protocol deviations by deviation category will be summarized by treatment and in total based on all randomized patients. A listing of CSR-reportable protocol deviations will be generated.

3.3.3 Analysis Populations

Counts and percentages of patients in each analysis population will be summarized by treatment and in total based on all randomized patients. 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)
- Sex
- Childbearing potential
- Race

- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) and BMI categories (<30 kg/m^2, ≥30 kg/m^2)
- Diabetes on entry
- Mean seated SBP (mmHg) and SBP categories (<145 mmHg, ≥145 mmHg)
- GFR (mL/min/1.73m^2) and GFR categories (<60 mL/min/1.73m^2, ≥60 mL/min/1.73m^2)
- Overall background antihypertension medications category (<3, 3, >3)
- Background Antihypertensive Medications

Demographic and baseline characteristics will be summarized with descriptive statistics as appropriate by treatment and in total for all randomized patients 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 23.0. Counts and percentages of patients with medical history by system organ class and preferred term will be summarized by treatment and in total based on all randomized patients.

3.3.6 Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHODrug Dictionary March 2020G B3. For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of double-blind study drug and concomitant medications if they were taken at any time after the first dose of double-blind study drug (i.e., started prior to the first dose of double-blind study drug and were ongoing or started after the first dose of double-blind 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 patients taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment and in total based on the Safety Population. Compliance to background antihypertensives during the double-blind treatment period by visit will be summarized by treatment and in total based on the Safety Population.

3.3.7 Study Drug Exposure and Compliance

Days of exposure to double-blind study drug will be calculated as:

date of last dose of study drug – date of first dose of study drug + 1.

If the date of last dose of double-blind study drug is unavailable, then days of exposure will be defined as:

date of completion/early termination from the end of study form – date of first dose + 1

The date of randomization will be used to assign the date of first dose. Note that the exposure calculation is intended to describe the length of time a patient was exposed to double-blind study drug and therefore does not take study drug interruptions into account.

Days of exposure to double-blind study drug will be summarized by treatment based on the Safety Population with descriptive statistics and with counts and percentages of patients with exposure in the following categories:

- <4 weeks (<28 days)
- 4 - <8 weeks (28 - 55 days)
- 8 - <12 weeks (56 – 83 days)
- 12 - <14 weeks (84 - 97 days)
- >=14 weeks (>=98 days)

Percent compliance to the double-blind study drug regimen will be calculated as:

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

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. The number of tablets returned will be calculated as:

number of tablets dispensed - min{*number of tablets dispensed*, [*end of treatment date – date dispensed* +1] x 2}

he number of analysis tablets taken will be calculated as:

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

The number of tablets expected will be calculated as:

[end of treatment date – date of randomization + 1] x 2

(i.e., the number of days double-blind study drug was expected to be taken x 2 tablets per day).

Percent compliance to the double-blind study drug regimen will be summarized by treatment based on the Safety Population with descriptive statistics and with counts and percentages of patients with compliance in the following categories:

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

3.4 Efficacy Assessment

Efficacy data will be summarized 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 Endpoint

Primary Analysis

The primary efficacy analysis will compare the change in mean seated SBP from baseline to Day 85 between each dose strength of CIN-107 and placebo. Baseline mean seated SBP is measured at the Randomization visit (Day 1/Visit 4) and at 7 post-baseline visits: Day 3 (Visit 5), Day 8 (Visit 6), Day 15 (Visit 7), Day 22 (Visit 8), Day 43 (Visit 9), Day 64 (Visit 10), and Day 85 (Visit 11/EOT). The primary analysis will be based on the mITT Population. The same analysis will be repeated for the ITT and PP Populations.

The change from baseline in mean seated SBP will be analyzed using a mixed model for repeated measures (MMRM) model. The analysis will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with covariates of the baseline mean seated SBP and baseline glomerular filtration rate. The restricted maximum likelihood estimation (REML) approach will be used with an unstructured covariance matrix.

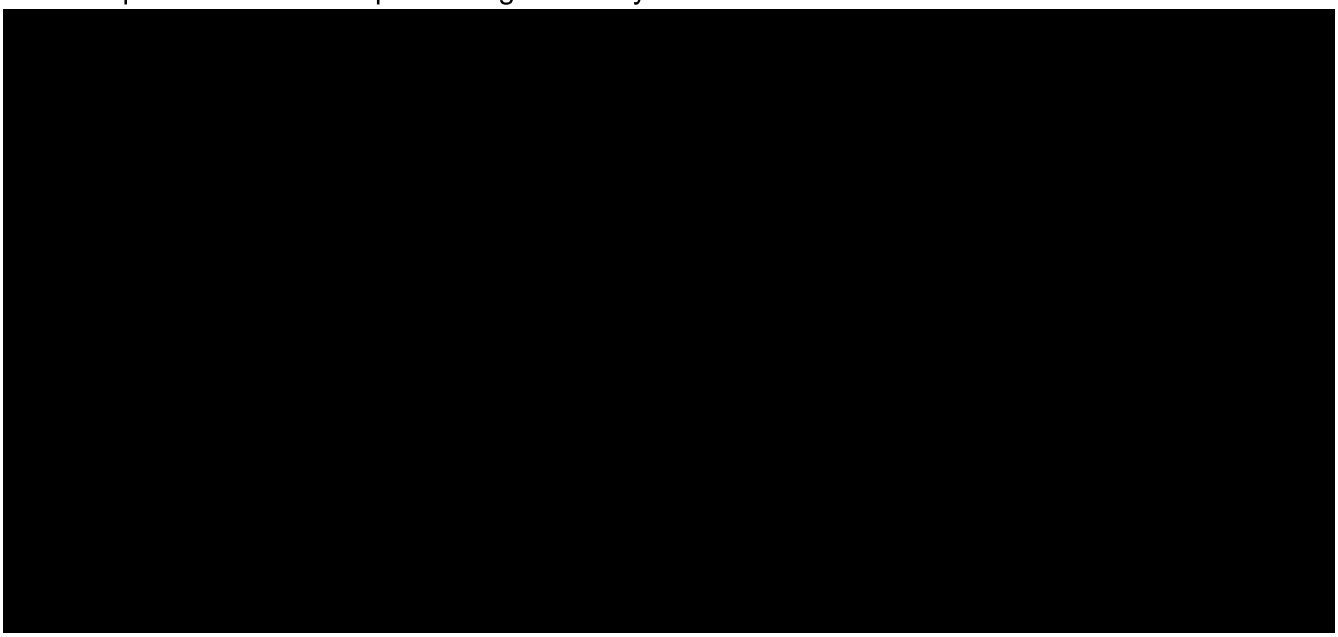
For each patient, the outcome variable for the MMRM is the difference between the baseline mean seated SBP and the mean seated SBP at each post-baseline visit. Specifically, the outcome variable, Y_{ij}, at visit i, $i = 1, \ldots, 7$, for the jth patient is

$$Y_{ij} = SBP_{ij} - SBP_{bj}$$

where SBP_{ij} is the mean seated SBP measured at visit i for the jth patient, and SBP_{bj} is the baseline mean seated SBP for the jth patient.

The least squares means for change in mean seated SBP, standard errors, 2-sided p-values, and 2-sided 95% confidence intervals (CIs) will be presented for each treatment group. 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. Missing data for the mean seated SBP value will be considered missing at random.

Example SAS® code for performing this analysis is as follows:



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 (minus the alpha spent at the interim analysis); 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.

Subgroup Analyses

The primary analysis model will also be used to compare the change in mean seated SBP from baseline to Day 85 between each dose strength of CIN-107 and placebo by subgroup. Subgroup analyses will be performed for the following:

- Sex (male or female)
- Race (White, Black or African American, or Other)
- Baseline SBP (<145 mmHg or ≥145 mmHg)
- Baseline GFR category (<60 mL/min/1.73m^2 or ≥60 mL/min/1.73m^2)
- Stratification GFR category (<60 mL/min/1.73m^2 or ≥60 mL/min/1.73m^2)
- Baseline serum aldosterone concentration (<6 ng/dL or ≥6 ng/dL)
- Background Antihypertension Medication Use defined by Standardized Drug Groupings (SDG) for WHODrug B3 Global, Mar 2020G and ATC classification. Groups will be defined as, in addition to a diuretic, taking at least one background antihypertension medication of the given category or not:
    - Beta Blocking Agents
    - Calcium Channel Blockers
    - Agent Acting on the Renin-Angiotensin System (Angiotensin II Receptor Antagonists [ARBs], ACE Inhibitors, and Renin Inhibitors)
    - General Antihypertensive (ATC classification C02)

Subgroup analyses will be based on the mITT Population. The least squares means for change in mean seated SBP, standard errors, 2-sided p-values, and 2-sided 95% confidence intervals (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.

Secondary Analyses

The primary analysis model will also be used to estimate the difference between treatment groups at each of the other 6 post-baseline visits: Day 3 (Visit 5), Day 8 (Visit 6), Day 15 (Visit 7), Day 22 (Visit 8), Day 43 (Visit 9), Day 64 (Visit 10). 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. Least squares mean change from baseline in mean seated SBP and standard error for each treatment

group will be graphed with target analysis day on the x-axis and mean change from baseline in mean seated SBP on the y-axis.

Sensitivity Analyses

As a sensitivity analysis, missing data will be imputed using a control-based pattern imputation model assuming the data are missing not at random. The multiple imputation will be performed such that only observations from the placebo group will be used to derive the imputation model for missing mean seated SBP values.

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.

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

[redacted]

For the monotone imputation method, at the first follow-up visit (Day 3), the data will be split into two groups as follows: (1) all placebo patients (whether they had missing Day 3 mean SBP values or not) and active treatment patients that had missing Day 3 mean SBP values; and (2) all active treatment patients who did not have missing Day 3 mean SBP values. The variables for the imputation model for the first group of patients will consist of baseline glomerular filtration rate and mean seated SBP values from baseline and Day 3. 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 placebo treatment arm. In this manner, missing data at the first time point for all patients without a Day 3 value will be estimated from the placebo treatment arm.

Example SAS® code for performing this analysis is as follows:

[redacted]

[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 placebo patients (whether they had missing Day 8 mean SBP values or not) and active treatment patients that had missing Day 8 mean SBP values; and (2) all active treatment patients who did not have missing Day 8 mean SBP values. The variables for the imputation model for the first group of patients will consist of baseline glomerular filtration rate and mean seated SBP values from baseline, Day 3, and Day 8. 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 placebo treatment arm.

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 Day 15, Day 22, Day 43, Day 64, and Day 85 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 the MMRM model described above. The results will be combined using Rubin's method to construct the treatment estimates using the parameter estimates and associated standard errors.

Example SAS® code for performing this analysis is as follows:

[redacted]

Supplementary Analyses

The first supplementary analysis will analyze the primary efficacy endpoint using an Analysis of Covariance (ANCOVA) model with fixed effects of treatment group and covariates of baseline mean seated SBP and baseline mean glomerular filtration rate. Only observed data will be used in the analysis model with no imputation for missing data.

The second supplementary analysis will analyze the primary efficacy endpoint using an ANCOVA model with fixed effects of treatment group and covariates of baseline mean seated SBP and baseline mean glomerular filtration rate. Missing observations will be imputed using the Last Observation Carried Forward (LOCF) method.

The least squares means for change in mean seated SBP, standard errors, 2-sided p-values, and 2-sided 95% confidence intervals (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 can be found below:

3.4.2 Secondary Efficacy Endpoints

3.4.2.1 Diastolic Blood Pressure (DBP)

The first secondary efficacy analysis will compare change in mean seated DBP from baseline to Day 85 between each dose strength of CIN-107 to placebo.

The difference in mean seated DBP from baseline will be analyzed using a MMRM model similar to the primary efficacy analysis. The analysis will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with covariates of the baseline mean seated DBP and baseline glomerular filtration rate. The restricted maximum likelihood estimation (REML) approach will be used with an unstructured covariance matrix and the Kenward-Roger approximation for degrees of freedom.

The least squares means for change in mean seated DBP, standard errors, 2-sided p-values, and 2-sided 95% confidence intervals (CIs) will be presented for each treatment group and for pairwise comparisons of each dose strength of CIN-107 to the placebo group. 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. Least squares mean change in mean seated DBP and standard error for each treatment group will be graphed with target analysis day on the x-axis and mean change in mean seated SBP on the y-axis.

3.4.2.2 BP < 130/80 mmHg

The second secondary efficacy analysis will evaluate the percentage of patients who achieved a mean seated BP response of <130/80 mmHg at Day 85 between each dose strength of CIN-107 and the placebo group. Patients with missing measures at Day 85 are considered non-responders.

Comparisons between the percent of patients achieving a seated BP response of <130/80 mmHg will be based on a logistic regression model with covariates of treatment group, baseline mean seated SBP, baseline mean seated DBP, and baseline glomerular filtration rate.

Comparisons between the percent of patients achieving a seated SBP response of <130 mmHg will be based on a logistic regression model with covariates of treatment group, baseline mean seated SBP, and baseline glomerular filtration rate.

Comparisons between the percent of patients achieving a seated DBP response of <80 mmHg will be based on a logistic regression model with covariates of treatment group, baseline mean seated DBP, and baseline glomerular filtration rate.

Odds ratios, 95% Wald CIs, and p-values will be presented. The number and percentage of patients achieving a seated BP response of <130/80 mmHg will be summarized for each treatment group at each post-baseline visit. The number and percentage of patients achieving a seated SBP of <130 mmHg will be summarized for each treatment group at each post-baseline visit. The sample SAS code can be found below:

3.5 Pharmacokinetic Assessment

Individual plasma concentration data for CIN-107 and its primary metabolite (CIN-107M), will be listed and summarized by visit, timepoint, and treatment group for the PK Population.

For patients participating in Part B of the study, relevant parameters for CIN-107 and CIN-107M will be listed by patient and be summarized by timepoint and treatment for active treatments in tabular format using descriptive statistics. Geometric mean and individual plasma concentrations of CIN-107 and CIN-107M will be plotted on a linear and semi-logarithmic scale against time points by treatment group for patients in Part B.

The following PK parameters will be determined for CIN-107 and CIN-107M as the data permit:

Parameters	**Description**	**Analyte**
C_{max}	Maximum plasma concentration; determined directly from the concentration time profile; if the maximum plasma concentration occurs at more than one time point, C_{max} is defined as the first maximum value	CIN-107 & CIN-107M
T_{max}	Time to C_{max}; If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.	CIN-107 & CIN-107M
AUC_{0-8h}	Area under the plasma concentration vs time curve (AUC) from predose (time 0) to 8 hours post-dose	CIN-107 & CIN-107M
AUC_{last}	Area under the concentration-time curve from time zero (pre-dose) to the last measurable concentration	CIN-107 & CIN-107M
C_{trough}	Concentration associated with the pre-dose sample	CIN-107 & CIN-107M

The Linear-Log Trapezoidal method (equivalent to the Linear Up/Log Down option in WinNonlin) will be used in the computation of all AUC values.

For plasma PK concentration data, if the actual sampling time is missing, but a valid concentration value has been measured, the PK profile will be reviewed. Generally, if the value with missing sampling time is near C_{max}, the concentration value will be flagged, and the scheduled time point may be used for the calculation of PK parameters. Otherwise, the concentration data will be excluded from statistics or analysis. In cases of missing pre-dose, the missing components will be assumed as zero for the first dose and as the minimum concentration during the dose interval for the final dose. For the other cases, the missing data will not be imputed.

For the individual concentration and PK parameter calculation, the following rules will be applied:

- If one or more values below the limit of quantification (BLQ) occur before the first measurable concentration, they will be assigned a value of zero for the first dose and lower limit of quantification (LLOQ) for all other doses.
- If BLQ values occur between measurable concentrations in a profile, the BLQ should be assigned a value of lower limit of quantification (LLOQ). An alternative approach of omitting these BLQ values (setting to missing) may be presented.
- If BLQ values occur after the last measurable concentration in a profile, the BLQ should be omitted (set to missing).

For the concentration summary and mean concentration plot preparation, the following rules will be applied:

- Mean concentration at any individual time point will only be calculated if at least half of the patients have valid values (i.e. quantifiable and not missing) at this time point

- In cases where a mean value is not calculated due to the above criterion not being met, the value will be set to missing
- BLQ values will be set to zero. The only exception is that the BLQ at trough or before the first quantifiable concentration for all doses following the first dose will be imputed as LLOQ.

3.5.1 Dose Proportionality

C_{max}, AUC_{last}, $AUC0_{-8h}$ of CIN-107 will be evaluated using a power model for the dose proportionality analysis. The power model is described below as:

$$y = \alpha \times \mathrm{Dose}^{\beta}$$

where *y* denotes the PK variables. Dose proportionality implies that *β=1* and will be assessed by estimating *β* along with its 95% confidence interval. The exponent, *β*, in the power model will be estimated by regressing the log-transformed PK parameter on log-transformed dose. The power model will be fitted by using the REML approach in SAS® Proc Mixed. The mean slope will be estimated from the power model and the corresponding 95% confidence interval will be calculated.

3.6 Pharmacodynamic Assessment

The PD Population will be the primary population for the PD analysis. PD parameters include aldosterone (ng/dL), cortisol (mcg/dL); plasma renin activity (ng/mL/hr), and B type Natriuretic Peptide (pg/mL). PD parameters will be collected according to Appendix B at Visits 4 (Day 1, Baseline), 7(Day 15), 8 (Day 22), and 11/EOT(Day 85) .

Urine PD measures will include analytes of aldosterone, potassium, sodium, creatinine, albumin and protein in the 24-hour urine samples. The total excreted aldosterone (µg/24 hr), aldosterone normalized by creatinine (ng/g), potassium (mmol/24 hr), potassium normalized by creatinine (mmol/g), sodium (mmol/24 hr), sodium normalized by creatinine (mmol/g), creatinine (mg/24 hr), albumin (mg/24 hr), albumin creatinine ratio (mg/g), protein (mg/24 hr), and protein creatinine ratio (mg/g) will be investigated. The normalized aldosterone, potassium, and sodium will be calculated by dividing the analyte by the urine creatinine concentration, given in grams, obtained in the same urine sample. Albumin excretion, albumin creatinine ratio, protein excretion, and protein creatinine ratio will be log-transformed for analysis. 24-hour urine samples will be collected at visits 4 (Day1) and visit 11/EOT (Day 85).

The effect of dose on concentration of aldosterone, cortisol, plasma renin activity, and B type natriuretic peptide will be investigated using an MMRM model on change in concentration from baseline. The analysis will include fixed effects for treatment, visit, and treatment-by-visit interaction and baseline seated SBP and baseline GFR as covariate variables. The REML approach will be used with an unstructured covariance matrix.

An ANCOVA model on the ratio of Day 85 to baseline with baseline seated SBP and GFR as covariate variables will be used to evaluate the effect of dose on log-transformed urine albumin creatinine ratio and log-transformed urine protein creatinine ratio.

The effect of dose on all other urine PD analytes will be investigated using an ANCOVA model on change in analyte from baseline to visit 11/EOT (Day 85) with baseline seated SBP and baseline GFR as covariate variables.

All PD variables will be summarized descriptively by visit, and treatment group. Descriptive statistics will be calculated for observed values, as well as for the change and percent change

from baseline. Categorical descriptive statistics will be presented for the number and percent of patients with aldosterone <6 ng/dL at each visit. Least squares mean for change in concentration, standard errors, 2-sided p-values and two-sided 95% confidence interval will be presented. No adjustments will be made for multiplicity.

3.7 Pharmacokinetic-Pharmacodynamic Assessment

An attempt will be made to correlate plasma concentrations and parameters (C_{max} and AUC_{0-8h}) with measures of safety, PD, and/or efficacy, if the data permit. PD parameters include aldosterone, cortisol, and B type Natriuretic Peptide.

PD parameters will be collected according to Appendix B Visits 7(Day 15), 8 (Day 22), and 11/EOT(Day 85). More PK-PD relationships may be explored if warranted.

3.8 Safety Assessment

Safety data will be summarized by actual treatment received (and in total for selected analyses) based on the Safety Population.

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 23.0. Treatment emergent- adverse events (TEAEs) are defined as AEs that start after the first dose of double-blind study drug.

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

- Any TEAEs (overall and by maximum severity)
- Any study drug related TEAEs
- Any TEAEs of special interest
- Any SAEs
- Any 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 patients (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 double-blind study drug.

3.8.2 Clinical Laboratory Tests

Blood and urine samples for clinical laboratory tests will be obtained as indicated in Appendix B and assessed at a central laboratory. A list of laboratory tests to be performed is included in Appendix C.

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 post-baseline 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 GFR 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. Shift from baseline for potassium categories <5.5 mEq/L, ≥5.5 and <6.0 mEq/L, and >6.0 mEq/L will be presented.

3.8.3 Vital Signs

Vital signs will include height, weight, BMI, heart rate, respiratory rate, and body temperature. Orthostatic vitals will include standing BP, difference between seated and standing BP, seated heart rate, and standing heart rate. Vital signs and BP will be measured at visits as indicated in Appendix B. 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.

3.8.4 Electrocardiograms

Standard 12-lead ECGs parameters (QRS interval, heart rate, RR interval, QT interval, and QTc [QTcF]) will be performed at Visits 1 (Day -70 to -14), 4 (Day 1), and 11 (Day 85) as indicated in Appendix B. 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 and treatment group.

3.8.5 Physical Examinations

A complete physical examination will include assessment of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system and will be performed at Visits 1 (Day -70 to -14) and 11 (Day 85) as indicated in Appendix B. A limited physical examination will consist of a minimum of general appearance, skin, heart, lungs, and abdomen and will be performed at the other clinical site visits.

Results of the physical examination will be presented in patient data listings by study visit. A listing of abnormal physical exam findings by visit will be provided.

3.8.6 Potassium Assessment

Drug Effect Model 220 non-compartmental methods (NCA) will be used for the calculation of safety parameters for potassium. The Linear-Log Trapezoidal method (equivalent to the Linear Up/Log Down option in WinNonlin) will be used in the computation of AUCs. Baseline will be set to zero and threshold will be set to 5.5 mmol/L. All potassium data analyses will be based on the Safety Population. The safety parameters for potassium calculated by NCA will be summarized descriptively by treatment for each part, including:

Parameters	**Description**
AUC_Above_T	Area under the response curve that is above the threshold value
Time_%Above_T	100 – Time_%Below_T

4 DATA REVIEW COMMITTEE

A data review committee (DRC) with multidisciplinary representation will be established to evaluate emerging data and to assess reports on cumulative SAEs. The DRC will determine the next safe dose(s) of CIN-107 (not to exceed 4 mg QD) based on review of data from approximately the first 25 randomized patients per group (1 mg CIN-107, 2 mg CIN-107, placebo) after they reach approximately 4 weeks of study drug dosing in the Double-Blind Treatment Period. Based on ongoing monitoring of the study, additional DRC reviews may be conducted.

The DRC will review all pertinent information in order to make a recommendation of whether the study should continue unchanged or whether protocol modifications are required to ensure patient safety and decide on a dose range most likely to have meaningful clinical benefit without undesired effects. To fulfil its responsibilities, the DRC may have access to unblinded data as described in the DRC Charter. The DRC Charter, detailing all aspects of the DRC's scope of review and procedures will be provided as a separate document.

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

A formal unblinded interim analysis will be conducted when approximately 200 randomized patients have completed the 12-week treatment period or have withdrawn early. Results of the interim analysis will be reviewed by an independent data monitoring committee (DMC). After the interim analysis, the DMC may recommend that the study continues, the study continues with sample size modifications, or the study is stopped for safety concerns or overwhelming evidence of efficacy. A small alpha value will be spent in order to protect the data integrity and to preserve an overall 2-sided significance level of 0.05 for the primary analysis.

To determine overwhelming efficacy, the DMC will be guided by a pre-specified stopping boundary based on Lan-DeMets (1983) cumulative error spending method using the approximate O'Brien-Fleming spending function. The primary endpoint is the comparison of change from baseline in SBP between the highest dose group (2 mg CIN-107) and placebo. Of the 200 patients randomized at the time of the interim analysis, we expect 51 patients to be randomized into both the 2 mg CIN-107 and placebo group. Therefore, approximately 102 out of the 154 total planned patients for these groups will be evaluable participants, and the Information Fraction used to determine the stopping boundary is 0.662. If the number of evaluable patients at the time of interim analysis is not 102, the Information Fraction will be updated based on the actual number of patients to be evaluated. The 1-sided null hypothesis is

the mean change in SBP in the treatment group is less than or equal to the mean change in SBP in the placebo group. The overall significance level for the one-sided test is 0.025 (or 0.05 for 2-sided test). The study will be stopped for overwhelming efficacy if the observed test statistic, z_1, is less than or equal to -2.520. The stopping boundary based on the p-value scale is such that the p-value is less than or equal to 0.00587. The table below gives the stopping boundaries for the interim and final analysis based on a 1-sided test at the 0.025 significance level.

Planned Analysis	Total Sample Size	Information Fraction	Efficacy Boundary		Boundary Crossing Probability (incremental)		Cumulative Alpha Spent
			Z Scale	Nominal p Value	Under H0	Under H1	
Interim	102	0.662	-2.51970	0.00587	0.006	0.412	0.00587
Final	154	1	-1.99195	0.02319	0.019	0.389	0.02500

Sample size re-estimation considerations will be based on the 2-sided test at significance level 0.05. The null hypothesis is the difference in mean change from baseline in SBP between the highest dose group (2 mg CIN-107) and placebo is zero. The Denne (2001) sample size re-estimation procedure will be utilized. At the time of the interim analysis, the conditional power will be calculated based on the interim data using the following formula

$$CP_\theta(n_2, c_2|z_1) = \Phi\left[\frac{c_2\sqrt{n_2} - z_1\sqrt{n_1} - \frac{(n_2 - n_1)}{\sqrt{2\sigma^2}}\theta}{\sqrt{n_2 - n_1}}\right]$$

where n_1 is the sample size per treatment group at the interim analysis review, the true difference in mean response θ is estimated by the current sample mean difference, and σ^2 is estimated by the current sample within group variance. The re-estimated sample size per treatment group n_2 is obtained by solving the conditional power be at least 80%.

It has been shown that the type I error rate can always be maintained at α if c_2 is calculated as:

$$c_2 = \tilde{c_2}\sqrt{\left\{\frac{\gamma_2 - \gamma_1}{\gamma_2(1 - \gamma_1)}\right\}} - z_1\sqrt{\left\{\frac{\gamma_1}{\gamma_2}\right\}}\left(\sqrt{\left\{\frac{\gamma_2 - \gamma_1}{1 - \gamma_1}\right\}} - 1\right),$$

where $\gamma_k = n_k/n_t$ with n_t being the planned target sample size and $\tilde{c_2}$ is the critical value for Z_2 by spending the remaining type I error after the interim analysis. If the re-estimated sample size is the same as the planned target sample size, then $c_2 = \tilde{c}_2$.

If the conditional power is greater than 50% at the interim analysis, no adjustment to the final statistic or the critical value is needed to protect the type I error rate for the final analysis (Chen, DeMets & Lan, 2004). Otherwise, the final test statistic is calculated as

$$Z_2 = z_1\sqrt{\left\{\frac{\gamma_1}{\gamma_2}\right\}} + \sqrt{(1 - \frac{\gamma_1}{\gamma_2})}z_{(2)},$$

where $z_{(2)}$ is the observed statistic from the $n_2 - n_1$ observations per treatment arm in the second stage. The hypothesis H_0 is rejected if $Z_2 > c_2$.

Sample size adjustments will be made if the re-estimated total sample size is larger than the planned total sample size of 348. The maximum sample size will be no more than 2 times the original number of planned randomized participants (696).

All calculations for the interim analysis and the unblinded sample size re-estimation will be conducted by an unblinded statistician. The DMC will review the results in a closed session and make appropriate recommendations to the Sponsor afterwards.

- Stop for overwhelming efficacy - Stop trial early due to strong evidence for efficacy due to test statistic being in the efficacy region.
- Continue without change - Continue with no changes due to test statistic not being in the efficacy region and the conditional power being >= 80%.
- Add required additional sample size, n, without exceeding the maximum sample size (696) and continue the trial.

The following list identifies all participants among the Modified Intent-to-Treat (mITT) Population who received a restricted blood-pressure altering therapy, outside of the current study design, at the time of the Interim Analysis of protocol CIN-107-121. According to the study protocol version 8.0, 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 systolic blood pressure assessment. Any efficacy measurement obtained after a patient received a restricted blood pressure altering therapy, outside of the current study design, will be removed from the mITT analysis. Treatment classification will be based on the randomized treatment. The mITT Population will be used for the primary analysis of all efficacy endpoints.

The listing of patients was reviewed jointly by the Medpace project team and the CinCor Pharma study team prior to the Data Monitoring Committee (DMC) receiving the unblinded analysis results. Medications were not considered to meet the protocol specified criteria if any of the following occurred: the medication was stopped prior to the patient's study randomization date, a beta blocker was listed as a background antihypertensive or had 'HYPERTENSION' as the primary indication, a beta blocker had a non-systemic route for dosing (i.e. eye drops, etc.), a non-steroidal anti-inflammatory drug (NSAID) was prescribed on an as needed basis (i.e. PRN) which is permitted per the protocol, a NSAID was not considered chronic in use (defined as a daily use for a duration of <30 days), a NSAID had a route for minimal systemic dosing (i.e. topical, etc.), if a CYP3A inducer was not considered as a strong inducer, or if a medication was determined to not be at risk of altering blood pressure.

The list below details the subjects with restricted medications whose assessments, following the start of the restricted medication, were removed from the analysis.

Subject ID	Medication	Date of Randomization	Medication Start Date	Medication Stop Date
23-005	Spironolactone	05/03/2021	06/26/2021	07/08/2021
52-001	Spironolactone	11/19/2020	02/17/2021	
74-007	Hydrochlorothiazide; Triamterene	01/29/2021	UNK/UNK/2017	
74-014	Spironolactone	03/26/2021	08/UNK/2020	05/25/2021

74-017	Carvedilol	02/11/2021	UNK/UNK/2016	
74-017	Spironolactone	02/11/2021	UNK/UNK/2018	

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 case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and Clinical Data Interchange Standards Consortium (CDISC) Define packages, including reviewer's guide, for both SDTM and ADaM data.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The incorporation of the stratification variable corresponding to the baseline glomerular filtration rate was not described in the protocol. Therefore, the continuous covariate of baseline glomerular filtration rate was included in the primary efficacy analysis model in order to be consistent with the analysis approach specified in the protocol that included the stratification variable of baseline SBP in the analysis model.

GFR used to stratify patients at randomization is based on Single Blind Run-In (Visit 3) laboratory results. Baseline GFR used in statistical analyses is determined using Randomization (Visit 4/Day 1) laboratory measures.

7 PROGRAMMING SPECIFICATIONS

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

Phoenix WinNonlin version 8.0 or higher will be used in the determination of the PK terminal phase and the calculation of PK parameters. PK parameters will also be calculated via SAS and verified with the Phoenix WinNonlin results.

APPENDIX A: REFERENCES

Chen, YH Joshua, David L. DeMets, and K. K. Gordon Lan. "Increasing the sample size when the unblinded interim result is promising." Statistics in Medicine 23.7 (2004): 1023-1038.

Denne, Jonathan S. Sample size recalculation using conditional power. Statistics in Medicine. 2001;20(17-18), 2645-2660.

Lan, K. K. G., and DeMets, D. L. (1983). “Discrete Sequential Boundaries for Clinical Trials.” Biometrika 70:659–663.

APPENDIX B: SCHEDULE OF PROCEDURES

	Screening Period		SB-RI Period	Double-Blind Treatment Period								Follow-up Period
	Screening Visit	Telephone Call 1										Telephone Call 2
Visit[a]	1	2	3	4	5	6	7	8	9	10	EOT/ET 11/NA	12
Week	-10 to -2	-4 to -2	-2 to 1	1	1	2	3	4	7	10	13/NA	14
Day (±Visit Window)	-70 to -14 (±2)	-28 to -14 (±2)	-14 to 1 (±2)	1 (±2)	3 (±2)	8 (±2)	15 (±2)	22 (±2)	43 (±2)	64 (±2)	85 (±2)/ NA	92 (±3)
Informed consent[b]	X											
Inclusion/Exclusion[c]	X		X	X[d]								
Demographics	X											
Medical/surgical history	X											
Adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications[f]	X[g]	X	X	X	X	X	X	X	X	X	X	X
Weight, height, and BMI[h]	X		X	X	X	X	X	X	X	X	X	
Vital signs[i]	X		X	X	X	X	X	X	X	X	X	
Seated BP[i]	X[j]		X	X[k]	X	X	X	X	X	X	X	
Standing BP and heart rate[l]	X		X	X	X	X	X	X	X	X	X	
Complete physical examination[m]	X										X	
Limited physical examination[n]			X	X	X	X	X	X	X	X		
12-lead ECG[o]	X			X							X	
Urinalysis	X		X	X	X	X	X	X	X	X	X	
Standard safety chemistry panel, hematology, coagulation	X		X	X	X	X	X	X	X	X	X	
HbA1c	X											
HIV, HBsAg, HCV screen	X											
Pregnancy test[p]	X			X							X	
FSH[q]	X											
PD blood sampling[r]				X			X	X			X	
PK blood sampling[s]								X			X[t]	
Send prescriptions to Central Pharmacy		X[u]		X[v]								

	Screening Period			Double-Blind Treatment Period								Follow-up Period
	Screening Visit	Telephone Call 1	SB-RI Period									Telephone Call 2
Visit[a]	1	2	3	4	5	6	7	8	9	10	EOT/ET 11/NA	12
Week	-10 to -2	-4 to -2	-2 to 1	1	1	2	3	4	7	10	13/NA	14
Day (±Visit Window)	-70 to -14 (±2)	-28 to -14 (±2)	-14 to 1 (±2)	1 (±2)	3 (±2)	8 (±2)	15 (±2)	22 (±2)	43 (±2)	64 (±2)	85 (±2)/ NA	92 (±3)
Dispense study drug			X[w]	←----------X[x]----------→								
Dispense antihypertensive medications			X		X[v]	X[v]						
Randomization				X								
Administer study drug[y]			X	X	X	X	X	X	X	X	X	
Assess treatment adherence[z]				X	X	X	X	X	X	X	X	
Adherence counselling[aa]		X	X	X	X	X	X	X	X	X		
Collect unused study drug				X[bb]							X[cc]	
Provide instructions for next visit[dd]		X	X	X	X	X	X	X	X	X[ee]		
PGx sample[ff]				←----------X----------→								
Provide materials for next 24-hour Urine Collection[gg]			X							X		
Obtain Sample from 24-hour Urine Collection[hh]				X							X	

a Unscheduled Visits may be scheduled at any time during the study period based on Investigator's discretion. See Section 6.2.7 for details of Unscheduled Visits.
b Written informed consent must be obtained before any protocol-specific procedures are performed.
c Screening laboratory evaluations, if abnormal, may be repeated once for eligibility purposes before excluding the patient. A patient who is screened and does not meet the study Inclusion/Exclusion Criteria or Randomization Criteria (screening failure) may be rescreened no less than 5 days after the last study visit, with Sponsor and/or Medical Monitor consultation and approval.
d Patients must meet the Randomization Criteria in addition to the Inclusion/Exclusion Criteria.
e Clinical sites will record the time of event (hour, min) for AEs that start and/or end on the first randomized study drug administration visit (Visit 4) or at Visit 11 (EOT).
f Clinical sites will record the time of concomitant medication administration (hour, min) if the medication is initiated and/or stopped on the first randomized study drug administration visit (Visit 4) or at Visit 11 (EOT).
g Patients taking an MRA or a potassium sparing diuretic (eg, triamterene, amiloride, etc) as an antihypertensive agent must be willing to discontinue this agent for study eligibility. The potassium sparing diuretic must be discontinued and replaced with a non-potassium sparing diuretic. If an MRA is a fourth antihypertensive agent, a replacement medication does not need to be initiated. If an MRA is a third antihypertensive agent, a replacement medication must be initiated. All patients who remain on a stable regimen of ≥3 antihypertensive agents, including a non-potassium sparing diuretic, for at least two weeks, will be eligible to enter the SB-RI Period.
h Height will be collected at Screening only and will be used to calculate BMI at subsequent visits.
i 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 using the standardized procedures listed in Section 9.10.

0.1

j 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 will then be used to take the Screening BP measurements (at least 5 minutes after determining laterality) and for all subsequent measurements.

k If the lowest and highest SBP measurements are >15 mmHg apart, additional readings should be performed. The last 3 consecutive, consistent SBP measurements will be averaged to determine the final value to be used to assess Randomization eligibility. If the lowest and highest SBP measurements are >20 mmHg apart after a total of 6 measurements, the measurements will not be used to assess study eligibility, but measurements may be reassessed after at least 72 hours. If the lowest and highest SBP values remain >20 mmHg apart after 6 measurements at a subsequent assessment, the patient will be excluded from the study.

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

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

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

o 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.

p For female patients of childbearing potential (ovulating, pre-menopausal, and not surgically sterile), serum pregnancy tests will be performed at Screening, EOT, and ET Visits. A POC pregnancy test will be performed at Randomization (Visit 4) to assess eligibility.

q FSH levels will be measured only for female patients who are post-menopausal for at least 1 year at Screening and are not surgically sterile.

r Pre-dose blood samples for PD analysis will be collected at specified visits. See Section 8.2.1 for details of blood sample collection for PD analysis.

s Pre-dose blood samples for PK analysis will be collected within approximately 15 minutes prior to dosing.

t Patients who provide written informed consent to participate in the optional Part B sub-study will undergo post-dose PK blood sampling at the following timepoints at Visit 11: 1, 2, 3, 4, 6, and 8 hours. A ±5 minutes window is permitted for the collection of post-dose PK samples; Additional PK samples may also be collected in the event of an SAE, AE leading to withdrawal, or any other safety event at the discretion of the Investigator, DRC, and/or Sponsor.

u Clinical sites will send prescriptions for background antihypertensive medications to the Central Pharmacy at Visit 2 or at least 1 week before Visit 3 to dispense at Visit 3.

v Clinical sites will send prescriptions for background antihypertensive medications to the Central Pharmacy on the day of randomization (Visit 4) to dispense at Visit 5 or Visit 6. The supply of background antihypertensive medications provided to the patient at Visit 5 or Visit 6 should be adequate to cover until Visit 11 (EOT).

w Study drug (a single-blind placebo) will be dispensed to cover the SB-RI period and dosing of the study drug will have been completed 1 day prior to Visit 4 for most patients.

x Randomized study drug (CIN-107 or placebo) dispensation may occur at any time starting at Visit 4 and before Visit 11 (EOT). A Study Reference Manual with details of study drug dispensation will be provided to clinical sites.

y During clinical site visits, patients will self-administer the study drug in the clinic to be witnessed by site staff after completion of pre-dose evaluations and laboratory sampling. Starting the following morning, patients will self-administer the study drug by mouth QD at home at approximately the same time each morning.

z Site staff will calculate treatment adherence based on pill counts. Between clinical site visits, site staff will utilize the electronic diary to ensure patient's adherence to background antihypertensive regimen and study drug.

aa Site staff will counsel patients about the importance of adhering to all of the following: background antihypertensive regimen, study drug, and the electronic diary.

bb After assessing treatment adherence, site staff will collect any remaining study drug (single-blind placebo) from the patient.

cc After assessing treatment adherence, patients will be permitted to keep the remaining background antihypertensive medications provided as part of this study and any remaining study drug will be collected by site staff.

dd Instruct patients to take their scheduled morning doses of background antihypertensive medications at home and to hold their dose of study drug on the morning of their next visit. Patients must bring their study drug and background antihypertensive medications to the clinical site at all visits. Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to the next visit.

ee Patients participating in the optional Part B sub-study should be instructed to present to the clinical site at Visit 11 in a fasting state for 8 hours relative to study drug administration and will remain so for 4 hours after study drug administration. Patients will not be able to eat or drink other than water during the 12 hours of fasting.

ff For patients who provide written informed consent to participate in the optional pharmacogenomic assessment, a blood sample will be collected at any time after Randomization.

gg Clinical sites will provide patients with Urine Collection materials (for Urine PD analytes) at Visits 3 and 10. Patients will be instructed to begin collecting all urine starting 24 hours prior to Visit 4 and 11 and to bring the entire sample to the clinical site.

hh A 24-hour urine collection can be repeated if the Investigator suspects that the sampling is insufficient and the patient is within the visit window; sites will aliquot urine into a transfer tube and send to Central Lab.

AE = adverse event; AOBPM = automated office BP monitoring; ARR = aldosterone/PRA ratio; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; EOT = End of Treatment; ET = Early Termination; FSH = follicle-stimulating hormone; HbA1c = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus;

HIV = human immunodeficiency virus; MRA = mineralocorticoid receptor antagonist; NA = not applicable; PD = pharmacodynamic(s); PGx = pharmacogenomic(s); PK = pharmacokinetic(s); POC = point-of-contact; PRA = plasma renin activity; SBP = systolic BP; SB-RI = Single Blind-Run In; QD = once daily.

APPENDIX C: 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
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid

Additional Chemistry Parameter

Glycosylated hemoglobin

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count

White blood cell count and differential [1]

1. Manual microscopic review is 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 is performed only as needed based on positive dipstick test results.

Endocrinology

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

1. Serum or point-of-care pregnancy tests will be performed only for female patients of childbearing potential (ovulating, pre-menopausal, and not surgically sterile).
2. FSH levels will be measured only for female patients who are post-menopausal for at least 1 year at Screening and are not surgically sterile.

Serology

Hepatitis B surface antigen	Hepatitis C virus RNA
HIV antibody	

Pharmacodynamic Analytes

Aldosterone	Cortisol [1]
Plasma renin activity	B type Natriuretic Peptide

1. Total cortisol will be measured. Measurement of free cortisol will be performed if changes are noted in total cortisol.

24-hour Urine Collection Analytes

Aldosterone

Potassium

Sodium

Creatine

Albumin

Protein