CLINICAL STUDY PROTOCOL

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)

Investigational Product: CIN-107
Protocol Number: CIN-107-121

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SIGNATURE PAGE

STUDY 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)

I, the und agree that it contains all necessary informatio
required to

Signature Date

[redacted]

CinCor Ph

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by CinCor Pharma, Inc. (hereinafter CinCor) to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to CinCor and that it may not be further disclosed to third parties. I understand that the study may be terminated, or enrollment suspended at any time by CinCor, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ ____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

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

INVESTIGATIONAL PRODUCT: CIN-107

PHASE: 2

INDICATION: Reduction of blood pressure (BP) in patients with rHTN

OBJECTIVES:

Part A

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 SBP after 12 weeks of treatment in patients with rHTN.

The secondary objectives are the following:

- To evaluate the change from baseline in mean seated diastolic BP (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 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.

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 (Visit 11).

The pharmacokinetic-pharmacodynamic (PK-PD) objective is to evaluate exposure-response relationships of CIN-107 using measures of safety, PD, and/or efficacy.

Part B

Part B is a sub-study, optional to both clinical sites and patients, to characterize the PK of CIN-107 in patients with rHTN and to obtain additional data to support the PK-PD objective of Part A.

POPULATION:

All Inclusion, Exclusion, and Randomization Criteria for patients participating in Part A are applicable to patients participating in Part B. No new patients will be enrolled into Part B, and there are no additional criteria for participation in Part B.

Inclusion Criteria

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

1. Are adult male and female patients ≥18 years;
2. Is on a stable regimen of ≥3 antihypertensive agents at the time of Screening, 1 of which is a diuretic, at maximum tolerated dose (MTD) based on Investigator judgment;

   Note: Patients taking a mineralocorticoid receptor antagonist (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 Single Blind-Run In (SB-RI) Period;

   Note: Anti-anginal nitrates including nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate are not considered antihypertensive agents;
3. Has a mean seated BP ≥130/80 mmHg;

   Note: Mean seated BP is defined as the average of 3 seated BP measurements at any single clinical site visit. Patients may have mean seated BP <130/80 mmHg at Screening if taking an MRA as part of their antihypertensive regimen; however, the mean seated BP must be ≥130/80 mmHg at Visit 3 after discontinuing the MRA, with or without replacement medication;
4. Agrees to comply with the contraception and reproduction restrictions of the study as follows:
   - Male subjects must agree to abstain from sperm donation from Day 1 through 90 days after the final dose of study drug;
   - Postmenopausal women must have had no menstrual bleeding for at least 1 year and either be >60 years or have an elevated plasma follicle-stimulating hormone level >40 mIU/mL at Screening;
   - Female patients of childbearing potential (ie, ovulating, pre-menopausal, and not surgically sterile) must have a documented negative pregnancy test at Screening and Randomization;

All male patients (unless surgically sterile) must use a highly effective method of contraception (ie, <1% failure rate) from Day 1 through 90 days after the last administration of study drug;

Acceptable methods of contraception for male patients enrolled in the study include the following:

- Condoms with spermicide; or
- Surgical sterilization (vasectomy) at least 26 weeks before Screening; and

Female patients of childbearing potential must use a highly effective method of contraception (ie, <1% failure rate) from Day 1 through 30 days after the last administration of study drug;

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

- Surgical sterilization (tubal ligation);
- Intrauterine device for at least 12 weeks before Screening;
- Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before Screening; or
- Diaphragm used in combination with spermicide; and

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

Exclusion Criteria

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

1. Has a mean seated SBP ≥180 mmHg or DBP ≥110 mmHg;

   Note: Mean seated BP is defined as the average of 3 seated BP measurements at any single clinical site visit. If the patient did not take their regularly scheduled antihypertensive medications prior to the visit (Visits 1, 3, or 4), 1 BP re-test is allowed within 2 days after taking the medications.

2. Has a body mass index (BMI) >45 kg/m^2 at Screening (provided they still satisfy the arm circumference requirements, see exclusion criteria #3);
3. Has an upper arm circumference <7 or >17 inches at Screening;
4. Has been on night shifts at any time during the 4 weeks before Screening;
5. Is using a beta blocker for any primary indication other than systemic hypertension (eg, migraine headache);
6. Is not willing or not able to discontinue an MRA or a potassium sparing diuretic as part of an existing antihypertensive regimen;
7. Is not willing to discontinue taking a potassium supplement;
8. Is expected to receive or is receiving any of the exclusionary drugs (strong cytochrome P450 3A inducers and/or chronic use of non-steroidal anti-inflammatory drugs [NSAIDs]);

Note: patients are using chronic NSAIDs at screening who are willing to come off during the course of the study, are allowed to participate

9. Has known secondary causes of hypertension (eg, renal artery stenosis, uncontrolled or untreated hyperthyroidism, uncontrolled or untreated hypothyroidism, hyperparathyroidism, pheochromocytoma, Cushing's syndrome, or aortic coarctation) except obstructive sleep apnea;

   Note: patients with primary aldosteronism CAN BE considered for enrollment unless an adrenalectomy is expected before the end of their participation in the study.

10. Has documented estimated glomerular filtration rate <45 mL/min/1.73m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation at Screening;
11. Has known and documented New York Heart Association stage III or IV chronic heart failure at Screening;
12. Has had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure within 6 months before Screening;
13. Has known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease diagnosed from a prior echocardiogram;
14. Has planned coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) or any major surgical procedure;
15. Has had CABG or other major cardiac surgery (eg, valve replacement), peripheral arterial bypass surgery, or PCI within 6 months before Screening;
16. Has chronic permanent atrial fibrillation;
17. Has uncontrolled diabetes with glycosylated hemoglobin >9.5% at Screening;
18. Has planned dialysis or kidney transplant during the course of this study;
19. Has had prior solid organ transplant and/or cell transplants;
20. Has known hypersensitivity to CIN-107 or drugs of the same class, or any of its excipients;
21. Has any clinically relevant medical or surgical conditions (including patients with unstable conditions and/or treated with systemic immunosuppressants including corticosteroids) that, in the opinion of the Investigator, would put the patient at risk by participating in the study;
22. Has evidence of the following at Screening or at the start of the SB-RI Period (1 retest is allowed):
    - White blood cell count >15 × 10^9/L or absolute neutrophil count <1 × 10^9/L;
    - Potassium <3.5 mEq/L;
    - Potassium >5.0 mEq/L;

- Hemoglobin <10.0 g/dL and/or anticipated initiation of erythropoietin-stimulating agents and/or planned transfusion within 2 months after Screening; or
- Serum aspartate aminotransferase and/or alanine aminotransferase >3 × the upper limit of normal range, with a corresponding bilirubin >2 mg/dL, unless patient has a history of Gilbert's syndrome;

23. Is positive for HIV antibody, hepatitis C virus RNA, or hepatitis B surface antigen;
24. Has typical consumption of ≥14 alcoholic drinks weekly. Note: 1 drink of alcohol is equivalent to ½ pint of beer (285 mL), 1 glass of spirits (25 mL), or 1 glass of wine (125 mL);
25. Is pregnant, breastfeeding, or planning to become pregnant during the study;
26. Has participated in another clinical study involving any investigational drug within 30 days prior to Screening, or plans to participate in another clinical study within 30 days of discontinuation of study drug;
27. Has received experimental therapy with a small molecule within 30 days of Day 1 or 5 half-lives, whichever is greater, or received experimental therapy with a large molecule within 90 days of Day 1 or 5 half-lives, whichever is greater; or
28. Is considered to be unsuitable for any other reason that may either place the patient at increased risk during participation or interfere with the interpretation of the study outcomes by the Investigator, after reviewing medical and psychiatric history, physical examination, and laboratory evaluation.

Randomization Criteria

Patients must meet all of the following criteria at Randomization (Visit 4):

1. Continues to satisfy all Inclusion/Exclusion Criteria;
2. Has no change in background therapy consisting of ≥3 antihypertensive medications for at least 4 weeks prior to Randomization;
3. Has ≥70% and ≤120% adherence to each antihypertensive medication and placebo during the SB-RI Period, based on pill counts on the morning of Randomization; and
4. Has a mean (the average of 3 measurements) seated BP ≥130/80 mmHg at Randomization.

STUDY DESIGN AND DURATION:

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 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. 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. PK variables analyzed during the study will include plasma concentrations of CIN-107 and any measured metabolite(s).

Patients will be instructed to bring their antihypertensive medications and/or study drug to all clinical site visits. Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical site visit. All clinical site visits should occur between 6:00 a.m. and 11:00 a.m.

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.

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 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 selected treatment groups at the conclusion of the study.

A formal unblinded interim analysis will be conducted when approximately 200 patients have completed the 12-week treatment period by an independent data monitoring committee (DMC). The DMC will convene to evaluate for safety, potential sample size re-estimation, and early stopping for overwhelming efficacy. Details related to the DMC responsibilities, authorities, and procedures will be documented in the DMC Charter.

Study visits

Part A of the study will consist of 4 periods:

- A Screening Period (Screening Visit [Visit 1] and Telephone Call 1 [Visit 2]) of up to 8 weeks;
- An SB-RI Period (Visit 3) of 2 weeks;
- A Double-Blind Treatment Period (Visits 4 to 11) of 12 weeks; and
- A Follow-up Period (Telephone Call 2 [Visit 12]) 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.

Screening Period (Visits 1 and 2)

Patients will provide informed consent at the Screening Visit (Visit 1) and undergo assessment for Inclusion/Exclusion Criteria.

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. 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. Eligible patients will be contacted via Telephone Call 1 (Visit 2) to be informed about study qualification and to schedule their SB-RI Period.

Patients may have a mean seated BP <130/80 mmHg at Screening if taking an MRA as part of their antihypertensive regimen; however, the mean seated BP must be ≥130/80 mmHg at SB-RI Period (Visit 3) after MRA discontinuation, with or without replacement medication, for study eligibility.

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.

SB-RI Period (Visit 3)

The SB-RI Period will last approximately 2 weeks (± 2 days). The objective of this period is to determine whether medication adherence is a factor in patients not achieving goal BP.

All patients will receive their background antihypertensive medications, unless requested otherwise through a Central Pharmacy from Visit 3 through Visit 11. Clinical sites will send prescriptions for background antihypertensive medications to the Central Pharmacy at Visit 2 or at least 1 week before Visit 3. These medications will be delivered directly to the clinical site. Background antihypertensive medications and study drug (single-blind placebo) will be dispensed at Visit 3.

Double-Blind Treatment Period (Visits 4 to 11)

Measurements of efficacy and safety variables at Randomization (Visit 4) will constitute "baseline" measurements. Measurements of efficacy and safety variables recorded prior to study drug administration at the clinical site will constitute "pre-dose" measurements.

Patients with ≥70% and ≤120% adherence (based on pill counts) to each antihypertensive medication and study drug during the SB-RI Period, and a baseline mean seated BP of ≥130/80 mmHg will continue with Randomization eligibility procedures.

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 DRC will evaluate emerging data and reports on cumulative SAEs. Based on their assessments, the DRC will determine the next dose level(s) (not to exceed 4 mg QD) 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. Based on ongoing safety monitoring of the study, additional DRC reviews may be conducted.

Study drug (CIN-107 or placebo) dispensing may occur at any time starting at Visit 4 and before Visit 11. Clinical sites will send prescriptions for background antihypertensive medications to the Central Pharmacy at Visit 4 and these medications will be dispensed at Visit 5 or Visit 6. It is expected that the patient's background antihypertensive regimen remains unchanged, and is not titrated, during the treatment period. On clinical site visit days, patients will self-administer the morning dose of background hypertensive medications at home and withhold the study drug. At the clinical site, patients will self-administer the morning dose of study drug to be witnessed by site staff after completion of pre-dose evaluations and laboratory sampling. Between clinical site visits, patients will continue taking their study drug once daily by mouth at approximately the same time each morning. An electronic diary will be utilized to ensure patient's adherence to background antihypertensive regimen and study drug. The primary efficacy endpoint evaluation will take place at the End of Treatment (EOT) (Visit 11).

Pre-dose blood samples for PD analysis will be collected at Visits 4, 7, 8, and 11. Pre-dose blood samples for PK analysis will be collected at Visits 8 and 11. Safety and adherence will be monitored all throughout the Double-Blind Treatment Period.

Urine for PD and electrolyte measurements will be collected over 24 hours prior to dosing at Visit 4 as well as prior to dosing at Visit 11/EOT.

Follow-up Period (Telephone Call 2, Visit 12)

Patients will have a Telephone Call 2 (Visit 12) at 1 week ±3 days following the last dose of the study drug to assess adverse events (AEs) and concomitant medications including background antihypertensive regimen since study completion.

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 the End of Treatment (Visit 11).

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. Patients will not be able to eat or drink other than water during the 12 hours of fasting. Additional post-dose PK sampling will be performed 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.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Placebo tablets, indistinguishable from the CIN-107 tablets, will be administered during the SB-RI Period.

The 2 initial dose strengths of CIN-107 (1 mg once daily [QD] and 2 mg QD) were chosen based upon the observed safety, tolerability, PK, and PD profile established in healthy subjects. Additional dose strengths will be selected by a DRC based on the emerging data from the 1 mg and 2 mg cohorts in this study.

Patients will receive CIN-107 tablets 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.

EFFICACY ENDPOINTS:

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

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.

SAFETY ENDPOINTS:

The safety of CIN-107 will be assessed from the time of informed consent until the end of the Follow-up Period. All safety endpoints will be summarized descriptively. 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 AEs;
- 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 End of Treatment (Visit 11).

STATISTICAL ANALYSES:

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

- 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;

- 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. Treatment classification will be based on the randomized treatment. The mITT Population will be used for the primary analysis of all efficacy endpoints.

- 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 an End of Treatment Visit (Visit 11) value for the SBP assessment, and who did not experience a major protocol deviation that potentially impacted

the primary efficacy endpoint. The PP Population, along with the reason for exclusion, will be finalized prior to study unblinding;

- 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;

- Pharmacokinetic Population;

  The PK Population will include all patients in the mITT Population who have at least 1 quantifiable plasma concentration; and

- Pharmacodynamic Population;

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

Efficacy analysis

The primary efficacy analysis will compare the change in mean seated SBP from baseline (Visit 4) to End of Treatment (Visit 11) between each dose strength of CIN-107 and placebo. A mixed model for repeated measures will be used to perform this analysis. The analysis will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with a covariate of the baseline value. The restricted maximum likelihood estimation approach will be used with an unstructured covariance matrix. The least squares means, standard errors, and 2-sided 95% confidence intervals for each treatment group and for pairwise comparisons of each dose strength of CIN-107 to the placebo group will be provided. 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 the 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.

Missing data will be imputed using multiple imputation methodology. Results will be combined using Rubin's method. Full details of the model and imputation will be provided in the Statistical Analysis Plan.

Similar models will be used to analyze DBP and PD variables. Logistic regression analyses will be used to analyze binary endpoints with model covariates of treatment group, baseline SBP, and baseline DBP. No adjustment will be made for multiplicity in testing the secondary efficacy endpoints.

Safety analysis

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

Pharmacokinetic analysis

Individual plasma concentration data for CIN-107 and any measured metabolite(s) 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 any measured metabolite(s) will be listed by individual patient and summarized by treatment for active treatments in tabular format using descriptive statistics. Mean and individual plasma concentrations of CIN-107 and any measured metabolite(s) will be plotted against time points by regimen for patients in Part B.

Pharmacodynamic analysis

The PD Population will be the primary population for the PD analysis. All PD variables will be summarized descriptively.

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.

Interim Analysis

An interim analysis will be conducted when approximately 200 patients have completed the 12-week double-blind treatment period or have withdrawn early. The DMC will convene to evaluate for safety, potential sample size re-estimation, and early stopping for overwhelming 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.

SAMPLE SIZE DETERMINATION:

Part A

A sample size of at least 308 evaluable patients (ie, 77 patients per treatment group) will provide >80% power to detect a 5 mmHg difference in mean seated SBP (standard deviation = 11 mmHg) after 12 weeks of treatment with 3 dose strengths of CIN-107 compared to placebo at a 2-sided significance level of 0.05.

The sample size for this study was determined in order to provide sufficient power for the analyses of the primary efficacy endpoint described above. Therefore, assuming an approximately 13% dropout rate, enrollment of approximately 348 patients (ie, 87 patients per treatment group) is planned for this study.

Patients will be stratified according to their baseline SBP (<145 or ≥145 mmHg) and their baseline glomerular filtration rate (<60 or ≥60 mL/min/1.73m^2).

Part B

Approximately 10-15% of the patients are expected to participate in this optional sub-study. The sample size was chosen empirically to support the stated objectives and without formal statistical considerations. The proposed sample size is considered adequate to characterize the PK of CIN-107 in patients with rHTN.

SITES: Approximately 90 clinical sites in the United States for Part A, of which approximately 12 clinical sites will also participate in Part B.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACEI	Angiotensin-converting enzyme inhibitor
AE	Adverse event
AESI	Adverse event of special interest
AOBPM	Automated office blood pressure monitoring
ARB	Angiotensin receptor blocker
ARR	Aldosterone/plasma renin activity ratio
ASI	Aldosterone synthase inhibitor
AUC	Area under the concentration time curve
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CRA	Clinical research associate
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DRC	Data review committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure in utero
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisatio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
MAD	Multiple-ascending dose
MATE	Multidrug and toxin extrusion

Abbreviation	Definition
mITT	Modified Intent-to-Treat
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonist
MTD	Maximum tolerated dose
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
POC	Point-of-care
PP	Per-Protocol
PRA	Plasma renin activity
QD	Once daily
QTc	Heart rate-corrected QT interval
QTcF	Heart rate-corrected QT interval using Fridericia's formula
RAAS	Renin-angiotensin-aldosterone system
rHTN	Treatment-resistant hypertension
RNA	Ribonucleic acid
SAD	Single-ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SB-RI	Single Blind-Run In
SD	Standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
T_{max}	Median time to maximum plasma concentration

1 INTRODUCTION AND BACKGROUND INFORMATION

Aldosterone is a hormone that has been implicated in a variety of cardiovascular and renal diseases. It is the principal mineralocorticoid in humans and is synthesized in the adrenal cortex by aldosterone synthase. It is a key component of the renin-angiotensin-aldosterone system (RAAS) and acts as a critical regulator of fluid and electrolyte homeostasis through its agonism of the mineralocorticoid receptor (MR). Aldosterone's effect on end organs has been shown to occur via its direct interaction with the MR (genomic effect) in addition to mechanisms independent of that direct interaction (non-genomic or non-receptor mediated effects).[1,2,3]

Blood pressure (BP) is significantly reduced by partially inhibiting the activity of the RAAS with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), direct renin inhibitors, or MR antagonists (MRAs). The mechanism of action of these agents involves a reduction in aldosterone levels. These effects are demonstrated to occur in the setting of both normal and inappropriately elevated aldosterone levels. Many patients with hypertension have inappropriately high aldosterone concentrations that promote cardiac, renal, and vascular injury. Inhibiting aldosterone synthesis represents a promising target for the reduction of BP and mitigation of BP-dependent target organ damage.[4] The association between plasma aldosterone and long-term survival has been demonstrated in patients with congestive heart failure,[5,6,7,8] acute myocardial infarction,[9] and coronary artery diseases outside the setting of heart failure or acute myocardial infarction.[10] The blockade of aldosterone thereby represents a means not only to reduce BP, but also to mitigate target organ damage. Therefore, directly inhibiting the synthesis of aldosterone represents a promising target for the reduction of BP and a mitigation of the genomic and non-genomic effects on end organ damage.[4]

One of the challenges that has impacted the development of aldosterone synthase inhibitors (ASIs) has been the difficulty in selectively inhibiting aldosterone synthase and not affecting the synthesis of cortisol. The synthesis pathway of cortisol is catalyzed by 11β-hydroxylase (encoded by the cytochrome P450 family 11 subfamily B member 1 [CYP11B1] gene) and shares high sequence homology with aldosterone synthase (encoded by the CYP11B2 gene). Undesired inhibition of 11β-hydroxylase leads to suppression of cortisol levels, compromised stress and immunologic responses, adverse effects on some metabolic functions, and possibly increased mortality rates.[11,12,13,14] LCI699, an ASI was taken into clinical trials by Novartis but was discontinued for both anti-hypertensive and primary aldosteronism indications due to its lack of specificity for aldosterone synthase. It has recently been approved for the treatment of Cushing's Disease.

CIN-107 (formerly RO6836191) was acquired in 2019 from Roche Pharmaceuticals, Inc. by CinCor Pharma, Inc., which is pursuing further clinical development of the compound.[15] CIN-107 is a highly potent, selective, and competitive inhibitor of human aldosterone synthase. In preclinical in-vivo studies (primarily conducted in primates), CIN-107 significantly lowered aldosterone without affecting cortisol levels over a wide dose range. The ability of CIN-107 to lower aldosterone without affecting cortisol was confirmed following administration of single oral doses in healthy subjects (Study WP28586) conducted by Roche[16] and in the multiple-ascending dose (MAD) study (Study CIN-107-111) conducted by CinCor.

1.1 Overview of Preclinical Studies With CIN-107

CIN-107 is a potent, highly selective, and competitive inhibitor of aldosterone synthase. Its inhibition of human aldosterone synthase is 100-fold more potent than that of the closely related 11β-hydroxylase (encoded by the CYP11B1 gene).[15]

Dose- and exposure-dependent inhibition of aldosterone synthesis was confirmed in acute and sub-chronic monkey models. In cynomolgus monkeys challenged with an injection of adrenocorticotrophic hormone, CIN-107 blocked aldosterone synthesis without interfering with cortisol levels.[15]

In rats and monkeys, hepatic metabolism was the primary clearance mechanism for CIN-107. Renal clearance did not appear to play a significant role in the disposition of CIN-107.[15]

The adrenal gland was the primarily affected tissue in both rats and monkeys. CIN-107 was well tolerated in cynomolgus monkeys up to 7 mg/kg/day for up to 4 weeks but was not well tolerated at 40 mg/kg/day. A mechanistic 4-week cynomolgus monkey study demonstrated dose-related hypertrophy of zona glomerulosa cells with increased thickness or expansion of the zona glomerulosa layer, increased aldosterone synthase (encoded by the CYP11B2 gene) immunostaining, vacuolation (lipid), apoptosis, and proliferation of zona glomerulosa cells. These pathological changes in the adrenal gland were ameliorated by electrolyte supplementation, indicating that they were exaggerated pharmacological effects and physiologic/adaptive responses to aldosterone inhibition.[15]

CIN-107 was not tolerated at 50 mg/kg/day in a pilot dose range-finding study on embryo fetal development in Wistar rats. There was no evidence for a mutagenic, clastogenic, or aneugenic potential of CIN-107.[15]

In vitro cardiovascular safety was assessed in a manual Good Laboratory Practice (GLP) human ether-à-go-go related gene assay. The inhibitory concentration 20 was >150-fold above the free maximum plasma concentration (C_{max}) concentrations expected to be efficacious in man (at a ≤10 mg once daily [QD] dose for the treatment of hypertension). This indicated a very low probability of any QT liability.[15]

In a modified Irwin test and in a whole-body plethysmography study in male rats, single oral administrations of CIN-107 up to a dose of 50 mg/kg did not induce any adverse effects on central nervous system or respiratory function. The no observed adverse effect level was considered to be ≥50 mg/kg CIN-107 for both studies.[15]

1.2 Overview of Clinical Studies With CIN-107

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

Results of the SAD study which investigated the safety, tolerability, PK and pharmacodynamics (PD) of CIN-107 in healthy male volunteers (Study WP28586) demonstrated that single oral doses of CIN-107 up to 360 mg were well tolerated. There were no deaths, serious adverse events (SAEs), or dose limiting events, and the maximum tolerated dose (MTD) observed was at the highest dose tested of 360 mg.[15]

Following oral administration, CIN-107 was rapidly absorbed with a median time to C_{max} (T_{max}) typically observed between 0.5 and 2 hours. A second, generally lower, peak was often observed at 3 to 4 hours post-dose. Thereafter, concentrations declined from peak in a biphasic manner with a long median terminal elimination half-life of approximately 25 to 31 hours. Over the anticipated therapeutically relevant dose range (through 10 mg), peak and overall exposures (as assessed by C_{max} and area under the concentration time curve [AUC]) increased in a generally dose-proportional manner. Approximately 11% of the dose was recovered unchanged in the urine.

Single doses of CIN-107 reduced plasma and urine aldosterone levels by approximately 85% to 90% in a dose-dependent manner, consistently reaching a maximum effect at a dose of 10 mg CIN-107 under the different conditions tested (Cortrosyn® challenge, standing, normal salt diet, and low salt diet conditions). No change in plasma cortisol levels was apparent across the full dose range tested (0 to 360 mg CIN-107). Although there was no effect on cortisol levels through 360 mg, some partial inhibition of the CYP11B1 enzyme at exposures well above those considered to be therapeutically relevant may be occurring based on observed increases in 11-deoxycortisol (at doses of 180 and 360 mg) and 11-deoxycorticosterone (at doses ≥90 mg).

Results of the subsequent MAD study indicate that multiple ascending doses of CIN-107 up to 5 mg QD for 10 days were also well tolerated by healthy subjects under low salt (2.5 and 5 mg) and normal salt conditions (0.5, 1.5, and 2.5 mg). Specifically, there were no deaths, SAEs, or treatment-emergent adverse events (TEAEs) leading to withdrawal and there were no clinically significant changes in electrocardiograms (ECGs) or vital signs. PK data from the MAD study indicate that exposure to CIN-107 (as assessed based on C_{max} and AUC) is generally 2- to 2.5-fold higher at steady state as compared to that observed following a single dose. Exposures within the dose range studied increased in an approximately dose-proportional manner. PD data from this study confirmed the ability of CIN-107 to lower aldosterone at doses ≤ 5 mg without affecting levels of cortisol or its precursor 11-deoxycortisol in healthy subjects. As expected with a reduction in aldosterone levels, there were mild, dose-dependent increases in plasma potassium levels, and reduction in plasma sodium levels.

Results of the relative bioavailability assessment indicate that exposure to CIN-107 and its primary metabolite following administration of the CIN-107 tablet formulation planned for use in future studies is equivalent to that observed following administration of the oral solution used in the SAD and MAD studies. Consumption of a high fat, high calorie meal had no substantial impact on the extent of absorption (as assessed by C_{max} and AUC) but did have a small effect on the rate of absorption. T_{max} occurred approximately 1 hour later (median of 4 hours) when CIN-107 was administered with the specified meal as compared to in a fasted state (median of 3 hours).

Finally, the metformin drug-drug interaction study demonstrated that systemic exposure to metformin is unchanged when administered with CIN-107. Specifically, the geometric mean ratio (associated 90% CI) for C_{max} was 0.99 (0.91, 1.07) while the geometric mean ratios and associated confidence intervals for $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ were 1.00 (0.94, 1.06) and 0.97 (0.91, 1.03), respectively. Consistent with the findings in plasma, CIN-107 did not affect renal clearance of metformin (CL_R = 27.99 L/hr when metformin was administered alone and 26.48 L/hr in the presence of CIN-107). Furthermore, the safety profile of metformin was similar in the presence and absence of CIN-107. Specifically, there were no deaths, SAEs, or treatment-emergent adverse events (TEAEs) leading to withdrawal and there were no clinically significant changes in electrocardiograms (ECGs) or vital signs.

1.3 Rationale

Suppression of the RAAS by using ACEIs or ARBs is an important therapeutic strategy for cardiovascular and renal diseases. However, the phenomenon of aldosterone breakthrough (in which initially reduced plasma aldosterone levels return to baseline levels over time) has been observed in long-term treatment with ACEIs and ARBs. MRAs inhibit the action of aldosterone by preventing receptor binding. They can lead to a compensatory increase in aldosterone secretion, which enhances the non-MR-mediated effects of aldosterone, and affect tissues not entirely protected by MRAs, such as the brain. Such breakthrough may contribute to treatment-resistant hypertension (rHTN) and the progression of end organ damage.[17] Damage may also occur in a permissive milieu with attendant high sodium intake, in which even normal concentrations of aldosterone produce BP-independent target organ damage, acting through inflammatory and pro-fibrotic pathways.[1,3] Thus, there is an unmet need for aldosterone synthase inhibition in the management of rHTN.

CIN-107 is a highly potent, selective, and competitive inhibitor of aldosterone synthase. Based on findings from preclinical studies and the SAD and MAD clinical studies, CIN-107 may be a novel treatment for the deleterious effects of inappropriately elevated aldosterone levels in patients with rHTN. It has the potential to offer a new therapeutic option aimed at decreasing aldosterone concentrations in plasma and tissues, thus reducing both the MR-dependent and MR-independent effects of aldosterone.

The overall purpose of this placebo-controlled Phase 2 study is to evaluate the efficacy and safety of multiple dose strengths of CIN-107 in the treatment of patients with rHTN on a stable background hypertensive regimen. Efficacy will be analyzed by the change from baseline of systolic BP (SBP), diastolic BP (DBP), PK, and PD parameters. Adverse events (AEs) will be monitored from the time of informed consent until the end of the Follow-up Period. An electronic diary (between clinical site visits) and pill counts (at clinical site visits) will be utilized to monitor medication adherence. All patients will receive their background antihypertensive medications, unless requested otherwise through a Central Pharmacy from the time of the Single Blind-Run In (SB-RI) Period (Visit 3) through the End of Treatment Visit (Visit 11).

1.4 Risk/Benefit

1.4.1 Potential Risks

1.4.1.1 Risk of hyperkalemia and hyponatremia

Aldosterone leads to increased reabsorption of sodium and water and secretion of potassium in the kidneys, thereby increasing blood volume and BP.[15] Based on the preclinical observations and the mode of action for CIN-107, reduction of circulating aldosterone levels may lead to natriuresis and subsequently to increased serum potassium, decreased serum sodium, possible dehydration, and decreased BP. Potassium and sodium levels will be closely monitored in this study.

1.4.1.2 Risk of hypovolemia and orthostatic hypotension

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

1.4.1.3 Risk of adrenal effects

While CIN-107 exhibits a highly selective CYP11B2 inhibition, CYP11B1 inhibition cannot be ruled out with repeat dosing and may result in reduction in cortisol levels, as seen at high doses in preclinical studies and in clinical studies for the non-selective CYP11B1/B2 inhibitor LCI699.[18,19,20]

1.4.1.4 Risk of sex hormone-related adverse events

Known side-effects of MRAs are gynecomastia, mastodynia, and abnormal vaginal bleeding, and were observed more frequently with spironolactone than with eplerenone. Occurrence of these events will be monitored in this study. A selective inhibitor of aldosterone synthase is nevertheless not expected to interfere with sexual hormone pathways.[15]

1.4.1.5 Risk of allergic reactions

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

1.4.2 Potential Benefits

Patients enrolled in this study could benefit from the BP lowering effect of CIN-107.

CIN-107 is an aldosterone synthase inhibitor. Aldosterone synthase inhibition is a new therapeutic option for the phenomenon of aldosterone breakthrough (in which initially reduced plasma aldosterone levels return to baseline levels over time). With aldosterone breakthrough, BP control may be diminished with the associated progression of end organ damage.[17]

Taken together, the preclinical data and existing clinical data support the activity and safety of CIN-107 and its continued clinical evaluation.

2 STUDY OBJECTIVES

2.1 Part A

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 SBP after 12 weeks of treatment in patients with rHTN.

2.1.2 Secondary Objectives

The secondary objectives are the following:

- To evaluate the change from baseline in mean seated 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 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 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 (Visit 11).

2.1.4 Pharmacokinetic-Pharmacodynamic Objective

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

2.2 Part B

Part B is a sub-study, optional to both clinical sites and patients, to characterize the PK of CIN-107 in patients with rHTN and to obtain additional data to support the PK-PD objective of Part A.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

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 multiple 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 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. 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 (ARR). PK variables analyzed during the study will include plasma concentrations of CIN-107 and any measured metabolite(s).

Patients will be instructed to bring their antihypertensive medications and/or study drug to all clinical site visits. Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical site visit. All clinical site visits should occur between 6:00 a.m. and 11:00 a.m.

3.1.1 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 multiple dose strengths of CIN-107 as compared to placebo after 12 weeks of treatment in patients with rHTN.

3.1.1.1 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 SAEs. Based on their assessments, the DRC will determine the next dose level(s) (not to exceed 4 mg 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.

A formal unblinded interim analysis will be conducted when approximately 200 patients have completed the 12-week treatment period by an independent data monitoring committee (DMC). The DMC will convene to evaluate for safety, potential sample size re-estimation, and early stopping for overwhelming efficacy. Details related to the DMC responsibilities, authorities, and procedures will be documented in the DMC Charter

3.1.1.2 Study visits

Part A of the study will consist of 4 periods:

- A Screening Period (Screening Visit [Visit 1] and Telephone Call 1 [Visit 2]) of up to 8 weeks;
- An SB-RI Period (Visit 3) of 2 weeks;
- A Double-Blind Treatment Period (Visits 4 to 11) of 12 weeks; and
- A Follow-up Period (Telephone Call 2 [Visit 12]) 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.

Screening Period (Visits 1 and 2)

Patients will provide informed consent at the Screening Visit (Visit 1) and undergo assessment for Inclusion/Exclusion Criteria.

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. 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. Eligible patients will be contacted via Telephone Call 1 (Visit 2) to be informed about study qualification and to schedule their SB-RI Period.

Patients may have a mean seated BP <130/80 mmHg at Screening if taking an MRA as part of their antihypertensive regimen; however, the mean seated BP must be ≥130/80 mmHg at SB-RI Period (Visit 3) after MRA discontinuation, with or without replacement medication, for study eligibility.

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.

SB-RI Period (Visit 3)

The SB-RI Period will last approximately 2 weeks (± 2 days). The objective of this period is to determine whether medication adherence is a factor in patients not achieving goal BP.

All patients will receive their background antihypertensive medications, unless requested otherwise through a Central Pharmacy from Visit 3 through Visit 11. Clinical sites will send prescriptions for background antihypertensive medications to the Central Pharmacy at Visit 2 or at least 1 week before Visit 3. These medications will be delivered directly to the clinical site. Background antihypertensive medications and study drug (single-blind placebo) will be dispensed at Visit 3.

Double-Blind Treatment Period (Visits 4 to 11)

Measurements of efficacy and safety variables at Randomization (Visit 4) will constitute "baseline" measurements. Measurements of efficacy and safety variables recorded prior to study drug administration at the clinical site will constitute "pre-dose" measurements.

Patients with ≥70% and ≤120% adherence (based on pill counts) to each antihypertensive medication and study drug during the SB-RI Period, and a baseline mean seated BP of ≥130/80 mmHg will continue with Randomization eligibility procedures.

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 DRC will evaluate emerging data and reports on cumulative SAEs. Based on their assessments, the DRC will determine the next dose level(s) (not to exceed 4 mg QD) 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. Based on ongoing monitoring of the study, additional DRC reviews may be conducted.

Study drug (CIN-107 or placebo) dispensing may occur at any time starting at Visit 4 and before Visit 11. Clinical sites will send prescriptions for background antihypertensive medications to the Central Pharmacy at Visit 4 and these medications will be dispensed at Visit 5 or Visit 6. It is expected that the patient's background antihypertensive regimen remains unchanged, and is not titrated, during the treatment period. On clinical site visit days, patients will self-administer the morning dose of background hypertensive medications at home and withhold the study drug. At the clinical site, patients will self-administer the morning dose of study drug to be witnessed by site staff after completion of pre-dose evaluations and laboratory sampling. Between clinical site visits, patients will continue taking their study drug QD by mouth at approximately the same time each morning. An electronic diary will be utilized to ensure patient's adherence to background antihypertensive regimen and study drug. The primary endpoint evaluation will take place at the End of Treatment (Visit 11).

Pre-dose blood samples for PD analysis will be collected at Visits 4, 7, 8, and 11. Pre-dose blood samples for PK analysis will be collected at Visits 8 and 11. Safety and adherence will be monitored all throughout the Double-Blind Treatment Period.

Urine for PD and electrolyte measurements will be collected starting 24 hours prior to dosing at Visit 4 as well as 24 hours prior to dosing at Visit 11/EOT.

Follow-up Period (Telephone Call 2, Visit 12)

Patients will have a Telephone Call 2 (Visit 12) at 1 week ±3 days following the last dose of the study drug to assess adverse events (AEs) and concomitant medications including background antihypertensive regimen since study completion.

Study visits will follow the Schedule of Procedures (Appendix A).

3.1.2 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 the End of Treatment (Visit 11).

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. Patients will not be able to eat or drink other than water during the 12 hours of fasting. Additional post-dose PK sampling will be performed 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.

3.2 Study Indication

CIN-107 is being studied for the reduction of BP in patients with rHTN.

4 SELECTION AND WITHDRAWAL OF PATIENTS

All Inclusion, Exclusion, and Randomization Criteria for patients participating in Part A are applicable to patients participating in Part B. No new patients will be enrolled into Part B, and there are no additional criteria for participation in Part B.

4.1 Inclusion Criteria

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

1. Are adult male and female patients ≥18 years;
2. Is on a stable regimen of ≥3 antihypertensive agents at the time of Screening, 1 of which is a diuretic, at MTD based on Investigator judgment;

   Note: Patients taking an MRA or a potassium sparing diuretic (eg, triamterene, amiloride, etc) as an antihypertensive agent must be willing to discontinue this agent for study eligibility. The potassium sparing diuretic 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;

   Note: Anti-anginal nitrates including nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate are not considered antihypertensive agents;
3. Has a mean seated BP ≥130/80 mmHg;

   Note: Mean seated BP is defined as the average of 3 seated BP measurements at any single clinical site visit. Patients may have mean seated BP <130/80 mmHg at Screening if taking an MRA as part of their antihypertensive regimen; however, the mean seated BP must be ≥130/80 mmHg at Visit 3 after discontinuing the MRA, with or without replacement medication;
4. Agrees to comply with the contraception and reproduction restrictions of the study as follows:
   - Male subjects must agree to abstain from sperm donation from Day 1 through 90 days after the final dose of study drug;
   - Postmenopausal women must have had no menstrual bleeding for at least 1 year and either be >60 years or have an elevated plasma follicle-stimulating hormone (FSH) level >40 mIU/mL at Screening;
   - Female patients of childbearing potential (ie, ovulating, pre-menopausal, and not surgically sterile) must have a documented negative pregnancy test at Screening and Randomization;
   - All male patients (unless surgically sterile) must use a highly effective method of contraception (ie, <1% failure rate) from Day 1 through 90 days after the last administration of study drug;

     Acceptable methods of contraception for male patients enrolled in the study include the following:

- Condoms with spermicide; or
- Surgical sterilization (vasectomy) at least 26 weeks before Screening; and

Female patients of childbearing potential must use a highly effective method of contraception (ie, <1% failure rate) from Day 1 through 30 days after the last administration of study drug;

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

- Surgical sterilization (tubal ligation);
- Intrauterine device for at least 12 weeks before Screening;
- Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before Screening; or
- Diaphragm used in combination with spermicide; and

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

4.2 Exclusion Criteria

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

1. Has a mean seated SBP ≥180 mmHg or DBP ≥110 mmHg;

   Note: Mean seated BP is defined as the average of 3 seated BP measurements at any single clinical site visit. If the patient did not take their regularly scheduled antihypertensive medications prior to the visit (Visits 1, 3, or 4), 1 BP re-test is allowed within 2 days after taking the medications.

2. Has a body mass index (BMI) >45 kg/m^2 at Screening (provided they still satisfy the arm circumference requirements, see exclusion criteria #3);
3. Has an upper arm circumference <7 or >17 inches at Screening;
4. Has been on night shifts at any time during the 4 weeks before Screening;
5. Is using a beta blocker for any primary indication other than systemic hypertension (eg, migraine headache);
6. Is not willing or not able to discontinue an MRA or a potassium sparing diuretic as part of an existing antihypertensive regimen;
7. Is not willing to discontinue taking a potassium supplement;
8. Is expected to receive or is receiving any of the exclusionary drugs (strong cytochrome P450 3A inducers and/or chronic use of non-steroidal anti-inflammatory drugs [NSAIDs]);

   Note: patients are using chronic NSAIDs at screening who are willing to come off during the course of the study, are allowed to participate;

9. Has known secondary causes of hypertension (eg, renal artery stenosis, uncontrolled or untreated hyperthyroidism, uncontrolled or untreated hypothyroidism, hyperparathyroidism, pheochromocytoma, Cushing's syndrome, or aortic coarctation) except obstructive sleep apnea;

Note: patients with primary aldosteronism CAN BE considered for enrollment unless an adrenalectomy is expected before the end of their participation in the study.

10. Has documented estimated glomerular filtration rate <45 mL/min/1.73m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation at Screening;[21]
11. Has known and documented New York Heart Association stage III or IV chronic heart failure at Screening;
12. Has had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure within 6 months before Screening;
13. Has known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease diagnosed from a prior echocardiogram;
14. Has planned coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) or any major surgical procedure;
15. Has had CABG or other major cardiac surgery (eg, valve replacement), peripheral arterial bypass surgery, or PCI within 6 months before Screening;
16. Has chronic permanent atrial fibrillation;
17. Has uncontrolled diabetes with glycosylated hemoglobin (HbA1c) >9.5% at Screening;
18. Has planned dialysis or kidney transplant during the course of this study;
19. Has had prior solid organ transplant and/or cell transplants;
20. Has known hypersensitivity to CIN-107 or drugs of the same class, or any of its excipients;
21. Has any clinically relevant medical or surgical conditions (including patients with unstable conditions and/or treated with systemic immunosuppressants including corticosteroids) that, in the opinion of the Investigator, would put the patient at risk by participating in the study;
22. Has evidence of the following at Screening or at the start of the SB-RI Period (1 retest is allowed):
    - White blood cell count >15 × 10^9/L or absolute neutrophil count <1 × 10^9/L;
    - Potassium <3.5 mEq/L;
    - Potassium >5.0 mEq/L;
    - Hemoglobin <10.0 g/dL and/or anticipated initiation of erythropoietin-stimulating agents and/or planned transfusion within 2 months after Screening; or
    - Serum aspartate aminotransferase and/or alanine aminotransferase >3 × the upper limit of normal range, with a corresponding bilirubin >2 mg/dL, unless patient has a history of Gilbert's syndrome;
23. Is positive for HIV antibody, hepatitis C virus (HCV) RNA, or hepatitis B surface antigen (HBsAg);
24. Has typical consumption of ≥14 alcoholic drinks weekly. Note: 1 drink of alcohol is equivalent to ½ pint of beer (285 mL), 1 glass of spirits (25 mL), or 1 glass of wine (125 mL);
25. Is pregnant, breastfeeding, or planning to become pregnant during the study;

26. Has participated in another clinical study involving any investigational drug within 30 days prior to Screening, or plans to participate in another clinical study within 30 days of discontinuation of study drug;
27. Has received experimental therapy with a small molecule within 30 days of Day 1 or 5 half-lives, whichever is greater, or received experimental therapy with a large molecule within 90 days of Day 1 or 5 half-lives, whichever is greater; or
28. Is considered to be unsuitable for any other reason that may either place the patient at increased risk during participation or interfere with the interpretation of the study outcomes by the Investigator, after reviewing medical and psychiatric history, physical examination, and laboratory evaluation.

4.3 Randomization Criteria

Patients must meet all of the following criteria at Randomization (Visit 4):

1. Continues to satisfy all Inclusion/Exclusion Criteria;
2. Has no change in background therapy consisting of ≥3 antihypertensive medications for at least 4 weeks prior to Randomization;
3. Has ≥70% and ≤120% adherence to each antihypertensive medication and placebo during the SB-RI Period, based on pill counts on the morning of Randomization; and
4. Has a mean (the average of 3 measurements) seated BP ≥130/80 mmHg at Randomization.

4.4 Screening Failure

Screening failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled in the study and do not receive the first dose of study drug at Visit 4. Minimal information collected regarding screening failures includes, but is not limited to, demography, reason for screening failures, and any SAEs.

4.4.1 Rescreening

A patient who is screened and does not meet the study Inclusion/Exclusion Criteria or Randomization Criteria (screening failure) may be considered for rescreening upon Sponsor and/or Medical Monitor consultation and approval. Rescreened patients will be assigned a new patient number. Rescreening should occur no less than 5 days after the last study visit.

4.5 Withdrawal Criteria

Participation of patients in this clinical study will be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason;
- The patient has mean seated BP >175/105 mmHg at 2 separate occasions during the Double-Blind Treatment Period;
- The patient has occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;

- The patient has any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;
- The patient has a requirement of prohibited concomitant medication;
- The patient fails to comply with protocol requirements or study-related procedures;
- The patient becomes pregnant; or
- The study is terminated by the Sponsor or the regulatory authority.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, they will be requested to undergo the Early Termination procedures and site staff should make every effort to complete the full panel of assessments scheduled for the End of Treatment (Visit 11). The reason for patient withdrawal must be documented in the electronic case report form (eCRF). Patients should still attend study visits after Early Termination for safety monitoring.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records. Withdrawn patients will not be replaced.

4.5.1 Criteria for Temporary Suspension of Dosing

Dosing of patients in this clinical study may be suspended temporarily for any of the following reasons. When one of the below criteria is met, the DRC will convene as soon as possible, but no later than 24 hours, after learning of the occurrence of a criteria in order to determine if all active subjects should suspend dosing.

- Any SAE that is deemed related to the study drug, including death;
- Withdrawal of a patient after randomization and who has received one or more doses of study drug for safety-related reasons;
- A study drug-related AE deemed by the Investigator to be severe in intensity (severity) in ≥2 patients;
- A study drug-related AE from a single System Organ Class deemed to be of moderate intensity (severity) in ≥4 patients; or
- Potassium ≥6 mEq/L; the patient should stop study drug dosing and present to the clinical site immediately for repeat testing. Note: This criterion is specific only to the individual subject suspending dosing. Other enrolled subjects do not need to suspend dosing unless determined necessary by the DRC. The patient may restart study drug following consultation and approval from the Medical Monitor.

This is not an exhaustive list. The Sponsor and/or DRC may also suspend dosing for any other reason based on emerging data from this study or other ongoing studies.

When the below event occurs, the DRC does not need to convene (unless it meets one of the above-mentioned criteria) but should be notified as soon as possible:

- The patient has evidence of hyponatremia (sodium concentrations <130 mmol/L with repeat confirmation within 72 hours upon notification) or SBP ≤90 mmHg with symptoms consistent with postural hypotension; Note: This criterion is specific only to

the individual subject suspending dosing. Other enrolled subjects do not need to suspend dosing. The patient may restart study drug following consultation and approval from the Sponsor and/or Medical Monitor.

5 STUDY TREATMENTS

5.1 Treatment Groups

Eligible patients will be randomized in a 1:1:1 ratio to one of the following groups:

- 1 mg CIN-107;
- 2 mg CIN-107; or
- Placebo.

After approximately the first 25 randomized patients per group reach approximately 4 weeks of study drug dosing, a DRC will review emerging data to determine the next dose level(s) (not to exceed 4 mg QD) 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 following treatment groups at the conclusion of the study:

- 1 mg CIN-107;
- 2 mg CIN-107;
- Dose(s) of CIN-107 selected by DRC;
- or Placebo.

5.2 Rationale for Dosing

Based on aldosterone response data from the SAD study, predicted steady-state PK, and established exposure-response relationships for aldosterone; selective and efficacious doses of CIN-107 within the range of 1 to 10 mg were anticipated at the time the MAD study commenced. Dose levels of 0.5, 1.5, 2.5, and 5 mg were ultimately assessed in the multiple dose study. Preliminary blinded results demonstrated that marked and selective inhibition of aldosterone in healthy subjects can be achieved with QD dosing of CIN-107 within the range studied in healthy subjects.

The 2 initial dose strengths of CIN-107 (1 mg QD and 2 mg QD) were chosen based upon the observed safety, tolerability, PK, and PD profile established in healthy subjects. Additional dose strengths (not to exceed 4mg QD) will be selected by a DRC based on the emerging data from the 1 mg and 2 mg cohorts in this study.

5.3 Single Blind-Run In Period

Placebo tablets, indistinguishable from the CIN-107 tablets, will be administered during the SB-RI Period to determine whether medication adherence is a factor in patients not achieving goal BP. The single-blind placebo will be included with the ongoing stable antihypertensive regimen.

5.4 Randomization and Double-Blind Treatment Period

Patients who meet all eligibility criteria 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.

An automated Interactive Response Technology (IRT) system will be used to randomize the patient to one of the treatment groups. Patients will be stratified according to their baseline SBP (<145 or ≥145 mmHg) and their baseline glomerular filtration rate (<60 or ≥60 mL/min/1.73m^2).

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, with the exception of an emergency situation involving a patient that requires unblinding of the treatment assignment (see Section 5.5).

5.5 Breaking the Blind

Blinding is not to be broken during the study unless considered necessary by the Investigator for emergency situations for reasons of patient safety or as determined by the DRC or Sponsor. Unblinding at the clinical site for any other reason will be considered a protocol deviation.

The Investigator should contact the Medical Monitor to discuss the event prior to unblinding. In the event this is not possible, the Investigator should contact the Medical Monitor as soon as possible to discuss the event. When the blind is broken, the reason must be fully documented. Documentation of the blind break must be retained in the patient's source documentation at the clinical site in such a way as to avoid unblinding the treatment assignment to other clinical sites or blinded study personnel.

5.6 Drug Supplies

5.6.1 Formulation and Packaging

CIN-107 is a white to yellow powder that has a low solubility in water and in non-polar organic solvents, but higher solubility in polar organic solvents. In the solid state, it exhibits good chemical stability.

CIN-107 tablets will be provided in the following strengths: 0.5 mg, 1 mg and 2 mg. The tablets will be packaged in blister packs to achieve the doses required for the study. CIN-107 tablets will contain the study drug as the active ingredient and lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate as inactive ingredients.

Matching placebo tablets will contain no active ingredient and the same inactive ingredients.

5.6.2 Study Drug Preparation and Dispensing

Blinded study drug will be delivered from the Central Depot to the clinical site. Once a patient has been assigned a randomized treatment via IRT, site staff who have been delegated the task of drug dispensing by the Investigator will dispense the appropriate treatment.

At Visit 3, 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. For the

Double-Blind Treatment Period, randomized study drug (CIN-107 or placebo) dispensation may occur at any time starting at Visit 4 and before Visit 11 (End of Treatment).

A Study Reference Manual with details of study drug dispensation will be provided to clinical sites.

5.6.3 Study Drug Administration

Patients will be allowed a normal diet every morning of study drug administration. On clinic visit days, patients will self-administer the morning dose of background hypertensive medications at home and withhold the morning dose of study drug. Patients will bring the study drug and all background antihypertensive medications to the clinic for assessment of treatment adherence and will self-administer the morning dose of study drug at the clinic to be witnessed by site staff after completion of pre-dose evaluations and laboratory sampling.

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. Patients will not be able to eat or drink other than water during the 12 hours of fasting.

See Study Reference Manual for details of study drug administration.

5.6.4 Treatment Adherence

Patients will self-administer the morning dose of study drug at the clinic to be witnessed by site staff during all clinic visits. The date and time of study drug administration will be recorded. A hand and mouth check will be performed by site staff.

At Visits 4 to 11, treatment adherence will be calculated by site staff using pill counts. A patient who is not at least 70%, and at most 120%, adherent to each antihypertensive medication and study drug during the SB-RI Period, based on pill counts on the morning of Visit 4, will not be eligible for Randomization. See Section 4.4.1 for details of rescreening. During the Double-Blind Treatment Period, site staff will collect information from the patient about delays with taking the study drug and missed study drug doses over the 3 days prior to PK sampling and record the information in source files and eCRF.

For all protocol-specified doses when the patient is not at the clinical site, patients will self-administer study drug at home and continue taking their background antihypertensive medications. Patients will use the electronic diary to record whether the daily dose(s) of study drug and each background antihypertensive medication were self-administered. Between clinical site visits, site staff will utilize the electronic diary to ensure patient's adherence to study drug and background antihypertensive regimen. Each patient will be counseled by site staff at every visit on the importance of adhering to their background antihypertensive regimen, study drug, and the electronic diary, and about bringing their medications to each clinical site visit.

5.6.5 Storage and Accountability

The study drug will be stored at controlled room temperature of 20°C to 25°C (68°F to 77°F). Consistent with U.S. Pharmacopeia (USP) references, excursions between 15°C and 30°C are allowed. During transport, excursions up to 40°C are permissible for up to 1 week.

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

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

5.7 Prior and Concomitant Medications and/or Procedures

5.7.1 Excluded Medications and/or Procedures

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

- Strong CYP3A inducers;

Note: Examples of the above excluded medications are provided in Appendix D, Table 1.

- Beta blockers for any primary indication other than systemic hypertension;
- MRAs;
- Chronic use of NSAIDs;

Note: patients are using chronic NSAIDs at screening who are willing to come off during the course of the study, are allowed to participate

- Potassium sparing diuretics; and/or
- Potassium supplements.

5.7.2 Documentation of Prior and Concomitant Medication Use

All medications used within 30 days of Screening will be recorded. 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).

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

6 STUDY PROCEDURES

6.1 Informed Consent

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

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

Patients will be given the option to participate in the pharmacogenomic assessment during the consenting process. The written informed consent for pharmacogenomic sample collection will be included in the main informed consent form (ICF). 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 during the patient's participation in the study.

A second ICF will explain the objectives of the optional Part B sub-study, potential risks and benefits, and the impact of early withdrawal on the scientific validity of the study.

See Section 12.3 for details on informed consent.

6.2 Part A

6.2.1 Screening Period (Visits 1 and 2)

6.2.1.1 Screening Visit (Visit 1, Week -10 to -2)

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.

The following procedures will be performed at Visit 1:

- Obtain informed consent;
- Assess eligibility based on Inclusion/Exclusion Criteria;
- Record demographics and medical/surgical history;
- Assess and record AEs;
- Record prior medications;

  Note: Patients taking an MRA or a potassium sparing diuretic (eg, triamterene, amiloride, etc) as an antihypertensive agent must be willing to discontinue this agent for study eligibility. The potassium sparing diuretic 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.

- Measure weight and height;
- Record vital signs including seated BP;

  Note: Seated BP will be measured in both upper arms (3 times/arm) using an appropriately sized cuff and automated office BP monitoring (AOBPM) to detect possible laterality differences. The arm with the higher mean seated BP value will then be used to take the Screening BP measurements (at least 5 minutes after determining laterality) and for all subsequent measurements. Subsequent BP measurements should be obtained at approximately the same time of day as the Screening measurements are obtained.

- Measure standing BP and heart rate;

  Note: Vital signs and BP measurements will be recorded using the list of standardized procedures in Section 9.10.

- Perform a complete physical examination (general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system);
- Perform 12-lead ECG after the patient has been resting in the supine position for at least 10 minutes;
- Collect urine sample for urinalysis; and
- Collect blood samples for the following:
  - Standard safety chemistry panel, hematology, and coagulation;
  - HbA1c;
  - HIV, HBsAg, and HCV screen;
  - Serum pregnancy test for female patients of childbearing potential; and
  - FSH for female patients who are postmenopausal for at least 1 year and are not surgically sterile.

6.2.1.2 Telephone Call 1 (Visit 2, Week -4 to -2)

Once all eligibility blood tests are available, 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. Eligible patients will be contacted via telephone to be informed about study qualification and to schedule their SB-RI Period.

The following procedures will be performed at Visit 2:

- Assess and record AEs;
- Record concomitant medications;
- Perform adherence counselling;

- Provide the following instructions for the next visit:
  - Patients should take their scheduled morning doses of background antihypertensive medications at home on the morning of their next visit;
  - Patients must bring their background antihypertensive medications to the clinical site for their next visit; and
  - Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to the next visit; and
- Send prescriptions for background antihypertensive medications to the Central Pharmacy at Visit 2 or at least 1 week before Visit 3.

  Note: These medications will be delivered directly to the clinical site and provided to the patient at Visit 3.

6.2.2 Single Blind-Run In Period (Visit 3, Week -2 to 1)

The objective of the SB-RI Period is to determine whether medication adherence is a factor in patients not achieving goal BP.

The following procedures will be performed at Visit 3:

- Assess eligibility based on Inclusion/Exclusion Criteria;
- Assess and record AEs;
- Record concomitant medications;
- Record pre-dose seated BP;
- Perform the following routine safety evaluations pre-dose:
  - Record weight;
  - Record vital signs;
  - Perform limited physical examination (general appearance, skin, heart, lungs, and abdomen);
  - Measure standing BP and heart rate;
  - Collect urine sample for urinalysis; and
  - Collect blood samples for standard safety chemistry panel, hematology, and coagulation;

    Note: Vital signs and BP measurements will be recorded using the list of standardized procedures in Section 9.10.
- Dispense study drug (a single-blind placebo for the SB-RI Period);
- Administer study drug after completion of pre-dose evaluations and laboratory sampling;

  Note: Patients will self-administer the first dose of study drug at the clinic to be witnessed by site staff. Starting the following morning, patients will self-administer the study drug by mouth QD at home at approximately the same time each morning. Dosing of the study drug will have been completed 1 day prior to Visit 4 for most patients.

- Dispense background antihypertensive medications supplied via the Central Pharmacy;
- Perform adherence counselling;

  Note: Site staff will counsel patients about the importance of adhering to all of the following: background antihypertensive regimen, study drug, electronic diary; and
- Supply the patient with materials/container for the next 24-hour urine collection, which should begin 24-hours prior to Visit 4.
- Provide the following instructions for the next visit:
  - Patients should take their scheduled morning doses of background antihypertensive medications at home and hold their dose of study drug on the morning of their next visit;
  - Patients must bring their background antihypertensive medications and any remaining study drug to the clinical site for their next visit; and
  - Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to the next visit.

6.2.3 Double-Blind Treatment Period (Visits 4 Through 11)

6.2.3.1 Baseline and Randomization (Visit 4, Day 1, Week 1)

The following procedures will be performed at Visit 4:

- Assess eligibility based on Inclusion/Exclusion and Randomization Criteria;
- Assess and record AEs;
- Record concomitant medications;
- Assess treatment adherence based on pill counts;
- Record pre-dose seated BP;

  Note: 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.

  Perform the following routine safety evaluations pre-dose;
  - Record weight;
  - Record vital signs;
  - Perform limited physical examination (general appearance, skin, heart, lungs, and abdomen);
  - Measure standing BP and heart rate;
  - Collect urine sample for urinalysis;

- Collect blood samples for standard safety chemistry panel, hematology, and coagulation; and
- Perform 12-lead ECG after the patient has been resting in the supine position for at least 10 minutes;

  Note: Vital signs and BP measurements will be recorded using the list of standardized procedures in Section 9.10.

- Perform point-of-care (POC) pregnancy test for female patients of childbearing potential;
- Collect blood samples for PD assessments after the patient has been seated in the clinic for approximately 15 minutes;
- Obtain the 24-hour urine sample (sample collected by the patient during the 24-hour period prior to the scheduled study visit);
- Collect blood sample for optional pharmacogenomic analysis for consented patients only;
- Collect any remaining study drug (single-blind placebo) from the patient after assessing treatment adherence;
- Perform Randomization;
- Dispense study drug;
- Administer study drug after completion of pre-dose evaluations and laboratory sampling;

  Note: Patients will self-administer the first dose of study drug at the clinic to be witnessed by site staff. Starting the following morning, patients will self-administer the study drug by mouth QD at home at approximately the same time each morning.

- Perform adherence counselling;

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

- Provide the following instructions for the next visit:
  - Patients should take their scheduled morning dose of background antihypertensive medications at home and hold their dose of study drug on the morning of their next visit;
  - Patients must bring their background antihypertensive medications and study drug to the clinical site for their next visit; and
  - Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to the next visit; and
- Send prescriptions for background antihypertensive medications to the Central Pharmacy.

  Note: These medications will be delivered directly to the clinical site and provided to the patient 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 (End of Treatment).

6.2.3.2 Visit 5 (Day 3, Week 1)

The following procedures will be performed at Visit 5:

- Assess and record AEs;
- Record concomitant medications;
- Record pre-dose seated BP;
- Perform the following routine safety evaluations pre-dose;
  - Record weight;
  - Record vital signs;
  - Perform limited physical examination (general appearance, skin, heart, lungs, and abdomen);
  - Measure standing BP and heart rate;
  - Collect urine sample for urinalysis; and
  - Collect blood samples for standard safety chemistry panel, hematology, and coagulation;

    Note: Vital signs and BP measurements will be recorded using the list of standardized procedures in Section 9.10.
- Collect blood sample for optional pharmacogenomic analysis for consented patients only, if not previously obtained;
- (Visit 5 or Visit 6) Dispense background antihypertensive medications supplied via the Central Pharmacy;

  Note: All patients will receive their background antihypertensive medications, unless requested otherwise through a Central Pharmacy.
- Dispense study drug as required;
- Administer study drug after completion of pre-dose evaluations and laboratory sampling;
- Assess treatment adherence based on pill counts;
- Perform adherence counselling; and

  Note: Site staff will counsel patients about the importance of adhering to all of the following: background antihypertensive regimen, study drug, electronic diary.
- Provide the following instructions for the next visit:
  - Patients should take their scheduled morning dose of background antihypertensive medications at home and hold their dose of study drug on the morning of their next visit;
  - Patients must bring their background antihypertensive medications and study drug to the clinical site for their next visit; and
  - Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to the next visit.

6.2.3.3 Visits 6, 9, and 10 (Weeks 2, 7, and 10, respectively)

The following procedures will be performed at Visits 6, 9, and 10:

- Assess and record AEs;

- Record concomitant medications;
- Record pre-dose seated BP;
- Perform the following routine safety evaluations pre-dose:
  - Record weight;
  - Record vital signs;
  - Perform limited physical examination (general appearance, skin, heart, lungs, and abdomen);
  - Measure standing BP and heart rate;
  - Collect urine sample for urinalysis; and
  - Collect blood samples for standard safety chemistry panel, hematology, and coagulation;

  Note: Vital signs and BP measurements will be recorded using the list of standardized procedures in Section 9.10.
- Collect blood sample for optional pharmacogenomic analysis for consented patients only, if not previously obtained;
- Dispense study drug as required;
- Administer study drug after completion of pre-dose evaluations and laboratory sampling;
- Assess treatment adherence based on pill counts;
- Perform adherence counselling; and

  Note: Site staff will counsel patients about the importance of adhering to all of the following: background antihypertensive regimen, study drug, electronic diary.
- (Visit 10 only) Supply the patient with materials/container for the next 24-hour urine collection, which should begin 24-hours prior to Visit 11.

- Provide the following instructions for the next visit:
  - Patients should take their scheduled morning dose of background antihypertensive medications at home and hold their dose of study drug on the morning of their next visit;
  - Patients must bring their background antihypertensive medications and study drug to the clinical site for their next visit;
  - Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to the next visit; and
  - At Visit 10, 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.

6.2.3.4 Visit 7 (Week 3)

The following procedures will be performed at Visit 7:

- Assess and record AEs;
- Record concomitant medications;
- Record pre-dose seated BP;
- Perform the following routine safety evaluations pre-dose:
  - Record weight;
  - Record vital signs;
  - Perform limited physical examination (general appearance, skin, heart, lungs, and abdomen);
  - Measure standing BP and heart rate;
  - Collect urine sample for urinalysis; and
  - Collect blood samples for standard safety chemistry panel, hematology, and coagulation;

    Note: Vital signs and BP measurements will be recorded using the list of standardized procedures in Section 9.10.
- Collect pre-dose blood samples for PD assessments after the patient has been seated in the clinic for approximately 15 minutes;
- Collect blood sample for optional pharmacogenomic analysis for consented patients only, if not previously obtained;
- Dispense study drug as required;
- Administer study drug after completion of pre-dose evaluations and laboratory sampling;
- Assess treatment adherence based on pill counts;
- Perform adherence counselling; and

  Note: Site staff will counsel patients about the importance of adhering to all of the following: background antihypertensive regimen, study drug, electronic diary.
- Provide the following instructions for the next visit:
  - Patients should take their scheduled morning dose of background antihypertensive medications at home and hold their dose of study drug on the morning of their next visit;
  - Patients must bring their background antihypertensive medications and study drug to the clinical site for their next visit; and
  - Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to the next visit.

6.2.4 Visit 8 (Week 4)

The following procedures will be performed at Visit 8:

- Assess and record AEs;
- Record concomitant medications;

- Record pre-dose seated BP;
- Perform the following routine safety evaluations pre-dose:
  - Record weight;
  - Record vital signs;
  - Perform limited physical examination (general appearance, skin, heart, lungs, and abdomen);
  - Measure standing BP and heart rate;
  - Collect urine sample for urinalysis; and
  - Collect blood samples for standard safety chemistry panel, hematology, and coagulation;

    Note: Vital signs and BP measurements will be recorded using the list of standardized procedures in Section 9.10.
- Collect pre-dose blood samples for PD assessments after the patient has been seated in the clinic for approximately 15 minutes;
- Collect pre-dose blood samples for PK assessments;
- Collect blood sample for optional pharmacogenomic analysis for consented patients only, if not previously obtained;
- Dispense study drug as required;
- Administer study drug after completion of pre-dose evaluations and laboratory sampling;
- Assess treatment adherence based on pill counts;
- Perform adherence counselling; and

  Note: Site staff will counsel patients about the importance of adhering to all of the following: background antihypertensive regimen, study drug, electronic diary.
- Provide the following instructions for the next visit:
  - Patients should take their scheduled morning dose of background antihypertensive medications at home and hold their dose of study drug on the morning of their next visit;
  - Patients must bring their background antihypertensive medications and study drug to the clinical site for their next visit; and
  - Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to the next visit.

6.2.5 End of Treatment (Visit 11, Week 13)

The following procedures will be performed at Visit 11:

- Assess and record AEs;
- Record concomitant medications;
- Record pre-dose seated BP;

Perform the following routine safety evaluations pre-dose:

- Record weight;
- Record vital signs;
- Perform complete physical examination (general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system);
- Measure standing BP and heart rate;
- Collect urine sample for urinalysis;
- Collect blood samples for standard safety chemistry panel, hematology, and coagulation; and
- Perform 12-lead ECG after the patient has been resting in the supine position for at least 10 minutes;

  Note: Vital signs and BP measurements will be recorded using the list of standardized procedures in Section 9.10.

- Perform serum pregnancy test for female patients of childbearing potential;
- Collect pre-dose blood samples for PD assessments after the patient has been seated in the clinic for approximately 15 minutes;
- Collect pre-dose blood samples for PK assessments;

  Note: Post-dose blood samples will be collected from patients participating in the optional Part B sub-study. See Section 6.3 for additional details.

- Collect blood sample for optional pharmacogenomic analysis for consented patients only, if not previously obtained;
- Administer study drug after completion of pre-dose evaluations and laboratory sampling;
- Obtain the 24-hour urine sample (sample collected by the patient during the 24-hour period prior to the scheduled study visit;
- Assess treatment adherence based on pill counts; and
- Collect any unused study drug from the patient after assessing treatment adherence.

  Note: Patients will be permitted to keep the remaining background antihypertensive medications provided as part of this study after assessing treatment adherence.

6.2.6 Follow-up Period (Telephone Call 2, Visit 12, Week 14)

The following follow-up procedures will be performed during Visit 12:

- Assess and record AEs; and
- Record changes to concomitant medications and background antihypertensive medications

6.2.7 Unscheduled Visits

Unscheduled Visits may occur at any time during the study period based on Investigator's discretion, including, but not limited to initiating replacement medication after discontinuing an MRA and/or a potassium sparing diuretic and/or for potassium ≥5.5 mEq/L.

The following procedures will be performed at any Unscheduled Visit:

- Assess continued eligibility based on Inclusion/Exclusion Criteria and Withdrawal Criteria;
- Record concomitant medications;
- Assess and record AEs;
- Record seated BP; and
- Perform adherence counselling.

Additional procedure(s) and investigation(s) may be performed depending on the reason for the visit at the Investigator's discretion.

6.3 Part B

Patients participating in the optional Part B sub-study at Visit 11 will first take part in the prior visits and procedures of Part A. See Section 6.1 for details on informed consent for Part B of the study.

Patients who provide written informed consent to participate in the optional Part B sub-study 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. Patients will not be able to eat or drink other than water during the 12 hours of fasting. Post-dose PK blood sampling will be performed 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.

In some situations, collection of specific individual PK samples (including but not limited to the collection of the sample at 8 hours post-dose) may not be required with prior written Sponsor approval.

6.4 Early Termination Visit and Withdrawal Procedures

The End of Treatment for patients completing the study is Visit 11. For patients who are withdrawn from the study prior to completion, all Visit 11 procedures (see Section 6.2.5) will be performed at the Early Termination Visit.

7 EFFICACY ASSESSMENTS

7.1 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.

7.2 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; and
- Percentage of patients achieving a seated BP response <130/80 mmHg of CIN-107 compared to placebo after 12 weeks of treatment for rHTN.

8 PHARMACOKINETIC, PHARMACODYNAMIC, AND PHARMACOGENOMIC ASSESSMENTS

8.1 Pharmacokinetic Assessments

8.1.1 Part A

Blood samples for PK analyses will be collected pre-dose at Visits 8 and 11 as specified in Appendix A. 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, if needed for comparison with safety and tolerability data. PK samples should be collected within approximately 15 minutes prior to dosing. The actual date and time of collection of each PK sample will be recorded. Site staff will collect information from the patient about delays with taking the study drug and missed study drug doses over the 3 days prior to PK sampling and record the information in source files and eCRF.

Samples will be analyzed to measure the plasma concentrations of CIN-107 and any measured metabolite(s) using validated liquid chromatography mass spectrometry methods. Analysis will be performed by Medpace Bioanalytical Laboratories, LLC.

Additional details regarding PK sample collection, processing, and shipment can be found in the Laboratory Manual.

8.1.2 Part B

The date and time of the study drug taken at the clinical site on the day of Visit 11 will be recorded. The actual date and time of collection of each post-dose PK sample will also be recorded. Site staff will collect information from the patient about delays with taking the study drug and missed study drug doses over the 3 days prior to PK sampling and record the information in source files and eCRF.

Patients in the optional Part B sub-study will have additional post-dose PK sampling performed 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.

The following plasma PK parameters will be determined for CIN-107 and any measured metabolite(s) using concentration data from the End of Treatment Visit (Visit 11), as the data permit:

- $C_{max;}$
- $T_{max;}$ and
- AUC from time 0 to the time of last measured plasma concentration.

8.2 Pharmacodynamic Assessments

Blood samples for PD analyses will be collected pre-dose at Visits 4, 7, 8, and 11 as specified in Appendix A. Urine samples from a 24-hour urine collection will be obtained over the 24 hours leading up to Visit 4 and 11 as specified in Appendix A.

Additional PD 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 and/or Sponsor. The actual date and time of collection of each PD sample will be recorded.

Plasma PD variables may include, but are not limited to, the following:

- Aldosterone and its precursors (18-hydroxycorticosterone, corticosterone, and 11-deoxycorticosterone);
- PRA; and
- Cortisol (total) and its precursor 11-deoxycortisol.

  Note: Measurement of free cortisol will be performed if changes are noted in total cortisol.

Levels of plasma electrolytes (collected as part of the standard safety chemistry panel, see Appendix B) 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 be limited to, urinary sodium and potassium (see Appendix B).

8.2.1 Blood Sample Collection

PD 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. Additional details regarding PD sample collection, processing, and shipment can be found in the Laboratory Manual.

8.3 Pharmacogenomic Assessments

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

Patients will be given the option to participate in the pharmacogenomic assessment during the consenting process. The written informed consent for pharmacogenomic sample collection will be included in the main ICF. 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. The patient may withdraw consent to participate in the pharmacogenomic assessment at any time during the study without withdrawing consent to participate in the study. See Section 8.3.1 for details regarding sample and data destruction following withdrawal of consent.

The DNA blood sample will not be immortalized, sold to anyone, or submitted to a public genetic database.

If analysis of the pharmacogenomic samples is undertaken, details of sample and data analyses will be provided in a separate protocol and/or analysis plan. The results obtained from analysis of the pharmacogenomic samples will be accessible to the Sponsor, the party(ies) performing sample analysis and data analyses, and the party involved in maintenance of the Sponsor's database. The results may be disclosed to the Investigator but are not intended to be provided to the patient. The

pharmacogenomic results may be reported or published without any of the patient's personal identification information.

8.3.1 Collection, Storage, and Destruction of Pharmacogenomic Samples

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

Samples will be retained until exhausted or until the Sponsor requests destruction.

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

9 SAFETY ASSESSMENTS

9.1 Safety Endpoints

The safety of CIN-107 will be assessed from the time of informed consent until the end of the Follow-up Period. All safety endpoints will be summarized descriptively.

The safety endpoints will include the following:

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

9.2 Adverse Events

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

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until the end of the Follow-up Period. Patients should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study drug. Beginning at Screening, Investigators should make an assessment for AEs at each visit and record the events on the appropriate AE eCRF.

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

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

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

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

9.2.1 Adverse Drug Reaction

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

9.2.2 Unexpected Adverse Drug Reaction

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

9.2.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of yes or no.

Assessment of severity

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality assessment

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

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

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

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

The following factors should also be considered:

- The temporal sequence from study drug administration.

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases.

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug.

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug.

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses.

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug.

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

9.2.4 Adverse Events of Special Interest

The Investigator will monitor each patient for clinical and laboratory evidence for pre-defined adverse events of special interest (AESIs) throughout the patient's participation in this study.

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

For this study, AESIs include the following:

- Events of hypotension that require clinical intervention;
- Sodium levels that require clinical intervention; or
- Potassium levels that require clinical intervention.

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

AESIs must be recorded in the eCRF.

9.3 Serious Adverse Events

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

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death;

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations;

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

9.4 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator considers related to study drug must be reported to Medpace Clinical Safety or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an e-mail to Medpace Safety at Medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (telephone

number listed below), and fax/e-mail the completed paper SAE form to Medpace (contact information listed in Section 9.8) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

9.5 Overdose Reporting

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

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

All reports of overdose as described above must be reported on the Special Situations Report form and faxed/e-mailed to Medpace Clinical Safety (see Section 9.8) within 24 hours of knowledge of the event. All AEs associated with these Special Situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

9.6 Safety Surveillance and Management of Potassium Levels

Serum potassium levels will be monitored systemically throughout the study. Potassium will be measured at the Central Laboratory at each visit as indicated in the Schedule of Procedures (Appendix A). Unscheduled assessments of potassium levels should be completed at the Investigator's discretion for acute management of the patient (eg, follow-up from elevated central lab potassium, acute changes in clinical condition, suspected dehydration, etc.).

For serum potassium ≥5.5 mEq/L and <6 mEq/L, the patient should present to the clinical site immediately for repeat testing, but study drug dosing may continue.

For serum potassium ≥6 mEq/L, the patient should suspend study drug dosing and present to the clinical site immediately for repeat testing.

Repeat and unscheduled testing for potassium should be measured at the local laboratory and Central Laboratory.

9.7 Pregnancy Reporting

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

A pregnancy is not considered to be an AE or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/clinical site the exposure in utero (EIU) form for completion. The Investigator/clinical site must complete the EIU form and fax/e-mail it back to Medpace Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety Follow-up Period defined in the protocol, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/e-mailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

9.8 Expedited Reporting

Medpace will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), and in any case no later than 7 days after knowledge by Medpace of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

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

Medpace will also inform all Investigators as required per local regulations.

The requirements above refer to the requirements relating to study drug.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE hotline – United States:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
E-mail: medpace-safetynotification@medpace.com

9.9 Clinical Laboratory Evaluations

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. PD samples will be obtained as indicated in Appendix A and assessed at the facility specified in the Laboratory Manual. PK samples will be obtained as indicated in Appendix A and assessed at the Medpace Bioanalytical Laboratories, LLC. See Appendix B for a complete list of analytes.

A serum or POC pregnancy test will be performed for female patients of childbearing potential as indicated in Appendix A.

Urine samples (including samples from 24-hour urine collection) will be obtained as indicated in Appendix A and assessed at the Central Laboratory per institutional guidelines for complete urinalysis.

Blood samples for pharmacogenomic assessments will be stored and analyzed at Cincinnati Children's Hospital Medical Center.

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

9.10 Vital Signs and Blood Pressure Measurement

Vital signs will include heart rate, respiratory rate, and body temperature. Orthostatic vitals will include standing BP and standing heart rate. Vitals signs and BP will be measured at visits as indicated in Appendix A using the following standardized procedures:

- Patients should not exercise, smoke, or consume caffeinated beverages or food 30 minutes prior to assessment of vital signs and AOBPM;
- On visits when study drug will be administered, vital signs and BP will be assessed pre-dose;
- Vitals signs and BP measurements should be obtained prior to ECG recordings; and
- For measuring BP by AOBPM, the following additional standardized procedures are recommended:
    - Patient should be seated for at least 5 minutes in the examination room with the back supported, feet flat on the floor, and the measurement arm supported so that the midpoint of the manometer cuff is at heart level;
    - A designated AOBPM device will be provided to each clinical site and must be used for all study-related measurements;
    - An appropriately sized cuff should be used with the bladder centered over the brachial artery;
    - The cuff size and arm used for the measurement should be recorded;
    - The arm with the higher mean BP value at Screening should be used for Screening and subsequent BP measurements;
    - All BP measurements should be obtained at approximately the same time of day as the Screening measurements are obtained.
    - 3 seated BP measurements (each measurement 1 to 2 minutes apart) should be obtained using the same arm and the AOBPM device at each clinical site visit. Mean seated BP is defined as the average of 3 seated BP measurements at any single clinical site visit;
    - If the lowest and highest SBP measurements are >15 mmHg apart, additional readings should be performed; and
    - 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, as required.

9.11 Electrocardiograms

Standard 12-lead ECGs will be performed at Visits 1, 4, and 11 as indicated in Appendix A.

ECGs will be performed after the patient has been resting in the supine position for at least 10 minutes. 12-lead ECGs will be printed and will be interpreted as soon as possible by a qualified Investigator (or Sub-investigator). All ECGs collected at the time of Randomization, End of Treatment, and Early Termination Visits must be evaluated for the presence of abnormalities by a qualified physician.

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

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

Investigators should contact the Sponsor or designee if any clinically meaningful changes from baseline are noted on review. See Appendix C for ECG alert criteria guidance.

9.12 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 and 11 as indicated in Appendix A.

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.

9.13 Height and Weight

Weight will be measured at the visits indicated in Appendix A. Height measured at Visit 1 will be used to calculate BMI at subsequent visits. Height will be measured with the patient's shoes off. Weight will be measured with the patient's shoes off and after the patient's bladder has been emptied.

10 STATISTICS

10.1 Analysis Populations

10.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will include all patients randomized into the study. Treatment classification will be based on the randomized treatment.

10.1.2 Modified Intent-to-Treat Population

The Modified ITT (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. Treatment classification will be based on the randomized treatment. The mITT Population will be used for the primary analysis of all efficacy endpoints.

10.1.3 Per-Protocol Population

The Per-Protocol (PP) Population will include all patients in the mITT Population who have a baseline value for the SBP assessment, have an End of Treatment Visit (Visit 11) value for the SBP assessment, and who did not experience a major protocol deviation that potentially impacted the primary efficacy endpoint. The PP Population, along with the reason for exclusion, will be finalized prior to study unblinding.

10.1.4 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.

10.1.5 Pharmacokinetic Population

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

10.1.6 Pharmacodynamic Population

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

10.2 Statistical Methods

A Statistical Analysis Plan (SAP) will be finalized before database lock. Any changes to the methods described in the final SAP will be described and justified as needed in the clinical study report.

All study-collected data will be summarized by treatment group using descriptive statistics, graphs, and/or raw data listings. Descriptive statistics for continuous variables will include number of patients (n), mean, standard deviation (SD), median, minimum, and maximum values. Analysis of categorical variables will include frequency and percentage.

10.2.1 Efficacy Analysis

The PP Population will be the primary population for the efficacy analyses. Efficacy will also be analyzed using the ITT Population and the mITT Population as supportive analyses.

The primary efficacy analysis will compare the change in mean seated SBP from baseline (Visit 4) to End of Treatment (Visit 11) between each dose strength of CIN-107 and placebo. A mixed model for repeated measures will be used to perform this analysis. The analysis will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with a covariate of the baseline value. The restricted maximum likelihood estimation approach will be used with an unstructured covariance matrix. The least squares means, standard errors, and 2-sided 95% confidence intervals for each treatment group and for pairwise comparisons of each dose strength of CIN-107 to the placebo group will be provided. 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 the 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.

Missing data will be imputed using multiple imputation methodology. Results will be combined using Rubin's method. Full details of the model and imputation will be provided in the SAP.

Similar models will be used to analyze DBP and PD variables. Logistic regression analyses will be used to analyze binary endpoints with model covariates of treatment group, baseline SBP, and baseline DBP. No adjustment will be made for multiplicity in testing the secondary efficacy endpoints.

10.2.2 Safety Analysis

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

10.2.3 Pharmacokinetic Analysis

Individual plasma concentration data for CIN-107 and any measured metabolite(s) 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 any measured metabolite(s) will be listed by individual patient and summarized by treatment for active treatments in tabular format using descriptive statistics. Mean and individual plasma concentrations of CIN-107 and any measured metabolite(s) will be plotted against time points by regimen for patients in Part B.

10.2.4 Pharmacodynamic Analysis

The PD Population will be the primary population for the PD analysis. All PD variables will be summarized descriptively.

10.2.5 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.

10.2.6 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 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. Additional details of the interim analysis will be provided in the DMC Charter and the SAP.

10.2.6.1 Data review committee

A 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.

10.2.6.2 Independent Data Monitoring Committee

An independent DMC will be established to evaluate for safety, potential sample size re-estimation, and early stopping for overwhelming efficacy. A DMC charter will specify details of

10.2.7

11 DATA MANAGEMENT AND RECORD KEEPING

11.1 Data Management

11.1.1 Data Handling

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

11.1.2 Computer Systems

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

11.1.3 Data Entry

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

11.1.4 Medical Information Coding

The following dictionaries will be used for coding medical information:

- Medical Dictionary for Regulatory Activities for medical history and AEs; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

11.1.5 Data Validation

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

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

11.2 Record Keeping

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

11.3 End of Study

The end of the study or study completion is defined as the date of the last protocol-specified visit or assessment (including telephone contact) for the last patient in the study.

12 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

12.2 Institutional Review Board

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

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

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

The study will only start in the respective clinical sites once the respective committee's written approval has been given.

12.3 Informed Consent

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

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

12.4 Study Monitoring Requirements

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

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site staff the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

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

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

12.5 Disclosure of Data

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

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

12.6 Retention of Records

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

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

12.7 Publication Policy

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

12.8 Financial Disclosure

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

13 STUDY ADMINISTRATIVE INFORMATION

13.1 Protocol Amendments

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

13.2 Address List

13.2.1 Sponsor

CinCor Pharma, Inc.
5375 Medpace Way
Cincinnati, OH 45227
United States

[redacted]

13.2.2 Contract Research Organization

Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-513-579-9977

[redacted]

13.2.3 Serious Adverse Event Reporting

Medpace Clinical Safety
Medpace SAE hotline – United States:

[redacted]

13.2.4 Biological Specimens

Central laboratory

Medpace Reference Laboratories, LLC
5365 Medpace Way
Cincinnati, OH 45227
United States

[redacted]

Pharmacokinetic laboratory

Medpace Bioanalytical Laboratories, LLC
5365 Medpace Way
Cincinnati, OH 45227
United States
[redacted]

Pharmacogenomic laboratory

Cincinnati Children's Hospital
ATTN: Discover Together Biobank
3333 Burnet Ave.
Bldg. R, Rm. 2530
Cincinnati, OH 45229
United States
[redacted]

13.2.5 Central Pharmacy

GoGoMeds
Specialty Medical Drugstore, LLC.
525 Alexandria Pike, Suite 100
Southgate, KY 41071
United States
[redacted]

13.2.6 Central Depot

Clinigen Clinical Supplies Management Inc
300 Technology Dr
Malvern, PA 19355
United States
[redacted]

13.2.7 Electronic Diary

ePRO/eDiary
5375 Medpace Way
Cincinnati, OH 45227
United States
[redacted]

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APPENDIX A: SCHEDULE OF PROCEDURES

	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)**
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	
Send prescriptions to Central Pharmacy		X[u]		X[v]								

	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)**
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.

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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 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 ra
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 differentia 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 resu

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 and its precursors (18-hydroxycorticosterone, corticosterone, and 11-deoxycorticosterone)	Cortisol [1] and its precursor 11-deoxycortisol
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.

Pharmacokinetic Analytes

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

24-hour Urine Collection Analytes

Aldosterone
Potassium
Sodium
Creatinine
Albumin
Protein

APPENDIX C: ELECTROCARDIOGRAM ALERT CRITERIA GUIDANCE

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

- QTcF ≥450 msec (male);
- QTcF ≥470 msec (female);
- A >60 msec increase in QTcF from baseline; or
- A ≥6% increase in QTcF from baseline.

New onset findings including, but not limited to, the following:

- Second degree atrioventricular (AV) block (Mobitz II);
- Third degree AV block (complete heart block);
- Acute myocardial infarction;
- New left bundle branch block;
- Severe bradycardia (ventricular rate ≤40 bpm);
- Supraventricular tachycardia (ventricular rate ≥150 bpm);
- Torsades de pointes;
- Ventricular tachycardia (≥3 beats regardless of rate);
- Ventricular fibrillation; or
- Atrial fibrillation/atrial flutter (ventricular rate ≥150 bpm)

APPENDIX D: EXAMPLES OF EXCLUDED MEDICATIONS

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

An extract of this website on 03-March-2020 is reflected in Table 1.

Table 1. Examples of Excluded Medications

Group	Gene	Excluded Medications
Strong CYP3A inducers [1]	-	Apalutamide, carbamazepine [2], enzalutamide [3], mitotane, phenytoin [4], rifampin [5], St. John's wort [6]

1. Examples of clinical inducers for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (12/03/2019).
   Note: Strong, moderate, and weak inducers are drugs that decrease the AUC of sensitive index substrates of a given metabolic pathway by ≥80%, ≥50% to <80%, and ≥20% to <50%, respectively.
2. Strong inducer of CYP2B6, CYP3A, and weak inducer of CYP2C9.
3. Strong inducer of CYP3A and moderate inducer of CYP2C9, and CYP2C19.
4. Strong inducer of CYP2C19, CYP3A, and moderate inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9.
5. Strong inducer of CYP3A and moderate inducer of CYP1A2, CYP2C19.
6. The effect of St. John's wort varies widely and is preparation dependent.

AUC = area under the concentration time curve; CYP = cytochrome P450; DDI = drug-drug interaction; .
Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers