CLINICAL STUDY PROTOCOL

A Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Multiple Dose Strengths of CIN-107 as Compared to Placebo After 8 Weeks of Treatment in Patients with Uncontrolled Hypertension

Investigational Product: CIN-107
Protocol Number: CIN-107-124
Short title: "HALO"

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SIGNATURE PAGE

STUDY TITLE: A Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Multiple Dose Strengths of CIN-107 as Compared to Placebo After 8 Weeks of Treatment in Patients with Uncontrolled Hypertension

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Date

_____

CinCor Pharma, Inc.

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/Ethic Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Multiple Dose Strengths of CIN-107 as Compared to Placebo After 8 Weeks of Treatment in Patients with Uncontrolled Hypertension

PROTOCOL NUMBER: CIN-107-124

INVESTIGATIONAL PRODUCT: CIN-107

PHASE: 2

INDICATION: Reduction of systolic blood pressure (SBP) in patients with hypertension (HTN)

OBJECTIVES:

This study is conducted in patients with uncontrolled HTN receiving background antihypertensive agent(s) that are either an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB), an ACEi/ARB plus a thiazide diuretic, or an ACEi/ARB plus a calcium channel blocker (CCB).

The primary objective is to demonstrate that at least 1 dose strength of CIN-107 is superior to placebo for the change from baseline in mean seated SBP after 8 weeks of treatment in these patients (Part 1).

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

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

The exploratory objectives are to evaluate the following:

- The relation between baseline plasma renin, aldosterone, and the aldosterone-to-renin ratio (ARR) and the SBP response to CIN-107;
- The change in 24-hour urine aldosterone and serum aldosterone levels from values measured at the end of Part 1 to those measured following 4 weeks of treatment with CIN-107 2 mg dose strength and no background antihypertensive agent(s) at the end of Part 2; and

- The percentage of patients maintaining a mean seated SBP <130 mmHg ("responders") when treated with CIN-107 2 mg dose strength alone and no background antihypertensive agent(s) for 4 weeks during Part 2.

The safety objectives for both Parts 1 and 2 are to evaluate the following:

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

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

POPULATION:

Inclusion Criteria

Patients must meet all the following criteria to be eligible to participate in the study:

1. Are adult male and female patients ≥18 years;
2. Are on a stable regimen of background antihypertensive agent(s) in the following class at the maximum tolerated dose (MTD) (in the opinion of the Investigator) for at least 8 weeks and would be considered a candidate for an additional antihypertensive agent at the time of Screening. A total of 50 to 100 patients are allowed in each of the three groups.
    a. An ACEi/ARB; or
    b. A combination drug of an ACEi/ARB and a thiazide diuretic ; or
    c. A combination drug of an ACEi/ARB and a CCB

    Note: Mineralocorticoid receptor antagonists [MRAs] or potassium sparing diuretics are not allowed in the study. Anti-anginal nitrates, including nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate are not considered antihypertensive agents.

    Note: Patients not on the maximal dose of an acceptable anti-hypertensive agent should have source documentation provided that explains the investigator's rationale for stipulating that the dose the patient is receiving is that patient's MTD;
3. Have a mean seated SBP ≥140 mmHg at Screening (Visit 1) and Visit 2;

    Note: Patients with mean seated SBP ≥130 mmHg may be eligible if diabetic.

Note: Mean seated SBP is defined as the average of 3 seated SBP measurements at any single clinical site visit.

4. Have ≥70% and ≤120% adherence to their antihypertensive medication(s) and the CIN-107 placebo during the Run-In Period, based on pill counts on the morning of Visit 2;

6. If taking a sodium-glucose cotransporter 2 (SGLT2) inhibitor at Screening (Visit 1), the regimen must be stable for a period of at least 8 weeks before Visit 2 and be expected to remain at that dose over the study period;

   Note: It is expected that patients not currently taking SGLT2 inhibitor(s) will not initiate this class of medication during the entire Treatment Period.

7. Agree to comply with the contraception and reproduction restrictions of the study as follows:
   a. Female patients who are postmenopausal must have had no menstrual bleeding for at least 1 year at Screening and either be >60 years or have an elevated plasma follicle-stimulating hormone level >40 mIU/mL at Screening;
   b. Female patients of childbearing potential (i.e., ovulating, pre-menopausal, and not surgically sterile) must have a documented negative pregnancy test at Screening (Visit 1) and Visit 2;
   c. Female patients of childbearing potential must use a highly effective method of contraception (i.e., <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:
      i. Surgical sterilization (tubal ligation);
      ii. Intrauterine device for at least 12 weeks before Screening;
      iii. Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before Screening; or
      iv. Diaphragm used in combination with spermicide.
   d. Male patients must agree to abstain from sperm donation from Day 1 through 90 days after the final dose of study drug.

8. Are 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. Have a mean seated SBP ≥180 mmHg at Screening (Visit 1) or baseline (Visit 2);
2. Have body mass index >50 kg/m^2 at Screening;
3. Have upper arm circumference that does not meet the cuff measurement criteria for the selected BP machine at Screening;
4. Are using an alpha or beta blocker for the treatment of systemic HTN or another primary condition/indication (eg, benign prostatic hyperplasia, migraine headache, heart failure);

5. Are not willing or not able to discontinue an MRA or a potassium sparing diuretic as part of an existing antihypertensive regimen;
6. Are not willing to discontinue taking a potassium supplement;
7. Are expected to receive or are receiving any of the exclusionary drugs (strong cytochrome P450 3A inducers [i.e, rifampin] and/or chronic use of non-steroidal anti-inflammatory drugs [NSAIDs]);

   Note: Patients on chronic NSAIDs who are willing to come off at Screening for the course of the study may be allowed to participate.
8. Have known renal artery stenosis, uncontrolled or untreated hyperthyroidism, uncontrolled or untreated hypothyroidism, hyperparathyroidism, pheochromocytoma, Cushing's syndrome, or aortic coarctation;

   Note: Patients with primary aldosteronism MAY BE considered for enrollment unless an adrenalectomy is expected before the end of their study participation.
9. Have documented estimated glomerular filtration rate <30 mL/min/1.73 m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration equation at Screening;
10. Have known and documented New York Heart Association stage III or IV chronic heart failure at Screening;
11. Have had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure within 6 months before Screening;
12. Have known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease diagnosed from a prior echocardiogram;
13. Have a planned coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) or any major surgical procedure;
14. Have had CABG or other major cardiac surgery (eg, valve replacement), peripheral arterial bypass surgery, or PCI within 6 months before Screening;
15. Have chronic permanent atrial fibrillation;
16. Have uncontrolled diabetes with glycated hemoglobin >10% at Screening;
17. Have dialysis or kidney transplantation planned during the course of this study;
18. Have had prior solid organ transplant and/or cell transplants;
19. Have known hypersensitivity to CIN-107, drugs of the same class, or any of its excipients;
20. Have any clinically relevant medical or surgical conditions, including unstable conditions and/or conditions treated with systemic immunosuppressants including corticosteroids that, in the opinion of the Investigator, would put the patient at risk by participating in the study;
21. Have evidence of any of the following (1 retest is allowed at Screening):

a. White blood cell count >15 × 10^9/L or absolute neutrophil count <1 × 10^9/L at Screening;

b. Sodium <130 mEq/L at Screening (Visit 1);

   Note: If the Investigator elects to correct the serum sodium level and/or offers to manage the condition, 1 retest for Screening is allowed at least 1 week prior to Visit 2. A repeat serum sodium <130 mEq/L will disqualify a patient from the study.

c. Potassium <3.5 mEq/L at Screening (Visit 1);

d. Potassium >5 mEq/L at Screening (Visit 1);

   Note: If the Investigator elects to correct the serum potassium level and/or offers to manage the condition, 1 retest for Screening is allowed at least 1 week prior to Visit 2. A repeat serum potassium >5 mEq/L will disqualify a patient from the study.

e. Hemoglobin <10 g/dL at Screening and/or anticipated initiation of erythropoietin stimulating agents and/or planned transfusion within 2 months after Screening; or

f. Serum aspartate aminotransferase and/or alanine aminotransferase >3 × the upper limit of normal range, with a corresponding total bilirubin >2 mg/dL at Screening.

   Note: If patient has a history of Gilbert's syndrome, bilirubin may be >2 mg/dL at Screening.

22. Are positive for HIV antibody, hepatitis C virus RNA, or hepatitis B surface antigen at Screening;

23. Have 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).

24. Are pregnant, breastfeeding, or planning to become pregnant during the study;

25. Have 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;

26. Have received experimental therapy with a small molecule within 30 days of Day 1 or 5 half-lives, whichever is greater, or a large molecule within 90 days of Day 1 or 5 half-lives, whichever is greater; or

27. Are 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.

STUDY DESIGN AND DURATION:

This is a Phase 2, randomized, multicenter study to evaluate the efficacy and safety of multiple dose strengths of CIN-107 in the treatment of patients with HTN. To be considered for study participation, patients must have uncontrolled HTN (mean seated SBP ≥ 140 mmHg [or ≥130 mmHg if diabetic]) despite being on a stable regimen of an ACEi/ARB inhibitor or a combination drug of an ACEi/ARB plus a thiazide diuretic or an ACEi/ARB plus a CCB background

antihypertensive agents at the MTD (in the opinion of the Investigator) for at least 8 weeks and would be considered a candidate for addition of a second or third antihypertensive agent at the time of Screening. At least 212 patients are expected to complete the study across approximately 75 clinical sites in the United States.

Screening laboratory evaluations, if abnormal, may be repeated once for eligibility purposes before excluding the patient. For patients with serum sodium <130 mEq/L and/or serum potassium >5 mEq/L at Screening that the Investigator elects to correct or manage, 1 retest for Screening (at an Unscheduled Visit) is allowed at least 1 week prior to Visit 2.

Patients who have previously screen-failed based on aldosterone ineligibility in prior protocol may consent to the revised protocol and rescreen for eligibility including the laboratory evaluations. Rescreened patients will be assigned a new patient number.

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

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

Upon return of the screening eligibility laboratory results, patients will be contacted via telephone (Telephone Visit) to inform them of their eligibility, and if eligible, to begin the Run-In Period and schedule their next visit: an Unscheduled Visit or Visit 2. For patients with serum sodium <130 mEq/L and/or serum potassium >5 mEq/L at Screening that the Investigator elects to correct or manage, 1 retest (at an Unscheduled Visit) is allowed at least 1 week prior to Visit 2 (see Exclusion Criterion 21). Eligible patients will also be instructed to begin the Run-In Period when they will take the placebo tablet once daily (QD) in addition to their background antihypertensive agent(s) until Visit 2. A patient who demonstrates treatment adherence (see Inclusion Criterion 4) and continues to satisfy all inclusion criteria and none of the exclusion criteria at Visit 2 will be randomized and enter the Part 1 Treatment Period.

Clinical sites will provide patients with a 24-hour urine collection kit at Visits 1, 5, and 8. Patients will be instructed to start the collection up to 3 days prior to Visits 2 (after confirmation of their eligibility during the Telephone Visit), 6, and 9, refrigerate the collected sample, and bring the entire sample to the clinical site at that visit.

During the double-blind Part 1 Treatment Period (Weeks 1 to 8; Visits 2 to 6), patients will be randomized (1:1:1:1) to 1 of 4 treatment arms: 0.5 mg CIN-107, 1 mg CIN-107, 2 mg CIN-107, or placebo, as add-on medications to their background antihypertensive agent(s). Patient randomization will be stratified according to their race (African American versus non-African American) and the type of background antihypertensive regimen (an ACEi/ARB or an ACEi/ARB plus a thiazide diuretic or an ACEi/ARB plus a CCB). A total of 50 to 100 patients are allowed in each of the three anti-hypertensive regimen groups so that the population taking these antihypertensive agents will be adequately represented.

On clinical site visit days, patients will self-administer the morning dose of background antihypertensive medications at home and withhold the study drug. At the clinical site, patients will self-administer 1 tablet 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 to self-administer 1 tablet of study drug QD by mouth at approximately the same time each morning. The primary endpoint will be evaluated at the end of Week 8.

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

Dosing Compliance

Patients will be instructed to bring their study drug and background antihypertensive medication(s) 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 at approximately the same time (intra-patient) and efforts should be made to have the visits occur between 6:00 AM and 11:00 AM.

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

The safety of CIN-107 will be assessed from the time of informed consent until the end of the Safety Follow-Up Period. Patients will be followed for efficacy and adherence as prespecified during the Treatment Period. PD variables analyzed during the study may include, but are not limited to, measures of aldosterone and its precursors, cortisol and its precursor, plasma renin activity (PRA), direct renin, and calculation of aldosterone/PRA ratio. PK variables analyzed during the study will include plasma concentrations of CIN-107 and any measured metabolite(s). A Data Safety Monitoring Board is planned to periodically evaluate emerging safety data and assess reports on cumulative serious AEs.

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

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

The dose strengths of CIN-107 (0.5 mg QD, 1 mg QD, and 2 mg QD) were chosen based on the observed safety, tolerability, PK, and PD profile established in healthy subjects.

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

During clinical site visits for the Treatment Period (Parts 1 and 2), patients will self-administer 1 tablet of study drug in the clinic to be witnessed by site staff, after completion of pre-dose evaluations and laboratory sampling. Between clinical site visits, patients will continue to self-administer 1 tablet of study drug QD by mouth at approximately the same time each morning.

EFFICACY ENDPOINTS:

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

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

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

The exploratory efficacy endpoints of this study are as follows:

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

SAFETY ENDPOINTS:

The safety endpoints of this study are as follows:

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

STATISTICAL ANALYSES:

Measurements recorded at randomization (Visit 2) will constitute "baseline" measurements and those recorded prior to study drug administration at the clinical site will constitute "pre-dose" measurements.

Analysis Populations

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

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

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

The Safety Population will include all patients who receive at least 1 dose of any 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.

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

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

Efficacy Analyses

The primary efficacy analysis will compare the change in mean seated SBP from baseline (Visit 2) to the end of Part 1 (Visit 6) 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 (LS) 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.

The primary estimand will correspond to a treatment policy estimand. The target population will comprise participants who are randomized into the study, receive at least 1 dose of any study drug, and have a baseline value for the SBP assessment. The primary summary measure to access the treatment effect will be the LS mean difference for the primary endpoint between CIN-107 and placebo based on the mixed model for repeated measures methodology. The primary estimand will be addressed using the in-study observation period (ie, including data collected post-treatment discontinuation or post-prohibited medication use).

Missing data for the primary efficacy analysis will be based on the assumption the data are missing at random.

To assess the primary efficacy analysis assumption that the data are missing at random, the first sensitivity analysis of the primary efficacy endpoint will be based on a pattern mixture model that uses a multiple imputation technique analyzed with analysis of covariance (ANCOVA) with pre-specified fixed factors and covariates. If appropriate, based on the number of retrieved dropouts, missing measurements of non-retrieved dropouts will be modeled by known measurements from retrieved dropouts (ie, participants who remain in the trial after treatment discontinuation) in the same treatment group. The imputation model will be further clarified in the Statistical Analysis Plan (SAP).

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

Additional sensitivity analyses and subgroup analyses may be carried out under secondary estimands and/or various assumptions for missing data. Full details will be provided in the SAP.

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

Safety Analysis

The Safety Population will be the primary population for the safety analysis. All safety endpoints will be summarized descriptively for records collected in Part 1. Additional safety endpoint analyses will be conducted including records collected in Part 2 and the post-dose follow up/end of study.

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

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.

No interim analysis is planned.

SAMPLE SIZE DETERMINATION:

[redacted]

SITES: Approximately 75 clinical sites in the United States

SPONSOR:

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[redacted]

TABLE OF CONTENTS

LIST OF FIGURES

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
ARR	aldosterone-to renin ratio
ARB	Angiotensin receptor blocker
AUC	Area under the concentration-time curve
BP	Blood pressure
CABG	Coronary artery bypass graft
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRA	Clinical research associate
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus
HTN	Hypertension
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
MAD	Multiple-ascending dose
mITT	Modified Intent-to-Treat
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonist
MTD	Maximum tolerated dose

Abbreviation	Definition
NSAID	Non-steroidal anti-inflammatory drug
OLE	Open Label Extension
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PGx	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
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
RNA	Ribonucleic acid
SAD	Single-ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SGLT2	Sodium-glucose cotransporter 2
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
T_{max}	Time to maximum plasma concentration
WHR	Waist-to-hip ratio

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 (HTN) have inappropriately high aldosterone that promotes 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 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 is 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 [CYP]11B1 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 (osilodrostat), an aldosterone synthase inhibitor, 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).

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.

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.

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 glands were ameliorated by electrolyte supplementation, indicating that they were exaggerated pharmacological effects and physiologic/adaptive responses to aldosterone inhibition.

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.

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}) expected to be efficacious in man (at a ≤10 mg once daily [QD] dose for the treatment of HTN). This indicated a very low probability of any QT liability.

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. For details, see the current version of the Investigator's Brochure.

1.2 Overview of Clinical Studies With CIN-107

Five 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;

- A study to assess the effect of CIN-107 on the PK of the multidrug and toxin extrusion substrate, metformin; and
- A study assessing the PK of CIN-107 in otherwise healthy subjects with varying degrees of renal function.

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.

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 of CIN-107) and normal salt conditions (0.5, 1.5, and 2.5 mg 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. 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).

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% confidence interval [CI]) for C_{max} was 0.99 (0.91, 1.07) while the geometric mean ratios and associated CIs for AUC from time 0 to infinity and AUC from time 0 to the last quantifiable concentration 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 (27.99 L/hour when metformin was administered alone and 26.48 L/hour in the presence of CIN-107). The safety profile of metformin was similar in the presence and absence of CIN-107. There were no deaths, SAEs, or TEAEs leading to withdrawal and there were no clinically significant changes in ECGs or vital signs.

The results of the renal impairment study indicated that a single 10 mg dose of CIN-107 was well tolerated by subjects with varying degrees of renal function, ranging from normal renal function to end stage disease receiving hemodialysis. One subject with end stage disease experienced an unrelated SAE of metabolic encephalopathy and a moderate unrelated adverse event (AE) of tremor. One control subject experienced a mild AE of diarrhea, which was considered to be related to study drug by the Investigator. There were no clinically significant changes in laboratory values (including potassium), ECGs, or vital signs. PK data from this study demonstrated that there was no noteworthy increase in systemic exposure or decrease in renal clearance in individuals with moderate or severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 59 mL/min) as compared to control subjects (normal renal function or mild renal impairment; eGFR ≥60 mL/min). Likewise, no noteworthy increase in plasma exposure to CIN-107 in subjects with end stage renal disease (eGFR <15 mL/min or on hemodialysis) was observed; however, these subjects did not produce adequate urine to assess differences in renal clearance in this population. The conclusions of this study suggest that it is not necessary to dose adjust CIN-107 for patients with renal impairment.

1.3 Rationale

Suppression of the RAAS by using ACEis or ARBs is an important therapeutic strategy for managing cardiovascular and renal diseases. However, the phenomenon of aldosterone breakthrough (in which the initially reduced serum aldosterone returns 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 HTN 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 HTN.

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 to address the deleterious effects of aldosterone effects in patients with HTN. 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.

This Phase 2, 2-part study aims to evaluate the efficacy and safety of multiple dose strengths of CIN-107 in patients with HTN that is uncontrolled despite being on a stable regimen of an ACEi/ARB or an ACEi/ARB in combination with a thiazide diuretic or a CCB antihypertensive agent at the MTD (in the opinion of the Investigator) for at least 8 weeks, and are likely to benefit from an additional antihypertensive agent. It is postulated that the addition of CIN-107 in the proposed patient population could help achieve target systolic BP (SBP) (<130 mmHg) as a result of its effect on aldosterone synthesis inhibition.

During Part 2, patients will receive CIN-107 2 mg and discontinue the background antihypertensive agent(s), to test whether potent inhibition of aldosterone synthesis alone has the potential to control SBP. Part 2 will also give "non-responder" patients not already treated with 2 mg CIN-107, an opportunity to achieve SBP control with the maximum dose (2 mg) CIN-107.

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 excretion of potassium in the kidneys, thereby increasing blood volume and BP. 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.[15] Patients with potassium and sodium levels outside of protocol-required levels will be excluded from study participation and these electrolytes will be closely monitored for the entire study duration.

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 and orthostatic vital signs (BP and heart rate).

1.4.1.3 Risk of adrenal effects

While CIN-107 exhibits highly selective CYP11B2 inhibition, CYP11B1 inhibition with repeat dosing cannot be ruled out 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 (osilodrostat).[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. These adverse effects occasioned by MRA usage are believed to be due to off-target inhibition of non-MRA receptors. Occurrence of these events will be monitored in this study, however, a selective inhibitor of aldosterone synthase is not expected to interfere with sexual hormone pathways.

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 a BP-lowering effect of CIN-107.

CIN-107 is an aldosterone synthase inhibitor. Aldosterone synthase inhibition is a new therapeutic option that could reduce or eliminate the phenomenon of aldosterone breakthrough (in which the initially reduced serum aldosterone returns to baseline levels over time) seen with other RAAS inhibitors.

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 Primary Objective

The primary objective is to demonstrate that at least 1 dose strength of CIN-107 is superior to placebo for the change from baseline in mean seated SBP after 8 weeks of treatment in patients with uncontrolled HTN and are receiving an ACEi/ARB, an ACEi/ARB plus a thiazide diuretic or an ACEi/ARB plus a CCB (Part 1).

2.2 Secondary Objectives

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

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

2.3 Exploratory Objectives

The exploratory objectives are to evaluate the following:

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

2.4 Safety Objectives

The safety objectives for both Parts 1 and 2 are to evaluate the following:

- Vital signs, standing BP and heart rate, physical examinations, ECG, body weight, and clinical laboratory assessments, including standard safety chemistry panel, hematology, coagulation, and urinalysis;
- TEAEs;
- Treatment-emergent SAEs (TESAEs);

- TEAEs leading to premature discontinuation of study drug;
- Treatment-emergent marked laboratory abnormalities; and
- Change in standing SBP (measured pre-dose at the clinical site) from baseline to End of Treatment (EOT) (Visit 9).

2.5 Pharmacokinetic-Pharmacodynamic Objective

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

3 STUDY DESCRIPTION

3.1 Summary of Study Design

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

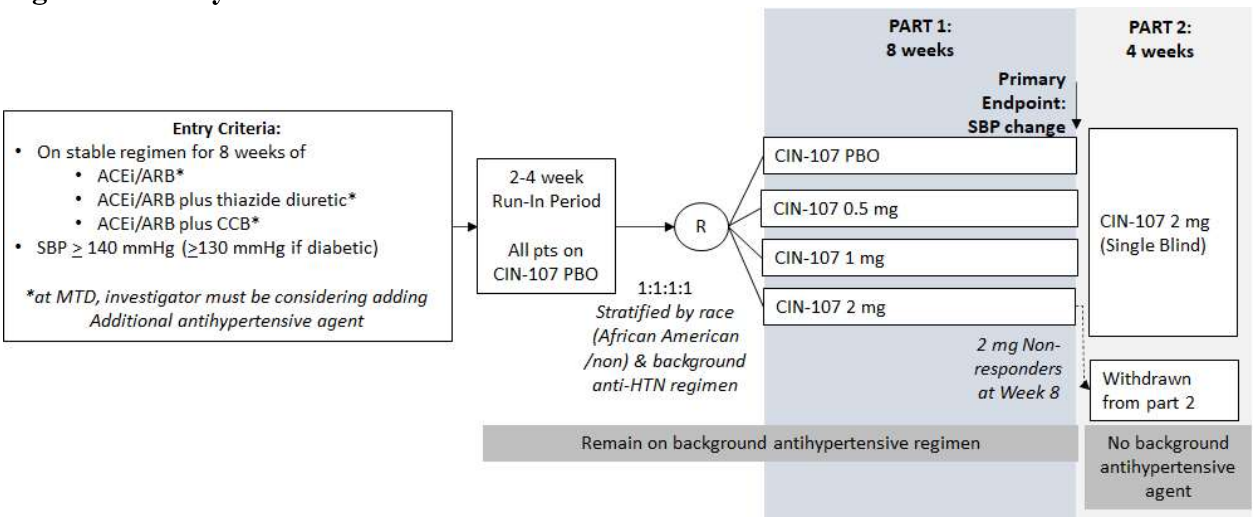
Screening laboratory evaluations, if abnormal, may be repeated once for eligibility purposes before excluding the patient. Screen failures may be rescreened no less than 5 days after the last study visit, with Sponsor and/or Medical Monitor consultation and approval.

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

- A Screening Period of at least 4 weeks consisting of:
  - A Screening Visit (Visit 1);
  - A Telephone Visit to convey patient eligibility for the study; and
  - A Run-In Period up to 4 weeks before randomization (Visit 2), to confirm the patient's adherence to their background antihypertensive medication(s) and placebo (see Section 4.1; Inclusion Criterion 4).
- A 2-part Treatment Period consisting of:
  - Part 1: A double-blind Treatment Period of 8 weeks (Weeks 1 to 8; Visits 2 to 6); and
  - Part 2: A Treatment Period of 4 weeks (Starting the day after Visit 6 through Visit 9).
- A Safety Follow-Up Period (Visit 10) of approximately 2 weeks after the last dose of study drug.

Upon return of the screening eligibility laboratory results, patients will be contacted via telephone (Telephone Visit) to inform them of their eligibility, and if eligible, to begin the Run-In Period and schedule their next visit: an Unscheduled Visit or Visit 2. For patients with serum sodium <130 mEq/L and/or serum potassium >5 mEq/L at Screening that the Investigator elects to correct or manage, 1 retest (at an Unscheduled Visit) is allowed at least 1 week prior to Visit 2 (see Section 4.2; Exclusion Criterion 21). Eligible patients will also be instructed to begin the Run-In Period when they will take the placebo tablet QD in addition to their background antihypertensive agent(s) until Visit 2. A patient who demonstrates treatment adherence (see Section 4.1; Inclusion Criterion 4) and continues to satisfy all inclusion criteria and none of the exclusion criteria at Visit 2 will be randomized and enter the Part 1 Treatment Period.

Figure 1. Study Schema



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

Clinical sites will provide patients with a 24-hour urine collection kit at Visits 1, 5, and 8. Patients will be instructed to start the collection up to 3 days prior to Visits 2 (after confirmation of their eligibility during the Telephone Visit), 6, and 9, refrigerate the collected sample, and bring the entire sample to the clinical site at that visit.

During the double-blind Part 1 Treatment Period (Weeks 1 to 8; Visits 2 to 6), patients will be randomized (1:1:1:1) to 1 of 4 treatment arms: 0.5 mg CIN-107, 1 mg CIN-107, 2 mg CIN-107, or placebo, as add-on medications to their background antihypertensive agent(s). Patient randomization will be stratified according to their race (African American versus non-African American) and the type of background antihypertensive regimen (an ACEi/ARB or an ACEi/ARB plus a thiazide diuretic or an ACEi/ARB plus a CCB). A total of 50 to 100 patients are allowed in each of the three background antihypertensive regimen groups so that the population taking these antihypertensive agents will be adequately represented.

On clinical site visit days, patients will self-administer the morning dose of background antihypertensive medications at home and withhold the study drug. At the clinical site, patients will self-administer 1 tablet 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 to self-administer 1 tablet of study drug QD by mouth at approximately the same time each morning. The primary endpoint will be evaluated at the end of Week 8.

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

study drug except 2 mg CIN-107 in Part 1 will move into Part 2, receive the 2 mg dose of CIN-107, and discontinue their background antihypertensive agent(s). A non-responder who decides not to participate in Part 2 or has already received the maximum dose strength (2 mg) of CIN-107 in Part 1, will be considered withdrawn from the study drug, and should complete their EOT (Visit 9) procedures at the end of Part 1 (Visit 6) and the 2-week Safety Follow-Up. The criteria for patient withdrawal from study and for temporary suspension of dosing are provided in Sections 4.5 and 4.6, respectively. The subject may be offered to participate in the open-labeled extension (OLE) study CIN-107-130 if the investigator determines that it is safe for the patient. Other medications may be added to the regimen per investigator's discretion during the OLE study.

Patients will be instructed to bring their study drug and background antihypertensive medication 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 at approximately the same time (intra-patient) and efforts should be made to have the visits occur between 6:00 AM and 11:00 AM.

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

The safety of CIN-107 will be assessed from the time of informed consent until the end of the Safety Follow-Up Period. Patients will be followed for efficacy and adherence as prespecified during the Treatment Period. PD variables analyzed during the study may include, but are not limited to, measures of aldosterone and its precursors, cortisol and its precursor, plasma renin activity (PRA), direct renin, and calculation of aldosterone/PRA ratio. PK variables analyzed during the study will include plasma concentrations of CIN-107 and any measured metabolite(s). A Data Safety Monitoring Board (DSMB) is planned to periodically evaluate emerging safety data and assess reports on cumulative SAEs.

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

3.2 Data Safety Monitoring Board

A DSMB with multidisciplinary representation is planned to periodically evaluate emerging safety data and assess reports on cumulative SAEs. Based on ongoing monitoring of the study, additional DSMB reviews may be conducted.

The DSMB will convene as soon as possible, after learning of the occurrence of a Criteria for Temporary Suspension of Dosing (Section 4.6) in order to determine if all active participants should suspend dosing.

The DSMB 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. To fulfil its responsibilities, the DSMB may have access to unblinded data as described in the DSMB Charter. Details related to the DSMB responsibilities, authorities, and procedures will be documented in the DSMB Charter.

3.3 Study Indication

CIN-107 is being studied for the reduction of SBP in patients with HTN.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Patients must meet all the following criteria to be eligible to participate in the study:

1. Are adult male and female patients ≥18 years;
2. Are on a stable regimen of background antihypertensive agent(s) in the following class at the maximum tolerated dose (MTD) (in the opinion of the Investigator) for at least 8 weeks and would be considered a candidate for an additional antihypertensive agent at the time of Screening. A total of 50 to 100 patients are allowed in each of the three groups.
    a. An ACEi/ARB; or
    b. A combination drug of an ACEi/ARB and a thiazide diuretic ; or
    c. A combination drug of an ACEi/ARB and a CCB

    Note: Mineralocorticoid receptor antagonists [MRAs] or potassium sparing diuretics are not allowed in the study. Anti-anginal nitrates, including nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate are not considered antihypertensive agents.

3. Have a mean seated SBP ≥140 mmHg at Screening (Visit 1) and Visit 2;

    Note: Patients with mean seated SBP ≥130 mmHg may be eligible if diabetic.

    Note: Mean seated SBP is defined as the average of 3 seated SBP measurements at any single clinical site visit.

4. Have ≥70% and ≤120% adherence to their antihypertensive medication and the CIN-107 placebo during the Run-In Period, based on pill counts on the morning of Visit 2;
6. If taking a sodium-glucose cotransporter 2 (SGLT2) inhibitor at Screening (Visit 1), the regimen must be stable for a period of at least 8 weeks before Visit 2 and be expected to remain at that dose over the study period;

    Note: It is expected that patients not currently taking SGLT2 inhibitor(s) will not initiate this class of medication during the entire Treatment Period.

7. Agree to comply with the contraception and reproduction restrictions of the study as follows:
    - Female patients who are postmenopausal must have had no menstrual bleeding for at least 1 year at Screening 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 (Visit 1) and Visit 2;

- 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.
- Male patients must agree to abstain from sperm donation from Day 1 through 90 days after the final dose of study drug.

8. Are 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. Have a mean seated SBP ≥180 mmHg at Screening (Visit 1) or baseline (Visit 2);
2. Have body mass index (BMI) >50 kg/m^2 at Screening;
3. Have upper arm circumference that does not meet the cuff measurement criteria for the selected BP machine at Screening;
4. Are using an alpha or beta blocker for the treatment of systemic HTN or another primary condition/indication (eg, benign prostatic hyperplasia, migraine headache, heart failure);
5. Are not willing or not able to discontinue an MRA or a potassium sparing diuretic as part of an existing antihypertensive regimen;
6. Are not willing to discontinue taking a potassium supplement;
7. Are expected to receive or are receiving any of the exclusionary drugs (strong CYP3A inducers [i.e, rifampin] and/or chronic use of non-steroidal anti-inflammatory drugs [NSAIDs]);

   Note: Patients on chronic NSAIDs who are willing to come off at Screening for the course of the study may be allowed to participate.
8. Have known renal artery stenosis, uncontrolled or untreated hyperthyroidism, uncontrolled or untreated hypothyroidism, hyperparathyroidism, pheochromocytoma, Cushing's syndrome, or aortic coarctation;

   Note: Patients with primary aldosteronism MAY BE considered for enrollment unless an adrenalectomy is expected before the end of their study participation.
9. Have documented eGFR <30 mL/min/1.73 m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration equation at Screening;
10. Have known and documented New York Heart Association stage III or IV chronic heart failure at Screening;

11. Have had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure within 6 months before Screening;
12. Have known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease diagnosed from a prior echocardiogram;
13. Have a planned coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) or any major surgical procedure;
14. Have had CABG or other major cardiac surgery (eg, valve replacement), peripheral arterial bypass surgery, or PCI within 6 months before Screening;
15. Have chronic permanent atrial fibrillation;
16. Have uncontrolled diabetes with glycated hemoglobin >10% at Screening;
17. Have dialysis or kidney transplantation planned during the course of this study;
18. Have had prior solid organ transplant and/or cell transplants;
19. Have known hypersensitivity to CIN-107, drugs of the same class, or any of its excipients;
20. Have any clinically relevant medical or surgical conditions, including unstable conditions and/or conditions treated with systemic immunosuppressants including corticosteroids that, in the opinion of the Investigator, would put the patient at risk by participating in the study;
21. Have evidence of any of the following (1 retest is allowed at Screening):
    a. White blood cell count >15 × 10^9/L or absolute neutrophil count <1 × 10^9/L at Screening;
    b. Sodium <130 mEq/L at Screening (Visit 1);

       Note: If the Investigator elects to correct the serum sodium level and/or offers to manage the condition, 1 retest for Screening is allowed at least 1 week prior to Visit 2. A repeat serum sodium <130 mEq/L will disqualify a patient from the study.
    c. Potassium <3.5 mEq/L at Screening (Visit 1);
    d. Potassium >5 mEq/L at Screening (Visit 1);

       Note: If the Investigator elects to correct the serum potassium level and/or offers to manage the condition, 1 retest for Screening is allowed at least 1 week prior to Visit 2. A repeat serum potassium >5 mEq/L will disqualify a patient from the study.
    e. Hemoglobin <10 g/dL at Screening and/or anticipated initiation of erythropoietin stimulating agents and/or planned transfusion within 2 months after Screening; or
    f. Serum aspartate aminotransferase and/or alanine aminotransferase >3 × the upper limit of normal range, with a corresponding total bilirubin >2 mg/dL at Screening;

       Note: If patient has a history of Gilbert's syndrome, bilirubin may be >2 mg/dL at Screening.
22. Are positive for HIV antibody, hepatitis C virus RNA, or hepatitis B surface antigen at Screening;

23. Have 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).

24. Are pregnant, breastfeeding, or planning to become pregnant during the study;
25. Have 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;
26. Have received experimental therapy with a small molecule within 30 days of Day 1 or 5 half-lives, whichever is greater, or a large molecule within 90 days of Day 1 or 5 half-lives, whichever is greater; or
27. Are 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 Eligibility

Patients must continue to satisfy all inclusion criteria and none of the exclusion criteria (see Sections 4.1 and 4.2, respectively) within 1 week of Visit 2 or at Visit 2 to be eligible for randomization.

To assess BP for randomization eligibility, the last 3 consecutive, consistent SBP measurements will be averaged to determine the final value. **Note: The standardized procedures for measuring BP are listed in Section 8.9.**

4.4 Screen Failures

Patients who provide informed consent but do not meet the study entry criteria during the Screening Period or at Visit 2 are screen failures. Minimal information collected from screen failures may include demographics, screen failure details, and any SAEs.

A screen failure may be considered for rescreening upon Sponsor and/or Medical Monitor consultation and approval as described in Section 4.4.1. Rescreened patients will be assigned a new patient number.

4.4.1 Retesting and Rescreening

Screening laboratory evaluations, if abnormal, may be repeated once for eligibility purposes before excluding the patient. For patients with serum sodium <130 mEq/L and/or serum potassium >5 mEq/L at Screening that the Investigator elects to correct or manage, 1 retest for Screening (at an Unscheduled Visit) is allowed at least 1 week prior to Visit 2.

Patients who have previously screen-failed based on aldosterone ineligibility in prior protocol may consent to the revised protocol and rescreen for eligibility including the laboratory evaluations. Rescreened patients will be assigned a new patient number.

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 SBP >170 mmHg at 2 separate occasions during the Part 1 or Part 2 Treatment Period;
- The patient has an increase in his/her mean seated SBP by ≥30 mmHg on 2 separate occasions from the end of Part 1;
- 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 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 (ET) procedures and site staff should make every effort to complete the full panel of assessments scheduled for EOT (Visit 9). The reason for patient withdrawal must be documented in the electronic case report form (eCRF). Patients should still attend study visits after ET for safety monitoring.

Withdrawn patients will not be replaced.

4.6 Criteria for Temporary Suspension of Dosing

When 1 of the below criteria is met, the DSMB will convene as soon as possible, after learning of the occurrence of a criteria in order to determine if all active participants should suspend dosing:

- Any SAE that is deemed related to the study drug, including death;
- Withdrawal of a patient for safety-related reason(s) deemed related to study drug by the Investigator;
- 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 patient suspending dosing. Other enrolled patients do not need to suspend dosing unless determined necessary by the DSMB. The patient may restart study drug following consultation and approval from the Medical Monitor.

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

When 1 of the below events occurs, the DSMB does not need to convene (unless it meets 1 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.

These criteria are specific only to the individual patient who is suspending dosing. Other enrolled patients do not need to suspend dosing. The patient may restart study drug following consultation and approval from the Sponsor and/or Medical Monitor.

4.7 Lost to Follow-Up

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.

5 STUDY TREATMENTS

5.1 Treatment Groups

The treatment groups planned for Part 1 of the study are the following:

- 0.5 mg CIN-107;
- 1 mg CIN-107;
- 2 mg CIN-107; and
- Placebo.

In Part 2, only the 2 mg CIN-107 dose strength will be studied.

5.2 Rationale for Dosing

Based on the 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. Results from the multiple dose study 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 dose strengths of CIN-107 (0.5 mg QD, 1 mg QD, and 2 mg QD) were chosen based on the observed safety, tolerability, PK, and PD profile established in healthy subjects.

5.3 Randomization and Blinding

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

Patients will receive either their assigned dose strength of CIN-107 or matching placebo as oral tablets in a double-blind manner during the Part 1 Treatment Period. During the Part 2 Treatment Period (Weeks 9 to 12; starting the day after Visit 6 and running through Visit 9), all responders (defined as achieving a mean seated SBP < 130 mmHg) at the end of Part 1 will move into Part 2. They will receive CIN-107 2 mg tablets (maximum in this study), and discontinue their background antihypertensive agent(s). Non-responders who received any study drug except 2 mg CIN-107 in Part 1 will move into Part 2, receive the 2 mg dose of CIN-107, and discontinue their

background antihypertensive agent(s). A non-responder who decides not to participate in Part 2 or has already received the maximum dose strength (2 mg) of CIN-107 in Part 1, will be considered withdrawn from the study drug, and should complete their EOT (Visit 9) procedures at the end of Part 1 (Visit 6) and the 2-week Safety Follow-Up.

The Sponsor, Investigators, and study team will be blinded to the treatment group of each patient, and patients will also be blinded to the treatment they receive during Part 1. The randomization information will be concealed until at least the end of Part 1 or during an emergency situation involving a patient that requires unblinding of the treatment assignment (see Section 5.4). Management of unblinded information will be described in a separate Blinding Plan and DSMB Charter.

5.4 Breaking the Blind

5.4.1 Emergency Unblinding

Individual treatment assignments may be unblinded when immediate knowledge of the treatment assignment is needed to optimize the clinical management of the patient. 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. 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.

5.5 Drug Supplies

5.5.1 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 dose 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 CIN-107 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 and will be indistinguishable from the CIN-107 tablets.

5.5.2 Drug Preparation and Dispensing

5.5.2.1 Background antihypertensive medication

All patients will receive their background antihypertensive medications, unless requested otherwise, through a Central Pharmacy starting at Visit 2. Clinical sites will send prescriptions for background antihypertensive medications to the Central Pharmacy at least 1 week before the planned dispensation.

5.5.2.2 Study drug

The 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 the scheduled visits (see Appendix A).

For the Run-In Period, placebo dispensation will occur at Visit 1 following initial eligibility confirmation. The randomized study drug (CIN-107 or placebo) dispensation may occur at any time during the Treatment Period.

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

5.5.3 Study Drug Administration

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

During clinical site visits for the Treatment Period (Parts 1 and 2), patients will self-administer 1 tablet of study drug in the clinic to be witnessed by site staff, after completion of pre-dose evaluations and laboratory sampling. Between clinical site visits, patients will continue to self-administer 1 tablet of study drug QD by mouth at approximately the same time each morning.

5.5.4 Treatment Compliance

For all protocol-specified doses when the patient is not at the clinical site, patients will self-administer 1 tablet of study drug at home. For doses that are administered at the clinical site, site staff will record the date and time of study drug administration.

Site staff will also 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 will be instructed to bring their study drug and background antihypertensive medications to all clinical site visits. Adherence to study drug will be calculated by pill counts. A patient who is not at least 70% and at most 120% adherent (based on pill counts determined at Visit 2) to background antihypertensive medications and placebo during the Run-In Period will not be eligible for treatment with study drug.

5.5.5 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 the United States Pharmacopeia references; excursions between 15°C and 30°C are allowed during storage. 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.

Patients deemed ineligible for the study and hence the Run-In Period will be asked to return the placebo (dispensed at Visit 1) to the clinical site in prepaid shipments.

After calculating treatment adherence (by pill counts), site staff will collect any remaining study drug from the patient at the specified visits and unused study drug will be destroyed at the clinical site per the clinical site's standard operating procedures. Clinical sites that do not allow 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. If no study drug remains, this will be indicated in the Drug Accountability Log.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 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 (examples are provided in Appendix D);
- Chronic use of NSAIDs;
- Alpha or beta blocker;
- MRA or a potassium sparing diuretic as part of an existing antihypertensive regimen;
- Potassium supplements;
- Dialysis;
- Kidney transplantation; or
- Any background hypertensive agents, other than the study drug, during Part 2 only.

5.6.2 Restricted Medications and/or Procedures

Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical site visit.

It is expected that patients already taking SGLT2 inhibitor(s) will not have their dosing changed during the entire Treatment Period, and for those not already on this class of medication, will not initiate them during the Treatment Period.

5.6.3 Allowed Medications and/or Procedures

In addition to the medications or supplements related to the patient's stand of care therapy, Part 1 of this study requires the use of a study-specific concomitant medication: an ACEi/ARB, an ACEi/ARB plus a thiazide diuretic or ACEi/ARB plus a CCB.

5.6.4 Dietary Guidance

Given the potential for predisposition to lower sodium values in the study population (eg, diuretic use), and to avoid potential additive effects on serum sodium values, Investigators should be cautious in advising patients to increase fluid intake/hydration during the study, as may sometimes be done prior to laboratory sampling. As such, patients should maintain their usual fluid intake as best as possible, unless additional oral hydration would be needed, such as in cases of assessed

volume depletion or dehydration. In addition, Investigators should consider encouraging patients who present with lower sodium levels (eg, approximately 128 to 133 mEq/L) to moderately liberalize their salt intake without necessarily increasing fluid intake.

5.6.5 Documentation of Prior and Concomitant Medication Use

All medications used within 30 days of Screening will be recorded. All concomitant medications and concurrent therapies (including fluids, electrolytes, vitamins, and supplements (including potassium supplements, as well as "as needed" medications) will be documented in the patient's eCRF at visits indicated in Appendix A. The 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. Clinical sites will record the time of concomitant medication administration (hour, minute) if the medication is initiated and/or stopped on the first randomized study drug administration visit (Visit 2) or at EOT/ET (Visit 9).

6 STUDY PROCEDURES

6.1 Informed Consent

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

Patients will be given the option to participate in a pharmacogenomic (PGx) assessment during the consenting process. The written informed consent for PGx sample collection will be included in the main informed consent form (ICF). For patients who provide written informed consent to participate in the optional PGx assessment, a blood sample will be collected at any time after randomization during the Treatment Period.

For additional details on the informed consent process, see Section 11.3.

6.2 Screening Period, Inclusive of the Run-In Period

The Screening Period includes a Screening Visit (Visit 1), a Telephone Visit to convey patient eligibility for the study, and a Run-In Period up to 4 weeks before randomization (Visit 2) to confirm the patient's adherence to their background antihypertensive medications and placebo (see Section 4.1; Inclusion Criterion 4).

Laterality and cuff size should be determined first before taking the Screening measurements. At Screening (Visit 1), BP will be measured in both upper arms (3 times/arm) using an appropriately sized cuff to detect possible laterality differences. The arm with the higher mean value from the laterality assessment will then be used to take the Screening BP measurements (at least 5 minutes after determining laterality) and for all subsequent measurements. **Note: The standardized procedures for measuring BP are listed in Section 8.9.**

Upon return of the screening eligibility laboratory results, patients will be contacted via telephone (Telephone Visit) to inform them of their eligibility, and if eligible, to begin the Run-In Period and schedule their next visit: an Unscheduled Visit or Visit 2. For patients with serum sodium <130 mEq/L and/or serum potassium >5 mEq/L at Screening that the Investigator elects to correct or manage, 1 retest (at an Unscheduled Visit) is allowed at least 1 week prior to Visit 2 (see Section 4.2; Exclusion Criterion 21). The procedure for retesting of screening results and rescreening is provided in Sections 4.4.1 and 4.2. Eligible patients will also be instructed to begin the Run-In Period when they will take the placebo tablet QD in addition to their background antihypertensive agents until Visit 2.

Patients who have previously screen-failed based on aldosterone ineligibility in prior protocol may consent to the revised protocol and rescreen for eligibility including the laboratory evaluations. Rescreened patients will be assigned a new patient number.

Clinical sites will provide patients with a 24-hour urine collection kit at Visit 1, and patients will be instructed to start the collection up to 3 days prior to Visit 2 (after confirmation of their eligibility during the Telephone Visit), refrigerate the collected sample, and bring the entire sample to the clinical site at that visit.

All patients will receive their background antihypertensive medications, unless requested otherwise, through a Central Pharmacy starting at Visit 2. Clinical sites will send prescriptions for background antihypertensive medications to the Central Pharmacy at least 1 week before the planned dispensation.

The procedures to be completed at Screening (Visit 1) and Telephone Visit are indicated in Appendix A.

6.3 Treatment Period

The 2-part Treatment Period will consist of:

- Part 1: A double-blind Treatment Period of 8 weeks (Weeks 1 to 8; Visits 2 to 6); and
- Part 2: A Treatment Period of 4 weeks (Weeks 9 to 12; Starting the day after Visit 6 through Visit 9).

6.3.1 Part 1

6.3.1.1 Randomization (Visit 2)

A patient who demonstrates treatment adherence (see Section 4.1; Inclusion Criterion 4) and continues to satisfy all inclusion criteria and none of the exclusion criteria at Visit 2 will be randomized (1:1:1:1) to 1 of the 4 treatment groups: 0.5 mg CIN-107, 1 mg CIN-107, 2 mg CIN-107, or placebo. After randomization, patients will enter the Part 1 Treatment Period.

To assess BP for randomization eligibility, the last 3 consecutive, consistent SBP measurements will be averaged to determine the final value. **Note: The standardized procedures for measuring BP are listed in Section 8.9.**

6.3.1.2 Part 1 Treatment Period

During the double-blind Part 1 Treatment Period (Weeks 1 to 8; Visits 2 to 6), patients will receive the randomized study drug as add-on medication to their background antihypertensive agent(s). Clinical sites will provide patients with a 24-hour urine collection kit at Visit 5, and patients will be instructed to start the collection up to 3 days prior to Visit 6, refrigerate the collected sample, and bring the entire sample to the clinical site at that visit. The primary endpoint (the change from baseline in mean seated SBP after 8 weeks of treatment) will be evaluated at the end of Week 8.

6.3.2 Part 2

6.3.2.1 Part 2 Treatment Period

During the Part 2 Treatment Period (Weeks 9 to 12; Starting the day after Visit 6 through Visit 9), all responders (defined as achieving a mean seated SBP <130 mmHg) at the end of Part 1 will move into Part 2, receive the maximum dose (2 mg) of CIN-107, and discontinue their background antihypertensive agent(s). The non-responders receiving any study drug except 2 mg CIN-107 will move into Part 2, receive the maximum dose (2 mg) of CIN-107, and discontinue their background antihypertensive agent(s). Clinical sites will provide patients with a 24-hour urine collection kit at Visit 8, and patients will be instructed to start the collection up to 3 days prior to Visit 9, refrigerate the collected sample, and bring the entire sample to the clinical site at that visit.

A non-responder who decides to not participate in Part 2 or has already received the maximum dose strength (2 mg) of CIN-107 in Part 1, will be considered withdrawn from the study drug, and should complete their EOT (Visit 9) procedures at the end of Part 1 (Visit 6) and the 2-week Safety Follow-Up.

Management of unblinded information will be described in a separate Blinding Plan and DSMB Charter.

The procedures to be completed during the Treatment Period are indicated in Appendix A.

6.4 Safety Follow-Up Period

The safety of CIN-107 will be assessed from the time of informed consent until the end of the Safety Follow-Up Period. During Safety Follow-Up (Visit 10), patients will be evaluated for vital signs, clinical laboratory assessments, AEs, and concomitant medication use including antihypertensive regimen since study completion.

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

6.5 Early Termination Visit and Withdrawal Procedures

The EOT for patients completing the study is Visit 9. For patients who are withdrawn from the study prior to completion, all Visit 9 procedures will be performed at an ET visit. The procedures to be completed at Visit 9 are indicated in Appendix A.

6.6 Unscheduled Procedures

Unscheduled procedures (repeat ECGs, vital sign assessments, BP monitoring, laboratory evaluations, collection of additional PK samples, etc) or visits and/or additional follow-up may be required for patients with clinically significant abnormal laboratory findings, unresolved TEAEs, SAEs, or clinically significant AEs that require follow-up laboratories and review. If, in the opinion of the Investigator, any patient has a clinically significant abnormal laboratory finding in comparison with baseline (pre-dose, Visit 2) or end of Visit 6 or unresolved TEAEs, additional follow-up visits will be scheduled. Patients will be followed approximately once a week (or more frequently as deemed appropriate) until the Investigator determines that repeat laboratory findings are clinically unremarkable in comparison with baseline, or unresolved AEs return to pre-study levels or clinically acceptable levels. If a patient experiences an SAE for which follow-up laboratories and review are required, the Investigator will schedule additional post-dose visits as necessary. If, in the opinion of the Investigator, any patient has a clinically significant AE at the follow-up visit, the Investigator will provide additional follow-up until the AE returns to clinically acceptable levels.

7 EFFICACY ASSESSMENTS

7.1 Primary Efficacy Endpoint

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

7.2 Secondary Efficacy Endpoints

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

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

7.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints of this study are as follows:

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

7.4 Pharmacodynamic Assessments

PD variables analyzed during the study may include, but are not limited to, measures of aldosterone and its precursors, cortisol and its precursor, PRA, and calculation of aldosterone/PRA ratio (Appendix B).

Additional PD samples, other than described below, 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.

7.4.1 Pharmacodynamic Blood Sampling

Pre-dose blood samples for PD analysis will be collected at the visits specified in Appendix A. The actual date and time of collection of each PD sample will be recorded. PD blood samples will

be collected in the morning at the clinical site, after the patient has been out of bed for approximately 2 hours and has been seated for 5 to 15 minutes. Samples will be analyzed using validated methods, as appropriate. Samples will be obtained after vital signs have been measured and prior to dosing of Study Drug. Additional details including PD sample collection, processing, facility, and shipment can be found in the Laboratory Manual.

7.4.2 24-Hour Urine Collection

Kits for 24-hour urine collection will be provided and 24-hour urine samples will be obtained as specified in Appendix A. Patients will be instructed to start the collection up to 3 days prior to Visits 2 (after confirmation of their eligibility during the Telephone Visit), 6, and 9, refrigerate the collected sample, and bring the entire sample to the clinical site at that visit.

A 24-hour urine collection will commence after the morning void on the first day and will include the morning void on the second day for a total duration of 24 ±2 hours. Patients must be instructed to keep the sample refrigerated at all times expect during their transit to the clinical site.

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

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

7.5 Pharmacokinetic Assessments

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

Pre-dose blood samples for PK analysis will be collected within approximately 30 minutes prior to dosing at the visits specified in Appendix A. The actual date and time of collection of each PK sample will be recorded. Site staff will collect information about delays with taking the study drug and missed study drug doses over the 3 days prior to PK sampling from the patient and record the information in source files and eCRF.

Samples will be analyzed 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.

7.6 Pharmacogenomic Assessments

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

Patients will be given the option to participate in the PGx assessment during the consenting process. The written informed consent for PGx sample collection will be included in the main ICF. The patient may withdraw consent to participate in the PGx assessment at any time during the study without withdrawing consent to participate in the study. For details regarding sample and data destruction following withdrawal of consent, see Sections 7.6.1 and 10.2, respectively.

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

If analysis of the PGx samples is undertaken, details of sample and data analyses will be provided in a separate protocol and/or analysis plan. The results obtained from analysis of the PGx 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 PGx results may be reported or published without any of the patient's personal identification information.

7.6.1 Collection, Storage, and Destruction of Pharmacogenomic Samples

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.

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

8 SAFETY ASSESSMENTS

The safety endpoints of this study are as follows:

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

8.1 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 an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory assessment variables, will be monitored and documented from the time of informed consent until the end of the Safety 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 treatment. Beginning at Screening, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF. Clinical sites will record the time of event (hour, minute) for AEs that start and/or end on the first randomized study drug administration visit (Visit 2) or at EOT/ET (Visit 9).

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.

8.1.1 Adverse (Drug) Reaction

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

8.1.2 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.

8.1.3 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 (unrelated, 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 AE 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 AE 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 AE 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 AE.

- The pharmacology and PK of the study drug-

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

8.1.4 Adverse Events of Special Interest

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

The Investigator/designee will assess and report any additional information on the AESI in detail on the appropriate AE eCRF which must be reported within 24 hours of awareness of the event.

For this study, AESIs include the following:

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

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

8.2 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 a 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 on 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.

8.3 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 the Medpace Clinical Safety or the Sponsor/designee.

To report the SAE, complete the SAE eCRF 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 email to Medpace Safety at ***medpace-safetynotification@medpace.com*** or call the Medpace SAE reporting line (phone

number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed in Section 8.7) 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 email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 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 (contact information listed in Section 8.7) 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.

8.5 Safety Surveillance and Management of Serum 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.

8.6 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. ET 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/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email 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.

8.7 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 the 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 regulation.

The requirements above refer to the requirements relating to investigational medicinal product.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
Email: medpace-safetynotification@medpace.com

8.8 Clinical Laboratory Assessments

Blood samples for standard safety chemistry panel, hematology, and coagulation will be obtained as indicated in Appendix A and assessed at the Central Laboratory per institutional guidelines. The complete list of analytes is available in Appendix B. All blood samples will be obtained after vital signs have been measured and prior to dosing of Study Drug.

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

8.9 Vital Signs

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

- Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical site visit;
- At clinical site visits when study drug will be administered, vital signs and BP will be assessed pre-dose only;
- Vital signs and BP measurements should be obtained prior to ECG recordings;
- Patient should be seated for at least 5 minutes in the examination room before measurement of vital signs and BP; and
- For measuring BP during clinical site visits, the following standardized procedures are recommended:
    - The patient should be seated with his/her 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 automated office BP monitoring (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;
    - At the Screening visit, laterality and cuff size should be determined first before taking the Screening measurements. BP will be measured in both upper arms (3 times/arm) using an appropriately sized cuff to detect possible laterality differences. The arm with the higher mean value from the laterality assessment will then be used to take the Screening BP measurements (at least 5 minutes after determining laterality) and for all subsequent measurements;
    - All BP measurements should be obtained at approximately the same time of day as the Screening measurements are obtained;
    - 3 seated BP measurements (approximately 1 minute apart) should be obtained using the same arm and the AOBPM device at each clinical site visit;
    - If the lowest and highest SBP measurements are >15 mmHg apart, 3 additional readings should be performed after waiting 2 to 5 minutes for 6 total measurements. 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 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, then the patient will be excluded from the study; and
    - Once the seated BP has been determined, the patient will be asked to stand and within approximately 1 minute after the patient's feet touch the ground, a single standing BP and heart rate (orthostatic vitals) measurement will be obtained, as required.

8.10 Electrocardiograms

Standard 12-lead ECGs will be performed at visits indicated in Appendix A.

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

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

- QRS interval;
- Heart rate;
- RR interval;
- PR 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.

8.11 Physical Examinations

A complete physical examination will consist of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system and will be performed at visits indicated in Appendix A.

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

8.12 Body Measurements

Body measurements to be collected include weight, height, waist and hip circumference, and upper arm circumference.

Weight will be measured at the visits indicated in Appendix A. Height will be measured at Screening only. Weight will be measured with the patient's shoes off and after the patient's bladder has been emptied. Height will be measured with the patient's shoes off. Once the patient's height and weight are entered into the EDC system, the system will compute the BMI.

Waist and hip circumference will be collected at visits specified in Appendix A and be used to calculate waist-to-hip ratio (WHR). Three consecutive measurements will be recorded for waist and hip circumference. The waist and hip circumferences will be measured in centimeters to 1 decimal place using a non-stretchable measuring tape to be provided by the Sponsor. Measurements should be made with the patient in the standing position and after emptying the bladder; the observer should sit in front of the patient during the measurement. The patient should stand with arms at his/her side and feet together.

Waist circumference: Waist circumference will be measured at the end of several consecutive natural breaths, at a level parallel to the floor, midpoint between the top of the iliac crest and the

lower margin of the last palpable rib in the mid axillary line. The tape should be placed around the abdomen at the level of this midway point and a reading taken when the tape is snug and flat against the skin without compressing the soft tissue.

Hip circumference: Hip circumference will be measured at a level parallel to the floor, at the largest circumference of the buttocks. The tape should be placed around the hips and a reading taken when the tape is snug and flat against the skin without compressing the soft tissue.

The measurements should be performed in the following order: waist, hip, waist, hip, waist, and hip. The WHR will be calculated based on the average of the 3 measurements taken.

Further details are provided in the Study Reference Manual.

9 STATISTICS

9.1 Analysis Populations

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

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

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

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

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

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

9.2 Statistical Methods

9.2.1 Analysis of Efficacy

9.2.1.1 Primary efficacy analysis

The primary efficacy analysis will compare the change in mean seated SBP from baseline to the end of Part 1 (Visit 6) between each dose strength of CIN-107 and placebo. Measurements recorded at randomization (Visit 2) will constitute “baseline” measurements and those recorded prior to study drug administration at the clinical site will constitute “pre-dose” measurements.

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 (LS) 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.

The primary estimand will correspond to a treatment policy estimand. The target population will comprise participants who are randomized into the study, receive at least 1 dose of any study drug, and have a baseline value for the SBP assessment. The primary summary measure to access the treatment effect will be the LS mean difference for the primary endpoint between CIN-107 and placebo based on the mixed model for repeated measures methodology. The primary estimand will

be addressed using the in-study observation period (ie, including data collected post-treatment discontinuation or post-prohibited medication use).

Missing data for the primary efficacy analysis will be based on the assumption the data are missing at random.

To assess the primary efficacy analysis assumption that the data are missing at random, the first sensitivity analysis of the primary efficacy endpoint will be based on a pattern mixture model that uses a multiple imputation technique analyzed with analysis of covariance (ANCOVA) with pre-specified fixed factors and covariates. If appropriate, based on the number of retrieved dropouts, missing measurements of non-retrieved dropouts will be modeled by known measurements from retrieved dropouts (ie, participants who remain in the trial after treatment discontinuation) in the same treatment group. The imputation model will be further clarified in the Statistical Analysis Plan (SAP).

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

Additional sensitivity analyses and subgroup analyses may be carried out under secondary estimands and/or various assumptions for missing data. Full details will be provided in the SAP.

9.2.1.2 Secondary and exploratory efficacy analysis

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

9.2.2 Analysis of Safety

The Safety Population will be the primary population for the safety analysis. All safety endpoints will be summarized descriptively for records collected in Part 1. Additional safety endpoint analyses will be conducted including records collected in Part 2 and the post-dose follow up/end of study.

9.2.3 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 2, relevant parameters for CIN-107 and any measured metabolite(s) will be listed by individual patient and summarized in tabular format using descriptive statistics. Mean and individual plasma concentrations of CIN-107 and any measured metabolite(s) will be plotted against time points for patients in Part 2.

9.2.4 Pharmacodynamic Analysis

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

9.2.5 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.

9.2.6 Interim Analysis

No interim analysis is planned.

9.2.7 Sample Size Determination

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the 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 has been accounted for.

10.1.2 Computer Systems

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

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All 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.

10.1.4 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.

10.1.5 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 site for resolution through data queries.

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

10.2 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 site. Source data are 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.

10.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last patient in the study. Patients who complete the study through Visit 9 or who were considered withdrawn at the end of Part 1 (Visit 6) may be eligible to enter a separate OLE study (Study CIN-107-130).

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 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 subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing 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.

11.2 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 sites where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, 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 drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF 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 study-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 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 will be given to the patient.

11.4 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 personnel 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 are entered by the 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 site by signature and date on the study-specific monitoring log.

11.5 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.

11.6 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.

11.7 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.

11.8 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.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study 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.

12.2 Address List

12.2.1 Sponsor

CinCor Pharma, Inc.
200 Clarendon Street
Boston, MA 02116
United States
[redacted]

12.2.2 Contract Research Organization

Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
United States
[redacted]

12.2.3 Serious Adverse Event Reporting

Medpace Clinical Safety
Medpace SAE hotline – United States:
[redacted]

12.2.4 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]

12.2.5 Central Pharmacy

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

12.2.6 Central Depot

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

Clinigen Clinical Supplies Management Inc.
342 42nd Street South
Fargo, ND 58103
United States
[redacted]

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APPENDIX A: SCHEDULE OF PROCEDURES

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

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

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

p. A complete physical examination will consist of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system.
q. A limited physical examination will consist of general appearance, skin, heart, lungs, and abdomen at a minimum.
r. Perform 12-lead ECG after the patient has been resting in the supine position for at least 10 minutes and after measuring vital signs and BP.
s. For female patients of childbearing potential (ie, ovulating, pre-menopausal, and not surgically sterile), serum pregnancy tests will be performed at Screening, EOT, and ET Visits. A POC (urine) pregnancy test will be performed at Visit 2 to assess eligibility.
t. FSH levels will be measured only for female patients who are ≤60 years, postmenopausal for at least 1 year at Screening, and are not surgically sterile.
u. Includes standard safety chemistry panel, hematology, and coagulation. All blood samples will be obtained after vital signs have been measured and prior to dosing of Study Drug. See Appendix B for the complete list of analytes.
v. Pre-dose blood samples for PD analysis will be collected at the specified visits. See Section 7.4.1 for details of blood sample collection for PD analysis.
w. Pre-dose blood samples for PK analysis will be collected within approximately 30 minutes prior to dosing at the specified visits. See Section 7.5 for details of blood sample collection for PK analysis.
x. For the Run-In Period, placebo dispensation will occur at Visit 1 following initial eligibility confirmation. The randomized study drug (CIN-107 or placebo) dispensation may occur at any time during the Treatment Period. A Study Reference Manual with details of study drug dispensation will be provided to the clinical sites.
y. During clinical site visits for the Treatment Periods (Parts 1 and 2), patients will self-administer 1 tablet of study drug in the clinic to be witnessed by site staff, after completion of pre-dose evaluations and laboratory sampling. Between clinical site visits, patients will continue to self-administer 1 tablet of study drug QD by mouth at approximately the same time each morning.
z. For the Run-In Period, all patients will self-administer 1 tablet of placebo QD by mouth at approximately the same time each morning.
aa. All patients will receive their background antihypertensive medications, unless requested otherwise, through a Central Pharmacy starting at Visit 2. Clinical sites will send prescriptions for background antihypertensive medications to the Central Pharmacy at least 1 week before the planned dispensation.
bb. Patients will be instructed to bring their study drug and background antihypertensive medication to all clinical site visits. After calculating treatment adherence (by pill counts), site staff will collect any remaining study drug from the patient at the specified visits.
cc. Clinical sites will provide patients with a 24-hour urine collection kit at Visits 1, 5, and 8. Patients will be instructed to start the collection up to 3 days prior to Visits 2 (after confirmation of their eligibility during the Telephone Visit), 6, and 9, refrigerate the collected sample, and bring the entire sample to the clinical site at that visit. A 24-hour urine collection will commence after the morning void on the first day and will include the morning void on the second day for a total duration of 24 ±2 hours.
dd. A 24-hour urine collection may be repeated if the Investigator suspects that the sampling is insufficient and the patient is within the visit window. Clinical sites will aliquot urine into a transfer tube and send it to the Central Laboratory.
ee. For patients who provide written informed consent to participate in the optional PGx assessment, a blood sample will be collected at any time after randomization during the Treatment Period.

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

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate [1]
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid

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

Additional Chemistry Parameters

Glycated hemoglobin

Endocrinology

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

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

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential [1]	

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

Coagulation

Activated partial thromboplastin time	International normalized ratio
Prothrombin time	

Urinalysis

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

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

Viral Testing and Serology

Hepatitis B surface antigen	Hepatitis C virus RNA
HIV antibody	

HIV = human immunodeficiency virus; RNA = ribonucleic acid.

Pharmacodynamic Analytes

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

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

Pharmacokinetic Analytes

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

24-Hour Urine Collection Analytes

Albumin	Aldosterone
Creatinine	Potassium
Protein	Sodium
	Renin

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 cytochrome 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 24 June 2021 is reflected in Table 1.

Table 1. Examples of Excluded Medications

Group	Examples
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.