CLINICAL STUDY PROTOCOL

An Open-Label Extension Study of Patients Previously Enrolled in Study CIN-107-124 to Evaluate the Long-Term Safety and Effectiveness of CIN-107

Investigational Product: CIN-107 (Generic Name: Baxdrostat)
Protocol D Code: D6971C00001
Study Name: HALO-OLE CIN-107-130

Sponsor:
AstraZeneca AB
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[redacted]

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SIGNATURE PAGE

STUDY TITLE: An Open-Label Extension Study of Patients Previously Enrolled in Study CIN-107-124 to Evaluate the Long-Term Safety and Effectiveness of CIN-107

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

Signature Date

[redacted] 4/8/2023

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 AstraZeneca, 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 AstraZeneca 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 AstraZeneca, 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: An Open-Label Extension Study of Patients Previously Enrolled in Study CIN-107-124 to Evaluate the Long-Term Safety and Effectiveness of CIN-107

PROTOCOL D Code: D6971C00001

Protocol Name: HALO-OLE CIN-107-130

INVESTIGATIONAL PRODUCT: CIN-107

PHASE: 2

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

OBJECTIVES:

The primary objective is to evaluate the long-term safety and tolerability of CIN-107 over an extended treatment period of up to 52 weeks.

The safety and tolerability objectives are the following:

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

The effectiveness objectives are to evaluate the following relative to baseline (Visit 1) in Study CIN-107-130 over 52 weeks:

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

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

POPULATION:

Patients who participated in and completed Part 1 or Part 2 of Study CIN-107-124 and did not discontinue the study drug for any reason, including an adverse event (AE), will be eligible for this study.

Inclusion Criteria

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

1. Have completed Part 1 or Part 2 of Study CIN-107-124;

   Note: Patients who have completed Part 1 but were not eligible for Part 2 of Study CIN-107-124 may consent to Study CIN-107-130.

2. Have had acceptable safety and tolerability during Study CIN-107-124 as determined by the Investigator or Medical Monitor;
3. Have demonstrated ≥70% and ≤120% adherence to their single background antihypertensive agent and the CIN-107 placebo during Study CIN-107-124;
4. Agree to comply with the contraception and reproduction restrictions of the study as follows:
   - Male patients must agree to abstain from sperm donation from Day 1 through 90 days after the final dose of study drug;
   - Female patients of childbearing potential (ie, ovulating, pre-menopausal, and not surgically sterile) must have a documented negative serum pregnancy test at enrollment (Visit 1); and

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

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

  - Surgical sterilization (eg, hysterectomy, bilateral oophorectomy, bilateral tubal ligation);
  - Intrauterine device for at least 12 weeks before enrollment (Visit 1);
  - Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before enrollment (Visit 1); or
  - Diaphragm used in combination with spermicide.

  Note: Postmenopausal female patients, who were either >60 years or had follicle-stimulating hormone (FSH) in the post-menopausal range during screening for Study CIN-107-124, must continue to have no menstrual bleeding for at least 1 year prior to enrollment (Visit 1), and therefore do not require FSH testing.

5. 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 met Protocol-defined stopping criteria, were withdrawn from the study, discontinued CIN-107 at the time of Visits 6 or 9, or were not compliant with the Protocol during Study CIN-107-124;
2. Have received treatment with any investigational agent for disease intervention (ie, other than study drug) during Study CIN-107-124, or since the last administration of study drug in Study CIN-107-124, or plans to participate in another clinical study within 30 days of discontinuation of study drug;
3. Have had any new, significant, or uncontrolled comorbidity since initially enrolling in Study CIN-107-124 that would increase the risk of the patient in Study CIN-107-130, as determined by the Investigator;
4. Have had a mean seated SBP ≥170 mmHg or DBP ≥105 mmHg at the end of Part 1 or Part 2 of Study CIN-107-124;

   Note: Mean seated BP is defined as the average of 3 seated BP measurements.

5. Have an upper arm circumference that does not meet the cuff measurement criteria for the selected BP machine at Visit 1 of Study CIN-107-130;
6. Have any uncontrolled or clinically significant laboratory abnormality that would affect safety, interpretation of study data, or the patient's participation in the study, as determined by the Investigator;

7. Have experienced a de novo or reactivated serious viral infection such as hepatitis B, hepatitis C, or HIV during Study CIN-107-124;

   Note: Patients who experienced a viral infection during Study CIN-107-124 (ie, seasonal flu, Coronavirus Disease 2019, etc) are not excluded if recovered and asymptomatic within 4 weeks of Visit 1 in Study CIN-107-130.

8. Have had any major episode of infection requiring hospitalization or treatment with intravenous antibiotics during Study CIN-107-124;
9. Have developed a malignancy (with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin) during Study CIN-107-124;
10. Have anticipated initiation of erythropoietin-stimulating agents and/or planned transfusion within 2 months after enrollment (Visit 1);
11. Are expected to receive or are receiving any of the exclusionary drugs (strong cytochrome P450 3A inducers);
12. Have known secondary causes of HTN (eg, renal artery stenosis, uncontrolled or untreated hyperthyroidism, uncontrolled or untreated hypothyroidism, hyperparathyroidism, pheochromocytoma, Cushing's syndrome, or aortic coarctation) except obstructive sleep apnea;

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

13. Have been diagnosed with New York Heart Association stage III or IV chronic heart failure during Study CIN-107-124;
14. Have had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure during Study CIN-107-124;
15. Have a known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease diagnosed from a prior echocardiogram;
16. Have a planned coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) or any major surgical procedure;
17. Have had a CABG or other major cardiac surgery (eg, valve replacement), peripheral arterial bypass surgery, or PCI during Study CIN-107-124;
18. Have a planned dialysis or kidney transplant during the course of this study;
19. Have a known hypersensitivity to CIN-107 or drugs of the same class, or any of its excipients;
20. Have any clinically relevant medical or surgical conditions (including unstable conditions and/or treatment with systemic immunosuppressants including corticosteroids) that, in the opinion of the Investigator, would put the patient at risk by participating in the study;

21. Are pregnant, breastfeeding, or planning to become pregnant during the study; or
22. 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, multicenter, open-label extension (OLE) study to evaluate the long-term safety, tolerability, and effectiveness of CIN-107 for up to 52 weeks in patients with HTN who have completed Part 1 or Part 2 of Study CIN-107-124. The study will be conducted at clinical sites that have participated in the double-blind, Phase 2 Study CIN-107-124. Patients will be assigned the same patient number they have had in Study CIN-107-124.

Written informed consent must be obtained before any Protocol-specific procedures are performed in this study (Study CIN-107-130). Eligible patients from Study CIN-107-124 who elect to participate in the OLE will be enrolled directly following the EOT assessments at the end of Part 1 or Part 2 of Study CIN-107-124 (ie, they will not undergo the safety follow-up in Study CIN-107-124). The EOT assessments at the end of Part 1 or Part 2 of Study CIN-107-124 will serve as the Day 1 pre-dose assessments for those enrolling in Study CIN-107-130.

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

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

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

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

To manage persistent or symptomatic hypotension, the Investigator should first reduce or discontinue any rescue medication, and then reduce or discontinue use of the single background antihypertensive (non-CIN-107) agent if medically sound. If the symptoms continue, the dose strength of CIN-107 may be down-titrated from 2 mg to 1 mg. The CIN-107 dose may be further

down-titrated to 0.5 mg if the SBP remains ≤100 mmHg for 3 consecutive days or if symptoms persist. CIN-107 may be temporarily discontinued if the SBP remains <90 mmHg for 3 consecutive days or if symptoms persist. Study drug dosing may be resumed or up-titrated after reassessments.

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

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

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

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

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

CIN-107 tablets will be provided in 0.5, 1, and 2 mg dose strengths. The tablets will be packaged in blister packs to achieve the doses required for the study.

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

STUDY WITHDRAWAL AND STUDY DRUG DISCONTINUATION CRITERIA:

A patient will be withdrawn from this clinical study for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason; or
- The study is terminated by the Sponsor or the regulatory authority.

The study drug will be discontinued for any of the following reasons:

- Occurrence of any medical condition or circumstance, SAE, clinically significant AE, severe laboratory abnormality, or intercurrent illness which exposes the patient to substantial risk, does not allow the patient to adhere to the requirements of the Protocol, and/or indicates to the Investigator that continued participation is not in the best interest of the patient;
- Requirement of excluded concomitant medication and/or procedure; or
- The patient becomes pregnant.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, he/she 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 7) at ET. The reason for patient withdrawal must be documented in the electronic case report form. Patients who prematurely discontinue study drug treatment should complete the remaining study visits for safety monitoring despite discontinuation of study drug. Withdrawn patients will not be replaced.

SAFETY AND TOLERABILITY ENDPOINTS:

The safety and tolerability of CIN-107 will be assessed from the day of the first dose of study drug in Study CIN-107-130 until the end of the follow-up visit. The safety and tolerability endpoints will include the following:

- TEAEs;
- Treatment-emergent SAEs;
- TEAEs of special interest;
- TEAEs leading to premature discontinuation of study drug;
- Treatment-emergent marked laboratory abnormalities;
- Change on standing SBP and DBP, measured pre-dose at the clinical site, from baseline (Visit 1) of Study CIN-107-130 to EOT (Visit 7);
- Vital signs, standing BP and heart rate, physical examinations, ECGs, body weight, and clinical laboratory evaluations, including standard safety chemistry panel, hematology, coagulation, and urinalysis;
- The percentage of patients with electrolyte imbalance;
- The percentage of laboratory results with electrolyte imbalance;
- The percentage of patients requiring down-titration of CIN-107 from the maximal dose strength of 2 mg to a lower dose strength of 1 mg or 0.5 mg;

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

EFFECTIVENESS ENDPOINTS:

The effectiveness endpoints include the following:

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

STATISTICAL ANALYSES:

Study CIN-107-130 is a multicenter, single arm, OLE study. The primary objective of this study is to assess the long-term safety and tolerability of CIN-107 in patients with HTN who have completed the parent Study CIN-107-124. The baseline values for safety and tolerability endpoints and effectiveness endpoints are defined as the values at Visit 1 prior to starting the first dose in Study CIN-107-130.

No formal hypothesis testing is planned. Additional details of analyses to be performed will be specified in the Statistical Analysis Plan.

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

All safety and tolerability endpoints will be summarized descriptively. The Safety Population will be the primary population used for analyses.

The effectiveness endpoints are secondary endpoints of this study. The change from baseline over time will be analyzed. The analyses will be performed descriptively based on data in the Safety Population.

Additional analyses may be conducted with data collected in the parent Study CIN-107-124 to assess safety, tolerability, and effectiveness of CIN-107 from the first exposure.

No interim analysis is planned.

SAMPLE SIZE DETERMINATION:

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

SITES: Clinical sites that participated in the Phase 2 Study CIN-107-124 are eligible to participate.

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AOBPM	Automated office blood pressure monitoring
AUC	Area under the concentration-time curve
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CRA	Clinical research associate
CYP	Cytochrome P450
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EIU	Exposure In Utero
EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HTN	Hypertension
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
MAD	Multiple-ascending dose
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonist
NOAEL	No observed adverse effect level
OLE	Open-label extension
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRA	Plasma renin activity
QD	Once daily

Abbreviation	Definition
QTc	Heart rate-corrected QT interval
QTcF	Heart rate-corrected QT interval using Fridericia's formula
SAD	Single-ascending dose
SAE	Serious adverse event
SBP	Systolic blood pressure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-emergent adverse event

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 the enzyme aldosterone synthase. Aldosterone is a key component of the renin angiotensin aldosterone system and acts as a critical regulator of fluid and electrolyte homeostasis through its agonism of the mineralocorticoid receptor (MR). Its effect on end organs has been shown to occur by 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]

One of the challenges that has impacted the development of aldosterone synthase inhibitors has been the difficulty in selectively inhibiting aldosterone synthase without 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 similarity 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.[4,5,6,7]

Baxdrostat is a highly potent, selective, and competitive inhibitor of human aldosterone synthase (encoded by the cytochrome P450 [CYP]11B2 gene). Baxdrostat (formerly CIN-107 or RO6836191) was acquired from Roche Pharmaceuticals, Inc. (hereinafter Roche) by CinCor Pharma, Inc. (hereinafter CinCor). CinCor is a wholly owned subsidiary of the AstraZeneca group of companies. AstraZeneca is pursuing further clinical development of the compound. 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 and in the multiple-ascending dose (MAD) in healthy human patients.

1.1 Overview of Non-Clinical Studies

The potential adverse effects of CIN-107 have been evaluated in standard safety pharmacology, genotoxicity, repeated-dose toxicity, and reproductive toxicity studies. Findings in animal models are available in the Investigator's Brochure and briefly summarized below.

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 adrenocorticotropic hormone, CIN-107 blocked aldosterone synthesis without interfering with cortisol levels.

Administration of CIN-107 up to 30 mg/kg/day for up to 13 weeks and up to 10 mg/kg/day for up to 26 weeks has been studied in Wistar Han rats. Most changes in the 13-week toxicity study were reversible and/or confined to the high dose level, with the exception of dose-related decreases in aldosterone in both sexes, which was noted at all dose levels. Based on preliminary data from the 26-week toxicity study (Study CIN-107-RETOX007), CIN-107-related mortality occurred in 2 female rats administered 10 mg/kg/day and who were sacrificed in moribund condition due to dehydration and loss of body weight. Mild, dose-responsive (females only), non-adverse increased serum cholesterol concentration was observed in males administered 10 mg/kg/day and females administered ≥1 mg/kg/day. Based on these data, the no observed adverse effect level (NOAEL) for CIN-107 in male rats is 10 mg/kg/day or a human equivalent dose of 81 mg/day. Due to the

CIN-107-related unscheduled sacrifice of 2 females administered 10 mg/kg/day, the NOAEL for CIN-107 in female rats is 3 mg/kg/day which is equivalent to 24 mg/day for a 50 kg human.

CIN-107 was administered in cynomolgus monkeys up to 6 mg/kg/day for up to 39 weeks. Based on preliminary results of Study CIN-107-RETOX006, no CIN-107-related clinical pathology changes were noted. CIN-107-related microscopic findings included adrenal hyperplasia (zona glomerulosa, minimal to moderate), renal juxtaglomerular hyperplasia (considered related to CIN-107 pharmacology), and decreased lymphocytes in multiple organs (spleen, thymus, and mesenteric lymph nodes) of animals administered ≥1 mg/kg/day. Microscopic findings showed evidence of reversibility. Due to the lack of impact on the health and well-being of animals, the NOAEL is 6 mg/kg/day for male and female monkeys or a human equivalent dose of 97 mg/day for a 50 kg human.

The adrenal gland was the primary tissue affected 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 adrenal zona glomerulosa cells with increased thickness or expansion of the zona glomerulosa layer, increased aldosterone synthase (CYP11B2) immunostaining, lipid vacuolation, apoptosis, and proliferation of zona glomerulosa cells. These pathological changes in the adrenal gland were ameliorated by electrolyte supplementation and angiotensin-converting enzyme inhibition, indicating that they were exaggerated pharmacological effects of and physiologic/adaptive responses to aldosterone inhibition.

There was no evidence for a mutagenic, clastogenic, or aneugenic potential of CIN-107.

In vitro cardiovascular safety was assessed in a human ether à-go-go-related gene assay. The concentration needed for 20% inhibition was >150-fold above the free maximum plasma concentration (C_{max}) expected to be efficacious in man (at ≤10 mg once daily [QD] dose for the treatment of hypertension [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 the central nervous system or respiratory function. The NOAEL was considered to be ≥50 mg/kg CIN-107 for both studies.

Details of the studies and results are available in the Investigator's Brochure.

1.2 Overview of Clinical Studies With CIN-107

1.2.1 Clinical Studies in Healthy Patients

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

Results of the SAD study which investigated the safety, tolerability, PK, and pharmacodynamics (PD) of CIN-107 in healthy male volunteers 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 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} 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.

Single doses of CIN-107 reduced plasma and urine aldosterone levels by approximately 85% to 90% in a dose-dependent manner. A maximum effect on aldosterone reduction was consistently achieved 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 after the Cortrosyn challenge 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 have occurred based on observed increases in 11-deoxycortisol (at doses of 180 mg and 360 mg) and 11-deoxycorticosterone (at doses ≥90 mg).

Single oral doses of up to 360 mg CIN-107 did not affect serum electrolyte (chloride, potassium, sodium, and phosphate) levels, with no difference for patients on active treatment versus those on placebo. Urine sodium and the sodium to potassium ratio both increased, with the sodium loss in urine greater than the potassium retention. No change in urine creatinine was apparent.

Results of the MAD study indicate that multiple ascending doses of CIN-107 up to 5 mg QD for 10 days were well tolerated by healthy patients taking low salt diet (for 2.5 and 5 mg CIN-107 dose groups) and normal salt diet (for 0.5, 1.5, and 2.5 mg CIN-107 dose groups). 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 by 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 patients. As expected with a reduction in aldosterone levels, there were mild, dose-dependent increases in plasma potassium levels and reductions in plasma sodium levels.

The drug product used in the Phase 1 SAD and MAD studies was provided as an oral solution. A tablet formulation was developed and used in the Phase 1 relative bioavailability and food effect study (CIN-107-112). The study was conducted with a 5 mg solution (fasted) and a 5 mg tablet. Results of the relative bioavailability assessment indicate that exposure to CIN-107 and its primary metabolite following administration of the CIN-107 tablet formulation is equivalent to that observed following administration of the oral solution. 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. Time to C_{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. The safety profile of metformin was similar in the

presence and absence of CIN-107. Specifically, 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 patients with varying degrees of renal function, ranging from normal renal function to end stage disease receiving hemodialysis. One patient with end stage disease experienced an unrelated SAE of metabolic encephalopathy and a moderate unrelated adverse event (AE) of tremor. One control patient 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 patients (normal renal function or mild renal impairment; eGFR ≥60 mL/min). The conclusions of this study suggest that it is not necessary to dose adjust CIN-107 for patients with renal impairment.

Details of the findings are available in the Investigator's Brochure.

1.3 Study CIN-107-124 (HALO Study)

Study CIN-107-124, the HALO study, is the parent clinical trial of the current Study CIN-107-130. It is a Phase 2, randomized, multicenter study to evaluate the efficacy and safety of multiple dose strengths of CIN-107 for the treatment of HTN in 2 parts. Eligible patients must have uncontrolled HTN (mean seated systolic blood pressure [SBP] ≥140 mmHg [or ≥130 mmHg if diabetic]) despite being on a stable regimen of a single background antihypertensive agent at the maximal tolerated dose (in the opinion of the Investigator) for at least 8 weeks and must have a serum aldosterone ≥7 ng/dL (≥6 ng/dL if on an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker) and meet all other enrollment criteria. Approximately 250 patients are to be enrolled in the clinical sites in the United States. A subsequent amendment of the protocol permitted patients 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 to be enrolled. The requirement of a baseline serum aldosterone ≥7 ng/dL (≥6 ng/dL if on an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker) was removed.

Patients in the HALO study are to be randomly assigned to CIN-107 0.5 mg, 1 mg, 2 mg, or placebo QD for 8 weeks as the add-on therapy to their single background antihypertensive agent in Part 1. All responders (defined as patients achieving a mean seated SBP <130 mmHg) at the end of Part 1 will be qualified to participate in Part 2. Responders will receive 2 mg CIN-107 tablets and discontinue their single background antihypertensive agent in Part 2. 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 for 4 weeks, and discontinue their single background antihypertensive agent. A non-responder who has already received the maximum dose strength (2 mg) of CIN-107 in Part 1 will be considered withdrawn from the study. Patients who complete the study through 12 weeks or who were considered withdrawn at the end of Part 1 may be eligible to enter the open-label extension (OLE) study (Study CIN-107-130).

1.4 Rationale for Conducting Study CIN-107-130

The rationale for conducting an OLE study is to evaluate the long-term safety, tolerability, and effectiveness on blood pressure (BP) management of CIN-107 over an extended treatment period of up to 52 weeks. As CIN-107, if approved, will be used chronically for managing HTN, collection of data from patients exposed for a minimum of 1 year at dosage levels intended for clinical use will ensure adequate safety assessment. Patients enrolled in Study CIN-107-124, who have uncontrolled HTN despite being on a stable regimen of a single background antihypertensive agent, represent a large portion of the hypertensive population.

1.5 Risk/Benefit

1.5.1 Potential Risks

1.5.1.1 Risk of hyperkalemia and hyponatremia

Aldosterone leads to increased reabsorption of sodium and water and secretion of potassium in the kidneys, thereby increasing blood volume and BP. Based on the preclinical observations and the mode of action of 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. 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.

1.5.1.2 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).

1.5.1.3 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).[8,9]

1.5.1.4 Risk of sex hormone-related adverse events

Known side effects of MR antagonists (MRAs) are gynecomastia, mastodynia, and abnormal vaginal bleeding, and were observed more frequently with spironolactone than with eplerenone. Occurrence of these events will be monitored in this study. Nevertheless, a selective inhibitor of aldosterone synthase is not expected to interfere with sexual hormone pathways.

1.5.1.5 Risk of allergic reactions

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

1.5.2 Potential Benefits

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

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

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 evaluate the long-term safety and tolerability of CIN-107 over an extended treatment period of up to 52 weeks.

2.1.1 Safety and Tolerability Objectives

The safety and tolerability objectives are the following:

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

2.2 Effectiveness Objectives

The effectiveness objectives are to evaluate the following relative to baseline (Visit 1) in Study CIN-107-130 over 52 weeks:

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

2.3 Pharmacokinetic-Pharmacodynamic Objective

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

3 STUDY DESCRIPTION

3.1 Summary of Study Design

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

Written informed consent must be obtained before any Protocol-specific procedures are performed in this study (Study CIN-107-130). Eligible patients from Study CIN-107-124 who elect to participate in the OLE will be enrolled directly following the EOT assessments at the end of Part 1 or Part 2 of Study CIN-107-124 (ie, they will not undergo the safety follow-up in Study CIN-107-124). The EOT assessments at the end of Part 1 or Part 2 of Study CIN-107-124 will serve as the Day 1 pre-dose assessments for those enrolling in Study CIN-107-130.

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

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

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

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

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

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

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

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

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

3.2 Study Indication

CIN-107 is being studied for the long-term safety, tolerability, and effectiveness in the reduction of SBP in patients with HTN.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Population

Patients who participated in and completed Part 1 or Part 2 of Study CIN-107-124 and did not discontinue the study drug for any reason, including an AE, will be eligible for this study.

4.2 Inclusion Criteria

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

1. Have completed Part 1 or Part 2 of Study CIN-107-124;

   Note: Patients who have completed Part 1 but were not eligible for Part 2 of Study CIN-107-124 may consent to Study CIN-107-130.

2. Have had acceptable safety and tolerability during Study CIN-107-124 as determined by the Investigator or Medical Monitor;

3. Have demonstrated ≥70% and ≤120% adherence to their single background antihypertensive agent and the CIN-107 placebo during Study CIN-107-124;

4. Agree to comply with the contraception and reproduction restrictions of the study as follows:

   - Male patients must agree to abstain from sperm donation from Day 1 through 90 days after the final dose of study drug;
   - Female patients of childbearing potential (ie, ovulating, pre-menopausal, and not surgically sterile) must have a documented negative serum pregnancy test at enrollment (Visit 1); and
   - Female patients of childbearing potential must use a highly effective method of contraception (ie, <1% failure rate) from Day 1 through 30 days after the last administration of study drug.

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

     - Surgical sterilization (eg, hysterectomy, bilateral oophorectomy, bilateral tubal ligation);
     - Intrauterine device for at least 12 weeks before enrollment (Visit 1);
     - Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before enrollment (Visit 1); or
     - Diaphragm used in combination with spermicide.

   Note: Postmenopausal female patients, who were either >60 years or had follicle-stimulating hormone (FSH) in the post-menopausal range during screening for Study CIN-107-124, must continue to have no menstrual bleeding for at least 1 year prior to enrollment (Visit 1), and therefore do not require FSH testing.

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

4.3 Exclusion Criteria

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

1. Have met Protocol-defined stopping criteria, were withdrawn from the study, discontinued CIN-107 at the time of Visits 6 or 9, or were not compliant with the Protocol during Study CIN-107-124;
2. Have received treatment with any investigational agent for disease intervention (ie, other than study drug) during Study CIN-107-124, or since the last administration of study drug in Study CIN-107-124, or plans to participate in another clinical study within 30 days of discontinuation of study drug;
3. Have had any new, significant, or uncontrolled comorbidity since initially enrolling in Study CIN-107-124 that would increase the risk of the patient in Study CIN-107-130, as determined by the Investigator;
4. Have had a mean seated SBP ≥170 mmHg or DBP ≥105 mmHg at the end of Part 1 or Part 2 of Study CIN-107-124;

   Note: Mean seated BP is defined as the average of 3 seated BP measurements.
5. Have an upper arm circumference that does not meet the cuff measurement criteria for the selected BP machine at Visit 1 of Study CIN-107-130;
6. Have any uncontrolled or clinically significant laboratory abnormality that would affect safety, interpretation of study data, or the patient's participation in the study, as determined by the Investigator;
7. Have experienced a de novo or reactivated serious viral infection such as hepatitis B, hepatitis C, or HIV during Study CIN-107-124;

   Note: Patients who experienced a viral infection during Study CIN-107-124 (ie, seasonal flu, Coronavirus Disease 2019, etc) are not excluded if recovered and asymptomatic within 4 weeks of Visit 1 in Study CIN-107-130.
8. Have had any major episode of infection requiring hospitalization or treatment with intravenous antibiotics during Study CIN-107-124;
9. Have developed a malignancy (with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin) during Study CIN-107-124;
10. Have anticipated initiation of erythropoietin-stimulating agents and/or planned transfusion within 2 months after enrollment (Visit 1);
11. Are expected to receive or are receiving any of the exclusionary drugs (strong CYP3A inducers; see Appendix D for examples);
12. Have known secondary causes of HTN (eg, renal artery stenosis, uncontrolled or untreated hyperthyroidism, uncontrolled or untreated hypothyroidism, hyperparathyroidism, pheochromocytoma, Cushing's syndrome, or aortic coarctation) except obstructive sleep apnea;

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

13. Have been diagnosed with New York Heart Association stage III or IV chronic heart failure during Study CIN-107-124;
14. Have had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure during Study CIN-107-124;
15. Have a known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease diagnosed from a prior echocardiogram;
16. Have a planned coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) or any major surgical procedure;
17. Have had a CABG or other major cardiac surgery (eg, valve replacement), peripheral arterial bypass surgery, or PCI during Study CIN-107-124;
18. Have a planned dialysis or kidney transplant during the course of this study;
19. Have a known hypersensitivity to CIN-107 or drugs of the same class, or any of its excipients;
20. Have any clinically relevant medical or surgical conditions (including unstable conditions and/or treatment with systemic immunosuppressants including corticosteroids) that, in the opinion of the Investigator, would put the patient at risk by participating in the study;
21. Are pregnant, breastfeeding, or planning to become pregnant during the study; or
22. 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.

4.4 Study Withdrawal and Study Drug Discontinuation Criteria

A patient will be withdrawn from this clinical study for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason; or
- The study is terminated by the Sponsor or the regulatory authority.

The study drug will be discontinued for any of the following reasons:

- Occurrence of any medical condition or circumstance, SAE, clinically significant AE, severe laboratory abnormality, or intercurrent illness which exposes the patient to substantial risk, does not allow the patient to adhere to the requirements of the Protocol, and/or indicates to the Investigator that continued participation is not in the best interest of the patient;
- Requirement of excluded concomitant medication and/or procedure; or
- The patient becomes pregnant.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, he/she 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 7) at ET. The reason for patient withdrawal must be documented in the electronic case report form (eCRF).

Patients who prematurely discontinue study drug treatment should complete the remaining study visits for safety monitoring despite discontinuation of study drug.

Withdrawn patients will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Groups

Eligible patients from Study CIN-107-124 who elect to participate in this study will continue treatment with 2 mg CIN-107 tablets QD after enrollment.

5.2 Rationale for Dosing

The OLE Study CIN-107-130 was designed to assess the long-term treatment effect of the 2 mg dose of CIN-107 on safety, tolerability, and BP management in patients with HTN. It is anticipated that the dose strengths used in the parent Study CIN-107-124 of up to 2 mg will be well tolerated and effective in lowering the aldosterone level based on results of non-clinical toxicity studies and completed clinical pharmacology studies.

Investigators will be allowed to determine whether the patient should start the OLE study with an additional single background antihypertensive (non-CIN-107) agent based on the patient's BP control in Study CIN-107-124 (ie, whether the patient in addition to the CIN-107 study drug would start the OLE study with an additional single background antihypertensive agent from another or same class as during Part 1 of Study CIN-107-124). Rescue medications may be used as detailed in Appendix E. Management of persistent or symptomatic hypotension is detailed in Appendix F.

5.3 Blinding

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

5.4 Drug Supplies

5.4.1 Formulation and Packaging

The study drug, CIN-107 tablets, are round, white tablets exhibiting a >70% release of the CIN-107 drug substance by 45 minutes in vitro.

CIN-107 tablets will be provided in 0.5, 1, and 2 mg dose strengths. The tablets will be packaged in blister packs to achieve the doses required for the study. [redacted]

5.4.2 Study Drug Preparation and Dispensing

5.4.2.1 Background antihypertensive agent

All patients who require a single background antihypertensive agent will receive it, unless requested otherwise, through a Central Pharmacy starting at Visit 1. Clinical sites will send prescriptions for background antihypertensive agent to the Central Pharmacy at least 1 week before the planned dispensation.

5.4.2.2 Study drug

The study drug, open-label CIN-107, will be delivered from the Central Depot to the clinical site. Once a patient has been enrolled in the study and registered by Interactive Response Technology,

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).

Study drug dispensation may occur at any time starting at enrollment (Visit 1) and before EOT (Visit 7). A Study Reference Manual with details of study drug dispensation and collection of unused study drug will be provided to the clinical sites.

5.4.3 Study Drug Administration

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

On clinical site visit days, patients will self-administer the morning dose of any other concomitant medications (if applicable) at home. CIN-107 should be withheld as it will be self-administered at the clinical site and witnessed by site staff, after completion of pre-dose evaluations and laboratory sampling.

Between clinical site visits, patients will continue to self-administer CIN-107 QD by mouth at approximately the same time each morning.

5.4.4 Treatment Compliance

For all Protocol-specified doses when the patient is not at the clinical site, patients will self-administer CIN-107 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 antihypertensive medication(s) to all clinical site visits. Site staff will calculate treatment adherence based on pill counts. Treatment compliance is defined as >70% and <120% over the course of the treatment period. If a trend of patient non-compliance is observed, then the patient may be discontinued based on the discretion of the Investigator (see Section 4.4). Individual missed doses or doses held due to abnormal laboratory values or AEs will not be reported as a deviation.

Site staff will counsel patients about the importance of adhering to the following: study drug, background antihypertensive regimen (if applicable), as indicated in Appendix A.

5.4.5 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 at Visit 1 of Study CIN-107-130 will be asked to return the study drug (dispensed at Visit 1) to the clinical site in prepaid shipments and complete the safety follow-up in Study CIN-107-124.

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.

5.5 Prior and Concomitant Medications and/or Procedures

5.5.1 Excluded Medications and/or Procedures

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

- Strong CYP3A inducers (examples are provided in Appendix D);
- Chronic use of non-steroidal anti-inflammatory drugs;
- MRA or a potassium-sparing diuretic as part of an existing antihypertensive regimen;
- Potassium supplements;
- Dialysis;
- Kidney transplantation;
- Erythropoietin-stimulating agents;
- Transfusion of blood and blood products; or
- Major surgical procedure.

5.5.2 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. All clinical site visits should occur between 6:00 a.m. and 11:00 a.m.

5.5.3 Allowed Medications and/or Procedures

Investigators will be allowed to determine whether the patient should start the OLE study with an additional background antihypertensive (non-CIN-107) agent based on the patient's BP control in Study CIN-107-124 (ie, whether the patient in addition to the CIN-107 study drug would start the OLE study with an additional background antihypertensive agent from another or same class as during Part 1 of Study CIN-107-124).

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

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

Rescue medications (see Appendix E for guidance) and down-titration of antihypertensive medication(s) (see Appendix F for recommendations) are allowed.

5.5.4 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.

5.5.5 Documentation of Prior and Concomitant Medication Use

All medications used within 30 days prior to enrollment (Visit 1) 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 study drug administration visit (Visit 1) or at EOT (Visit 7)/ET.

6 STUDY PROCEDURES

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

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

7 EFFECTIVENESS ASSESSMENTS

7.1 Effectiveness Endpoints

The effectiveness endpoints include the following:

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

7.2 Pharmacokinetic and Pharmacodynamic Assessment

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

7.2.1 Pharmacodynamic Blood Sampling

Pre-dose blood samples for PD analysis will be collected at the visits specified in Appendix A. The actual date and time of collection of each PD sample will be recorded. PD blood samples will be collected in the morning at the clinical site, after the patient has been out of bed for approximately 2 hours and has been seated for 5 to 15 minutes. Samples will be analyzed using validated methods, as appropriate. Additional details including PD sample collection, processing, facility, and shipment can be found in the Laboratory Manual.

7.2.2 Twenty-Four-Hour Urine Collection

Kits for 24-hour urine collection will be provided, and 24-hour urine samples will be obtained as specified in Appendix A.

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

7.3 Pharmacokinetic Assessments

PK variables to be 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 15 minutes prior to dosing at the visits specified in Appendix A. The actual date and time of collection of each PK sample will be recorded. 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.

8 SAFETY AND TOLERABILITY ASSESSMENTS

The safety and tolerability of CIN-107 will be assessed from the day of the first dose of study drug in Study CIN-107-130 until the end of the follow-up visit. The safety and tolerability endpoints will include the following:

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

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject 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 test variables, will be monitored and documented from the day of the first dose of study drug in Study CIN-107-130 until the end of the follow-up visit. Patients should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study drug. Beginning from the day of the first dose of study drug in Study CIN-107-130 until the end of the follow-up visit, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an

observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at enrollment (Visit 1) 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, ECGs) findings that are detected during the study or are present at enrollment (Visit 1) 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 event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

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

- Underlying, concomitant, intercurrent diseases-

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

- Concomitant drug-

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

- Known response pattern for this class of study drug-

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

- Exposure to physical and/or mental stresses-

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

- The pharmacology and PK of the study drug-

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

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

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

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one 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/emailed 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

Patient serum potassium levels will be monitored systematically throughout the study. Serum potassium will be measured at the Central Laboratory at each visit as indicated in the Schedule of Procedures (Appendix A). Unscheduled assessments of serum potassium levels should be completed at the Investigator's discretion for acute management of the patient (follow-up from elevated Central Laboratory 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 serum 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/clinical site the Exposure In Utero (EIU) form for completion. The Investigator/clinical 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/emailed 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

The Sponsor/designee 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), applicable competent authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor/designee 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, applicable competent authorities concerned and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee 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:
[redacted]

8.8 Clinical Laboratory Evaluations

Blood samples for standard safety chemistry panel, hematology, and coagulation and urine samples for urinalysis 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.

A serum 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 enrollment (Visit 1), laterality should be determined first before taking the enrollment (Visit 1) 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 will then be used to take the enrollment (Visit 1) 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 enrollment (Visit 1) measurements are obtained;
- 3 seated BP measurements (each measurement 1 to 2 minutes apart) should be obtained using the same arm and the AOBPM device at each clinical site visit;
- 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 after 60 seconds, a single standing BP and heart rate (orthostatic vital signs) 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;
- PR interval:
- RR interval;
- QT interval; and
- QTc (QTcF).

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

8.11 Physical Examination

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

A limited physical examination will consist of a minimum of general appearance, skin, heart, lungs, and abdomen at the visits indicated in Appendix A.

8.12 Body Measurement

Body measurements to be collected include weight, height, body mass index (BMI), and upper arm circumference.

Height will be collected at enrollment (Visit 1) only and will be used to calculate BMI at subsequent visits.

Weight will be measured at the visits indicated in Appendix A. 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.

Upper arm circumference will be measured at enrollment (Visit 1) to ensure that the cuff measurement criteria for the selected BP machine is met.

9 STATISTICS

Study CIN-107-130 is a multicenter, single arm, OLE study. The primary objective of this study is to assess the long-term safety and tolerability of CIN-107 in patients with HTN who have completed the parent Study CIN-107-124.

The baseline values for safety and tolerability endpoints and effectiveness endpoints are defined as the values at Visit 1 prior to starting the first dose in Study CIN-107-130.

No formal hypothesis testing is planned. Additional details of analyses to be performed will be specified in the Statistical Analysis Plan.

9.1 Analysis Populations

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

9.2 Statistical Methods

9.2.1 Analysis of Safety

All safety and tolerability endpoints will be summarized descriptively. The Safety Population will be the primary population used for analyses.

9.2.2 Analysis of Effectiveness

9.2.2.1 Analysis of effectiveness endpoints

The effectiveness endpoints are secondary endpoints of this study. The change from baseline over time will be analyzed. The analyses will be performed descriptively based on data in the Safety Population.

9.2.2.2 Other effectiveness analyses

Additional analyses may be conducted with data collected in the parent Study CIN-107-124 to assess safety, tolerability, and effectiveness of CIN-107 from the first exposure.

9.2.3 Interim Analysis

No interim analysis is planned.

9.2.4 Sample Size Determination

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

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

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

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 user name 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

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) 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 clinical 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 clinical 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 for the last patient in the study.

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 patients. 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/Independent Ethics Committee

The Institutional Review Board (IRB) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at clinical sites where IRB approval has been obtained. The Protocol, Investigator's Brochure, informed consent form (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 clinical 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 CRA'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 is entered by the clinical site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the CRA and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the clinical 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

AstraZeneca AB
Västra Mälarehamnen, SE-151 85
Södertälje, Sweden
[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]

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 Drive
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

Table 1. Schedule of Procedures – Open-Label Extension

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

a. All clinical site visits should occur between 6:00 a.m. and 11:00 a.m. Unscheduled visits may be scheduled at any time during the study period based on the Investigator's discretion.
b. The EOT assessments at the end of Part 1 or Part 2 of Study CIN-107-124 will serve as the Day 1 pre-dose assessments for those enrolling in Study CIN-107-130.
c. Written informed consent must be obtained before any Protocol-specific procedures are performed.
d. Procedure to be completed pre-dose on Day 1 of Study CIN-107-130.
e. Height will be collected at enrollment (Visit 1) only and will be used to calculate BMI at subsequent visits. See Section 8.12 for details on body measurements.
f. The patient should be seated for at least 5 minutes in the examination room before measurement of vital signs and BP. Vital signs and BP will be measured pre-dose using the standardized procedures listed in Section 8.9.
g. Once the seated BP has been determined, the patient will be asked to stand, and after 60 seconds, a single standing BP and heart rate (orthostatic vital signs) measurement will be obtained.
h. A complete physical examination will consist of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system.
i. A limited physical examination will consist of a minimum of general appearance, skin, heart, lungs, and abdomen.
j. Perform 12-lead ECG after the patient has been resting in the supine position for at least 10 minutes and after measuring vital signs and BP.
k. For female patients of childbearing potential (ie, ovulating, pre-menopausal, and not surgically sterile), perform serum pregnancy tests at enrollment (Visit 1) and EOT (Visit 7)/ET.
l. Pre-dose blood samples for PD analysis will be collected at specified visits. See Section 7.2.1 for details of blood sample collection for PD analysis.
m. Pre-dose blood samples for PK analysis will be collected within approximately 15 minutes prior to dosing. See Section 7.3 for details of blood sample collection for PK analysis.
n. Study drug dispensation may occur at any time starting at enrollment (Visit 1) and before EOT (Visit 7). A Study Reference Manual with details of study drug dispensation and collection of unused study drug will be provided to clinical sites.
o. On clinical site visit days, patients will self-administer the morning dose of any other concomitant medications (if applicable) at home. CIN-107 should be withheld as it will be self-administered at the clinical site and witnessed by site staff, after completion of pre-dose evaluations and laboratory sampling. Between clinical site visits, patients will continue to self-administer CIN-107 QD by mouth at approximately the same time each morning.
p. Site staff will calculate treatment adherence based on pill counts.
q. Site staff will counsel patients about the importance of adhering to the following: study drug, background antihypertensive regimen (if applicable).
r. Instruct patients to take their scheduled morning doses of the antihypertensive medication(s) at home and to hold their dose of CIN-107 on the morning of their next visit. Instruct patients to bring their antihypertensive medication(s) and study drug to all clinical site visits for pill counts. Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical site visit.
s. Clinical sites will provide patients with a 24-hour urine collection kit at Visit 6. Patients will be instructed to start the collection up to 3 days prior to Visit 7, refrigerate the collected sample, and bring the entire sample to the clinical site at Visit 7. A 24-hour urine collection will commence after the first morning void on the first day and will include the first morning void on the second day for a total duration of 24 (±2) hours. Patients must be instructed to keep the sample refrigerated at all times except during their transit to the clinical site.
t. A 24-hour urine collection may be repeated if the Investigator suspects that the sampling is insufficient and the patient is within the visit window. Clinical sites will aliquot urine into a transfer tube and send it to the Central Laboratory.

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

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

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

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

Endocrinology

β-human chorionic gonadotropin [1]

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

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count

White blood cell count and differential [1]

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

Urinalysis

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

Urobilinogen

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

Coagulation

Activated partial thromboplastin time	International normalized ratio
Prothrombin time	

Pharmacodynamic Analytes

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

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

Pharmacokinetic Analytes

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

Twenty-Four-Hour Urine Collection Analytes

Albumin	Aldosterone
Creatinine	Potassium
Protein	Renin
Sodium	

APPENDIX C: ELECTROCARDIOGRAM ALERT CRITERIA GUIDANCE

Investigators should contact the Sponsor or designee if any clinically meaningful changes from baseline (Visit 1) electrocardiograms, including but not limited to those listed below, are noted upon review:

- Heart rate-corrected QT interval using Fridericia's formula (QTcF) ≥450 msec (male);
- QTcF ≥470 msec (female);
- A >60 msec increase in QTcF from baseline;
- A ≥6% increase in QTcF from baseline; or
- 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 beats per minute [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 2.

Table 2. 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, and CYP2C9.
5. Strong inducer of CYP3A and moderate inducer of CYP1A2, and 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.

APPENDIX E: RESCUE MEDICATION GUIDANCE

The following guidelines should be utilized for selection of rescue medication:

- If a hypertensive emergency appears imminent, refer the patient to seek urgent care in a clinic or hospital.
- Rescue medication use is permitted and recommended if the following blood pressure (BP) measurements are recorded in office:
  - Systolic BP (SBP) shows an acute and sustained increase of 30 mmHg (or greater) from baseline (Visit 1) measurement; and/or
  - SBP is ≥170 mmHg; and/or
  - Diastolic blood pressure is ≥105 mmHg.
- BP must be determined prior to initiation of any rescue medication. Additional study procedures for safety, tolerability, and effectiveness endpoints assessments will be performed as outlined in Appendix A.
- Investigators should use their best clinical judgment when determining the need for rescue medications.
  - The following classes of antihypertensive agents may be used during the study:
    - Vasodilators;
    - Calcium channel blockers;
    - Angiotensin-converting enzyme inhibitors;
    - Angiotensin II receptor blockers;
    - Beta blockers;
    - Diuretics (Note: Use of potassium-sparing diuretics and mineralocorticoid receptor antagonists are not allowed); and
    - Alpha blockers.
  - The following class of antihypertensive agents should not be used during the study:
    - Potassium-sparing diuretics; and
    - Mineralocorticoid receptor antagonists.
- Investigators are encouraged to discuss selection of rescue medications with the study Medical Monitors.
- Rescue medications may be continued until end of the study or discontinued at the Investigator's discretion.
- Down-titration of antihypertensive medication(s) is allowed as detailed in Appendix F.

APPENDIX F: DOWN-TITRATION OF ANTIHYPERTENSIVE MEDICATION(S)

Down-titration of antihypertensive medication(s) is recommended for management of persistent or symptomatic hypotension in study patients. The following recommendations are provided as guidance to the Investigator:

- The guiding principle for medical decision making with regard to blood pressure (BP) management in this study is to try to maintain patients on the highest dose of CIN-107 that is safe and medically reasonable. Study drug should be continued unless the Investigator feels it is necessary to stop for the safety of the patient.
- To manage persistent or symptomatic hypotension in a step-wise fashion, the following are recommended to Investigators:
  - First, any rescue medication (see Appendix E) that may have been started should be reduced or discontinued;
  - Then, the use of the single background antihypertensive (non-CIN-107) agent should be reduced or discontinued, if medically sound;
  - If the symptoms continue, the dose strength of CIN-107 may be down-titrated from 2 mg to 1 mg;
  - If the systolic BP (SBP) remains ≤100 mmHg on 3 consecutive days or if symptoms persist, the CIN-107 dose may be further down titrated to 0.5 mg;
  - CIN-107 may be temporarily discontinued if the SBP remains <90 mmHg for 3 consecutive days or if symptoms persist; and
  - Study drug dosing may be resumed or up-titrated after reassessments.