CLINICAL STUDY PROTOCOL

A Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, and Effectiveness of CIN-107 for the Management of Blood Pressure in Patients with Primary Aldosteronism

Investigational Product.: CIN-107 (generic name: baxdrostat)
Protocol D Code: D6970C00001
Protocol Number: SPARK-PA CIN-107-122
Date: 31 March 2023
Version No.: 7.0

Sponsor: AstraZeneca AB

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CONFIDENTIALITY STATEMENT

SIGNATURE PAGE

Study Title	A Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, and Effectiveness of CIN-107 for the Management of Blood Pressure in Patients with Primary Aldosteronism
Study D Code	D6970C00001
Study Name	SPARK-PA CIN-107-122
Original Protocol	12 August 2020
Version 2.0	09 October 2020
Version 3.0	03 March 2021
Version 4.0	09 July 2021
Version 5.0	02 April 2022
Version 6.0	15 September 2022
Version 7.0	31 March 2023

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

Signature [redacted] Date

[redacted]

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, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

Protocol Title:
A Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, and Effectiveness of CIN-107 for the Management of Blood Pressure in Patients with Primary Aldosteronism

Protocol Number: D6970C00001

Protocol Name: SPARK-PA CIN-107-122

Name of Investigational Product:
CIN-107 (2, 4, and 8 mg)

Estimated Number of Study Centers:
Multiple clinical sites in the United States

Trial Duration (months):	**Phase of Development:**
Up to 5 months for Part 1 only. Up to 19 months Part 1 plus Part 2/extension	Phase 2

Rationale:
Primary aldosteronism (PA) is characterized by autonomous secretion of aldosterone from the zona glomerulosa of the adrenal cortex. Aldosterone synthetase inhibitors, by inhibiting aldosterone synthesis, provide a direct mechanism to address the primary pathogenesis of the disease. Reducing aldosterone levels has the potential to reduce blood pressure (BP), either alone or in combination with other antihypertensive agents, improve potassium levels, and reduce the risk of end organ damage. CIN-107 is a highly potent, selective, and competitive inhibitor of aldosterone synthase. Based on findings from nonclinical studies and single-ascending and multiple-ascending dose clinical studies, CIN-107 may be a novel treatment for the deleterious effects of inappropriately elevated aldosterone levels resulting in elevated BP in patients with PA. CIN-107 has the potential to offer a new therapeutic option aimed at decreasing aldosterone concentrations in plasma and tissues, thus reducing both the mineralocorticoid receptor-dependent and mineralocorticoid receptor-independent effects of aldosterone.

Objectives:

Primary Objectives:
The primary objectives of Study D6970C00001 are to evaluate:

- The safety and tolerability of CIN-107 in patients with PA at doses from 2 to 8 mg per day for 12 weeks
- The reduction in systolic blood pressure (SBP) with CIN-107 in patients with PA after 12 weeks of treatment

Secondary Objectives:
The secondary objectives of Study D6970C00001 are to evaluate:

- The reduction in diastolic blood pressure (DBP) as a function of dose in patients with PA after 12 weeks of treatment
- The change in serum potassium and requirement for potassium supplementation as a function of CIN-107 dose
- The change in serum sodium and requirement for fluid or mineral replacement as a function of CIN-107 dose

Exploratory Objectives:

Exploratory objectives are to evaluate:

- The correlation of serum aldosterone and plasma aldosterone-to-renin ratio (ARR) changes to drug dosage of CIN-107
- Relationship between BP reduction and changes in aldosterone and renin levels with CIN-107 dosages
- The changes in concentration in pharmacodynamic (PD) markers, including but not limited to:
  - plasma aldosterone and its relevant precursors (18-OH corticosterone, corticosterone, and 11-deoxycorticosterone)
  - plasma cortisol (free and total) and its relevant precursor
  - NT-pro (B-type natriuretic peptide) (NT-proBNP)
  - plasma renin concentration and activity
  - 24-hour urine analytes sodium, potassium, creatinine, albumin, protein, and aldosterone

Pharmacokinetic and Pharmacodynamic Objectives

The PK-PD objectives are to evaluate:

- The exposure-response relationships of CIN-107 in patients with PA using measures of safety, effectiveness, and/or PD
- The relationship between plasma renin, aldosterone, and ARR to the SBP response to CIN-107

Extension Part (Part 2) Additional Objectives

To assess:

- The safety and tolerability of CIN-107 in patients with PA at doses from 2 to 8 mg per day for patients who elect to participate in the extension study for up to 74 weeks
- The management of blood pressure control for patients who elect to participate in the extension study for up to 74 weeks
- The CIN-107 long term treatment effects on PD markers

Endpoints:

Primary Endpoints:

The primary endpoints include the following:

- Safety parameters measured by adverse events (AEs), electrocardiograms (ECGs), hematology and chemistry laboratory values, vital signs, and physical examination
- Effectiveness measured by change in mean seated SBP after 12 weeks of treatment in patients with PA

Secondary Endpoints:

The secondary efficacy endpoints include the following:

- Effectiveness measured by change in mean seated DBP after 12 weeks of treatment in patients with PA
- The percentage of patients who achieve a seated BP response < 140/90 mmHg with CIN-107 after treatment at each dose
- The percentage of patients who achieve a seated BP response < 130/80 mmHg with CIN-107 after treatment at each dose
- The percentage of patients who, after 12 weeks of treatment with CIN-107 for PA, achieve either:

- a plasma aldosterone concentration (PAC) < 15 ng/dL and a plasma renin activity (PRA) ≥ 0.5 ng/mL/h; or
- an ARR < 15; or
- unsuppressed renin activity PRA ≥ 1.0 ng/mL/h

Exploratory Endpoints:

The exploratory endpoints include the following:

- Changes in the concentrations from baseline to end of treatment (EOT) in PD markers, including but not limited to, PAC, 11-deoxycorticosterone, PRA, direct renin concentration, calculated ARR, and 24-hour urinary aldosterone, NT-proBNP, sodium, and potassium with CIN-107 treatment
- Relationship between BP reduction and changes in aldosterone and renin levels and ARR with CIN-107, and as a function of CIN-107 dose

Extension Part (Part 2) Additional Endpoints

- Safety parameters measured by adverse events (AEs), electrocardiograms (ECGs), hematology and chemistry laboratory values, vital signs, and physical examination for patients who elect to participate in the extension study for up to 74 weeks

Inclusion Criteria

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

1. Are male or female patients ≥ 18 years of age
2. Have been diagnosed with PA. The diagnosis may be based on meeting all three of the criteria of 1) elevated aldosterone level > 20 ng/dL (555 pmol/L), 2) plasma renin concentration (PRC) < lower limit of renin assay or plasma renin activity (PRA) < 1 ng/mL/min, and 3) hypokalemia (no confirmatory testing is needed in these cases). Otherwise, the diagnosis of PA must include BOTH:
    - Historical evidence of plasma aldosterone to renin activity ratio (ARR) of > 15 if the PRA was measured in ng/mL/hr or aldosterone to direct renin ratio (ADRR) > 50 if aldosterone was measured in pmol/L and direct renin concentration in mU/L (see protocol section 3.1.2 for conversion factors if needed to calculate ARR or ADRR), AND
    - Historical or newly conducted confirmatory testing by one of the following methods: the fludrocortisone-suppression test, the oral saline load test, the intravenous saline load test, or the captopril challenge test
3. Are taking mineralocorticoid receptor antagonist (MRA) to control BP; or are newly diagnosed with PA and have not started MRA treatment
   Note: the MRAs can be taken with or without other antihypertensive agents including beta blockers, clonidine, methyldopa, minoxidil, angiotensin-converting enzyme inhibitors, diuretics, angiotensin receptor blockers, and/or dihydropyridine calcium channel blockers
4. Are willing and able to cease dosing of MRA for up to 4 weeks in patients taking MRA
5. Are willing to be compliant with the contraception and reproduction restrictions of the study as follows:
    a. Male patients must agree to abstain from sperm donation from Day 1 through 90 days after the final dose of study drug
    b. Postmenopausal women must not have had menstrual bleeding for at least 1 year before initial dosing and either be > 60 years or have an elevated follicle stimulating hormone level of > 40 mIU/mL at Screening

c. Female patients of childbearing potential (i.e., ovulating, pre-menopausal, and not surgically sterile) must have a documented negative pregnancy test at Screening
d. Female patients of childbearing potential must use a highly effective method of contraception (i.e., <1% failure rate) from Day 1 through 30 days after the last administration of study drug. Acceptable methods of contraception include:
    i. Surgical sterilization (tubal ligation)
    ii. Intra-uterine device for at least 12 weeks prior to Screening Visit
    iii. Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before the Screening Visit or
    iv. Diaphragm used in combination with spermicide

6. Are willing and able to give informed consent for participation in the study
7. Have increased SBP by ≥ 20 mmHg or have SBP ≥ 160 mmHg after dosing of MRA treatment is ceased for up to 4 weeks duration, or have SBP ≥ 150 mmHg for patients who are newly diagnosed with PA and have not taken an MRA in the past 12 weeks

Exclusion Criteria

Patients who meet any of the following criteria at Screening (Visit 1) will be excluded from participation in the study:

1. During the Screening, have a single occurrence of mean seated SBP > 180 mmHg or DBP > 110 mmHg if not taking an MRA; or have a mean seated SBP ≥ 160 mmHg or DBP ≥ 100 mmHg if currently taking an MRA
   Note: Mean seated BP is defined as the average of 3 measurements obtained at any 1 clinical site visit. If the patient missed regularly scheduled antihypertensive medication(s) prior to the visit, and in the opinion of the Investigator has been otherwise adherent to their antihypertensive regiment, 1 BP re-test is allowed ≥ 2 hours after taking medication(s)
2. Have a body mass index > 45 kg/m^2 at the Screening Visit
3. Have an upper arm circumference < 7 or > 17 inches at the Screening Visit
4. Have had a previous surgical intervention for an adrenal adenoma or have a planned adrenal carcinoma, adrenalectomy, renal nerve denervation, or adrenal ablative procedure during the course of the study
   Note: Patients who have had a procedure > 6 months prior to Screening but still have elevated PAC (> 15 ng/dL) and meet BP and other eligibly criteria may be considered
5. Have a documented estimated glomerular filtration rate < 45 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology equation at the Screening Visit
6. Have a planned dialysis or kidney transplantation during the course of the study
7. Have known documented New York Heart Association class III or IV chronic heart failure
8. Have had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure within 6 months before the Screening Visit
9. Have known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease, diagnosed from a prior echocardiogram
10. Have a planned coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) or any major surgical procedure during the study
11. Have had PCI, CABG, other major cardiac surgery (e.g., valve replacement), or peripheral arterial bypass surgery within 6 months before the Screening Visit
12. Have chronic, permanent atrial fibrillation
13. Have a history of, or currently experiencing, clinically significant arrhythmias as judged by the Investigator, including ventricular tachycardia, ventricular fibrillation, Torsades de pointes, and supraventricular arrhythmias. Patients with minor forms of ectopy (e.g., premature atrial contractions) are not excluded per Investigator discretion
14. Have had a prior solid organ transplant or cell transplant

15. Are expected to receive or are receiving any of the exclusionary drugs such as strong inducers of cytochrome P450 3A, drugs known to prolong QT, and/or chronic use of NSAIDs or steroids within 28 days or 5 half-lives, whichever is longer prior to the first dose of study drug until the end of treatment
    Note: patients who are using medication(s) noted above at Screening who are willing to come off during the course of the study are allowed to participate
16. Have a known hypersensitivity to CIN-107 or excipients in CIN-107
17. Are positive for HIV antibody, hepatitis C virus RNA, or hepatitis B surface antigen
18. Have typical consumption of > 14 alcoholic drinks weekly
    Note: One drink of alcohol is equivalent to ½ pint of beer (285 mL), 1 glass of spirits (25 mL), or 1 glass of wine (125 mL)
19. Have participated in another clinical study involving any investigational drug within 30 days prior to the Screening Visit, or plans to participate in another clinical study within 30 days of discontinuation of study drug
20. Have received experimental therapy with a small molecule within 30 days of the Screening Visit or 5 half-lives, whichever is longer, or received experimental therapy with a large molecule within 90 days of the Screening Visit or 5 half-lives, whichever is longer
21. Have been on night shifts at any time during the 4 weeks before the Screening Visit and/or plans to begin night shift at any time during Screening
22. Is pregnant, breastfeeding, or planning to become pregnant during the study
23. Is considered by the Investigator, after reviewing medical and psychiatric history, physical examination, and laboratory evaluations, 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

At Visit 2 prior to enrollment:

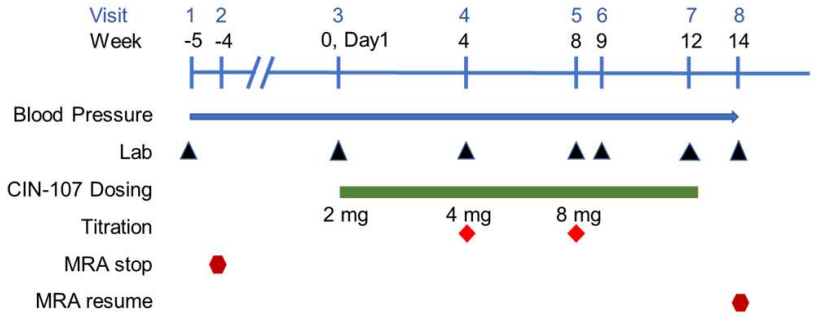
24. Mean seated SBP > 180 mmHg or DBP > 110 mmHg or has 2 consecutive occurrences of mean seated SBP ≥ 160 mmHg or DBP ≥ 100 mmHg. Note that for patients whose BP exceeds these values after stopping their MRA, they may receive rescue antihypertensive medications (which are not MRAs) to control their blood pressure and have their BP reassessed for eligibility.
25. Have evidence of any of the following at Screening:
    a. White blood cell count > 15×10^9/L or absolute neutrophil count < 1×10^9/L
    b. Serum potassium < 2.5 mEq/L. Note: Patients with a serum potassium level below normal range may continue in the study if the Investigator elects to correct the serum potassium level with supplementation and offers to manage the condition
    c. Serum potassium >5.0 mEq/L
    d. Hemoglobin < 10.0 g/dL or anticipated initiation of erythropoietin-stimulating agents or planned transfusion within 2 months after the Screening Visit
    e. Serum aspartate aminotransferase or alanine aminotransferase >3 × upper limit of normal (ULN) or
    f. Total bilirubin >2 × ULN, unless due to Gilbert's syndrome
    g. Uncontrolled diabetes with glycosylated hemoglobin > 9.5% at the Screening Visit

Overall Study Design:

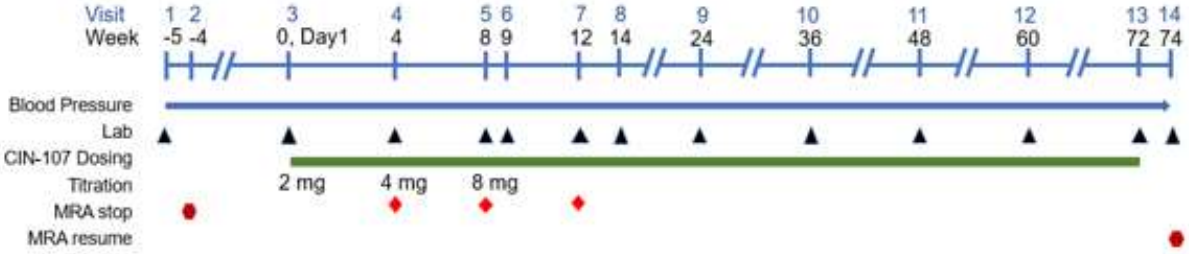
This is a multicenter, open-label study in adult patients with PA to evaluate the effectiveness and safety of CIN-107 after up to 12 weeks of treatment (Part 1), and then for eligible, consenting patients follow patients in Part 2 for up to 74 weeks for evidence of long-term safety and tolerability. Twelve to 18 patients with a confirmed diagnosis of PA will be enrolled at clinical sites in the United States. Patients will complete 14 visits over a period of approximately 74 weeks. Additional unscheduled visits may occur as per the Investigator's discretion to manage BP and electrolyte balance during the study.

Schedule of Visits for Study D6970C00001

Top Panel-Part 1 Only



Bottom Panel-Part 1 + Part 2 (Extension)



Number of participants:

Twelve to 18 patients with a confirmed diagnosis of PA, who consent to participate in the study and meet the eligibility criteria, will be enrolled.

CIN-107 Dosage and Administration:

At Visit 3, after eligibility is confirmed, pre-dose vital signs recorded, and safety and PD samples drawn, patients will be provided with an initial dose of CIN-107 and start once daily (QD) dosing of CIN-107 tablets at 2 mg. At Visit 4, CIN-107 dose may be up-titrated to 4 mg QD if the patient has tolerated dosing of CIN-107 at 2 mg and the BP records indicate minimal hypotension risk. The Investigator will contact the patient by phone approximately 7 days after the dose is up titrated and the laboratory results are available. CIN-107 dose may be down-titrated to 2 mg if the safety laboratory results indicate hyperkalemia or hyponatremia, or other abnormal safety laboratory findings suggest that the patient is not tolerating CIN-107 4 mg dosing. At Visit 5, CIN-107 dose may be up-titrated to 8 mg QD if the patient has tolerated dosing of CIN-107 at 4 mg. CIN-107 dose may be down-titrated to the 2 mg initial dose or continued with 4 mg. The final CIN-107 dose level will be determined by the investigator based on the BP and safety laboratory values. Patients will be instructed to take 1, 2, or 4 tablets, per day for dosing at 2, 4, or 8 mg, respectively, by mouth QD with or without food. After Visit 7, for patients eligible and willing to proceed to the extension (Part 2), the patient will continue their dose level subject to titration based on the investigators discretion until Visit 13, when dosing in the extension part of the study stops.

Study Drug:

CIN-107 tablets with 2 mg strength will be provided as white tablets in bottles of 32 tablets per bottle. 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 to 30°C are allowed during storage. During transport, excursions up to 40°C permissible up to 1 week.

Safety:

The safety of CIN-107 will be assessed from the time of informed consent until Visit 14 (Week 74). All safety endpoints will be summarized descriptively. The safety endpoints will include the following:

- Change from baseline in potassium levels and/or potassium supplementation requirements, with CIN-107 after 12 weeks of treatment in patients with PA
- Vital signs (heart rate, respiratory rate, body temperature), mean SBP, mean DBP, orthostatic vitals (standing BP and heart rate), physical examinations, electrocardiography, weight measurement, and clinical laboratory evaluations including standard safety chemistry panel, hematology, coagulation, and urinalysis
- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious adverse events (SAEs)
- TEAEs leading to premature discontinuation of the study drug
- Treatment-emergent marked laboratory abnormalities
- Change in standing SBP and DBP (measured at the clinical site prior to administration of study drug)
- Safety will be reassessed by review of the above endpoints at the end of 74 weeks of treatment for patients who elect to participate in the extension part of the study (Part 2)

Statistical Analyses

General

The following analysis populations are defined for the different types of data analyses, and additional analysis population(s) may be added in the Statistical Analysis Plan (SAP).

- Intent-to Treat Population (ITT): All patients enrolled in the study
- Per-Protocol Population: All patients in the ITT population who have a baseline value for the SBP assessment, have at least one post-dose value for the SBP assessment, and have no major protocol deviations that could potentially impact the primary efficacy endpoint
- Safety Population: All patients who receive at least 1 dose of study drug will be used for safety analysis
- PK Population: All patients in the ITT Population who have at least 1 quantifiable plasma concentration
- PD population: All patients in the ITT Population who have at least 1 quantifiable concentration of a PD variable

Safety Analyses

The Safety Population will be the primary population for the safety analysis. All safety endpoints will be summarized descriptively. The assessment of safety will be based primarily on the frequency of AEs, clinical laboratory assessments, vital signs, and 12-lead ECGs. Other safety data will be summarized as appropriate. Summary statistics at baseline, at each visit, and of changes from baseline to each visit for laboratory parameters, vital signs, and other safety measurements will be provided. The occurrence of significant abnormalities in change from baseline of laboratory values will be summarized. Physical examination data will be listed.

Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. TEAEs, defined as AEs that newly occur or worsen in severity during the treatment period, will be summarized by system organ class and preferred term. A list of patients with SAEs and those who discontinue from study treatment due to an AE will be provided.

Pharmacokinetic Analysis

Individual plasma concentration data for CIN-107 and any measured metabolite(s) will be listed and summarized by visit, timepoint, and CIN-107 dose level in the PK population.

Pharmacodynamic Analysis

All PD variables will be summarized descriptively in the PD population.

Pharmacokinetic/Pharmacodynamic Analysis

An attempt will be made to correlate plasma concentration data with measures of safety, PD, and/or efficacy.

Interim Analysis

No formal interim analysis is planned. A Data Review Committee (DRC) will be formed in order to conduct data reviews to assess safety and tolerability. Details related to the DRC responsibilities, authorities, and procedures will be documented in the DRC Charter.

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ACTH	adrenocorticotropic hormone
AE	adverse event
AESI	adverse event of special interest
ARR	aldosterone-to-renin ratio
ASI	aldosterone synthase inhibitor
AUC	area under the concentration time curve
$AUC_{0\text{-inf}}$	area under the concentration-time curve from time zero to infinity
$AUC_{0\text{-last}}$	area under the concentration-time curve from time zero to last measurable concentration
BP	blood pressure
CABG	coronary artery bypass graft
CFR	Code of Federal Regulations
CL_R	renal clearance
C_{max}	maximum plasma concentration
CRA	Clinical Research Associate
CYP	cytochrome P450
DBP	diastolic blood pressure
DRC	Data Review Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EIU	exposure in utero
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-Treat
MAD	multiple-ascending dose
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MR	mineralocorticoid receptor
MRA	mineralocorticoid receptor antagonist
NSAID	nonsteroidal anti-inflammatory drug
PA	primary aldosteronism
PAC	plasma aldosterone concentration
PCI	percutaneous coronary intervention
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRA	plasma renin activity

Abbreviation or Specialist Term	Explanation
QD	once daily
QTc	heart rate-corrected QT interval
QTcF	heart rate-corrected QT interval using Fridericia's formula
RAAS	renin-angiotensin-aldosterone system
SAD	single-ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USP	United States Pharmacopeia

1 INTRODUCTION

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 (RAAS) 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 via its direct interaction with the MR (genomic effect) in addition to mechanisms independent of that direct interaction (non-genomic or non-receptor mediated effects) (Duprez 2007, Funder 2009, Sato 2004).

The association between plasma aldosterone and long-term survival has been demonstrated in patients with congestive heart failure or acute myocardial infarction (Swedberg 1990, Latini 2004, Güder 2007, Beygui 2006), and in patients with coronary artery disease (Ivanes 2012). Furthermore, the Framingham Offspring Study suggests that plasma aldosterone concentration (PAC) in normotensive patients predicts subsequent increases in blood pressure (BP) and the development of hypertension (Vasan 2004). Therefore, directly inhibiting the synthesis of aldosterone represents a promising target for the reduction of BP and a mitigation of the genomic and non-genomic effects on end organ damage (Marney 2007).

Primary aldosteronism (PA) represents a group of disorders characterized by inappropriate production of aldosterone. The secretion of aldosterone is independent of the normal feedback influences of renin, angiotensin II, and sodium. It is the most common cause of secondary hypertension, with an estimated prevalence > 5% in patients with hypertension and up to 15% to 20% in patients with treatment-resistant hypertension (Fogari 2007, Calhoun 2002). PA is caused by unilateral or bilateral adrenal hyperplasia, an adrenal adenoma, and, in rare cases, an adrenal carcinoma. There is also a rare condition of inherited familial hyperaldosteronism (Funder 2016). Excess aldosterone in patients with PA promotes increased distal renal tubular resorption of sodium and water by the kidneys and also contributes to end organ damage. This can lead to the development of hypertension in association with suppression of plasma renin; increased potassium excretion can lead to hypokalemia (Wrenn 2020, Hundemer 2017).

Patients with PA demonstrate increased cardiovascular morbidity and mortality compared to age- and sex-matched patients with essential hypertension with the same degree of BP elevation (Milliez 2005, Stowasser 2005, Monticone 2018). In patients with PA, the spectrum of end organ adverse effects associated with autonomous secretion of elevated levels of aldosterone include endothelial dysfunction, vascular remodeling, enhanced sympathetic outflow, and impaired baroreflex function. These patients also exhibit increased left ventricular dimensions, myocardial fibrosis, increased carotid intima-media thickness, and femoral pulse wave velocity. These effects increase the risk of cardiovascular events including coronary artery disease, myocardial infarction, heart failure, stroke, and atrial fibrillation (Milliez 2005, Stowasser 2005, Catena 2008, Born-Frontsberg 2009).

Despite the consequences of excess aldosterone and the relative common prevalence of PA, its screening is often overlooked. As many general practitioners consider PA to be relatively rare, screening rates as low as 1% to 2% among hypertensive patients have been reported and may only be considered when a patient is hypokalemic and hypertensive (Rossi 2019, Mulatero 2016). The Primary Aldosteronism Prevalence in Hypertension study reported a rate of confirmed PA of 11.2% in 1125 consecutive newly diagnosed hypertensive patients (Rossi 2006). However, in this study, over half of patients with an aldosterone-producing adenoma, and 82% with bilateral hyperplasia, were normokalemic. A retrospective evaluation from clinical centers across 5 continents demonstrated that only 9% to 37% of patients with PA present with hypokalemia (Funder 2016, Mulatero 2004). Furthermore, many clinicians believe that PA patients can be adequately managed in the same manner as patients with primary hypertension.

The goals of treatment in patients with PA involve both the normalization of BP and the neutralization of effects of pathologic aldosterone-mineralocorticoid interactions. By addressing these elements, the risk of long-term cardiovascular and renal damage is reduced.

Mineralocorticoid receptor antagonists (MRAs) are the recommended medical treatment of choice in patients with PA due to bilateral adrenal hyperplasia or those with unilateral hyperplasia/adenoma who are unable or unwilling to undergo laparoscopic adrenalectomy (Funder 2016). MRAs exert their action by competitively inhibiting the binding of aldosterone to MRs (Monticone 2018).

Besides the activity of MRAs on the MR, these drugs also act as antagonists at the androgen receptor and agonists at the progesterone receptor. Consequently, men treated with MRAs may experience gynecomastia and erectile dysfunction, while women may present with menstrual irregularities (Manolis 2019). MRAs can also lead to a compensatory increase in aldosterone secretion, which enhances the non-MR-mediated effects of aldosterone, and affects tissues not entirely protected by MRAs such as the brain (Bomback 2007). Spironolactone (Aldactone®) is the only Food and Drug Administration (FDA)-approved MRA for the treatment of PA (Aldactone 2014 package insert). Eplerenone (Inspra®) is used off-label as the MRA of choice for men at some PA centers. Although eplerenone is more selective than spironolactone with fewer adverse effects, its BP-lowering effect is typically less than that of spironolactone.

By inhibiting the synthesis of aldosterone in patients with PA, CIN-107 provides an opportunity to treat the elevated BP as well as reduce the risks of aldosterone-mediated end organ effects.

One of the challenges that has affected the development of aldosterone synthase inhibitors (ASIs) has been the difficulty in selectively inhibiting aldosterone synthase without also reducing the synthesis of cortisol. The synthesis pathway of cortisol is catalyzed by 11β-hydroxylase (cytochrome P450 [CYP]11B1), an enzyme that shares very high sequence similarity with aldosterone synthase (CYP11B2). Undesired inhibition of 11β-hydroxylase leads to suppression of cortisol levels and compromises stress and immunologic responses, adversely influencing some metabolic functions and possibly increasing mortality rates (Weldon 2019, Oelkers 1996, Wagner

1984a, Wagner 1984b). LCI699, an ASI, was evaluated in clinical trials by Novartis but was discontinued in both antihypertensive and PA indications due to lack of specificity for aldosterone synthase (Amar 2010). It has recently been approved for the treatment of Cushing's Disease.

Baxdrostat (formerly CIN-107 or RO6836191) is a highly potent, selective, and competitive inhibitor of human aldosterone synthase (encoded by the cytochrome P450 [CYP]11B2 gene). Baxdrostat 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 nonclinical in vivo studies (primarily conducted in primates), CIN-107 lowered aldosterone levels significantly without affecting basal- or adrenocorticotropic hormone (ACTH)-induced cortisol levels over a wide dose range. The ability of CIN-107 to lower aldosterone without affecting cortisol was confirmed following administration of single oral doses in healthy subjects (Study WP28586) conducted by Roche (Clinical Trial NCT01995383) and in the multiple-ascending dose (MAD) study (Study CIN-107-111) conducted by CinCor.

This study is designed to evaluate the BP and aldosterone lowering effects of CIN-107 in patients with PA. Patients will need to wash out the MRA drug (such as spironolactone) and monitor BP daily for up to 4 weeks prior to administration of study drug. Other antihypertensive agents including beta blockers, thiazide diuretics, clonidine, methyldopa, minoxidil, chronic nonsteroidal anti-inflammatory drugs (NSAIDS), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and/or dihydropyridine calcium channel blockers may be continued. After establishing a rise in BP after MRA withdrawal, if applicable, and with other anti-hypertensives agents remaining stable, treatment with CIN-107 for 12 weeks will be initiated.

1.1 Overview of Preclinical Studies with CIN-107

CIN-107 is a highly selective, potent, and competitive ASI. Its inhibition of human aldosterone synthase is 100-fold more potent than that of the closely related 11β-hydrolase (encoded by the CYP11B1 gene) (CIN-107 IB Version 4).

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 ACTH, CIN-107 blocked aldosterone synthesis without interfering with cortisol levels (CIN-107 IB Version 4).

In rats and monkeys, hepatic metabolism was the primary clearance mechanism for CIN-107. Renal clearance did not appear to play a significant role in the disposition of CIN-107 (CIN-107 IB Version 4).

The adrenal gland was the primarily affected tissue in both rats and monkeys. CIN-107 was well tolerated in cynomolgus monkeys up to 7 mg/kg/day for up to 4 weeks but was not well tolerated at 40 mg/kg/day. A mechanistic 4-week cynomolgus monkey study demonstrated dose-related hypertrophy of 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 (CIN-107 IB Version 4).

CIN-107 was not well tolerated at 50 mg/kg/day in a pilot dose range-finding study on embryo-fetal development in Wistar rates. There was no evidence for a mutagenic, clastogenic, or aneugenic potential of CIN-107 (CIN-107 IB Version 4).

In vitro cardiovascular safety was assessed in a manual Good Laboratory Practice (GLP) 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). This indicated a very low probability of any QT liability (CIN-107 IB Version 4).

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 no observed adverse effect level was considered to be ≥ 50 mg/kg CIN107 for both studies (CIN-107 IB Version 4).

1.2 Overview of Clinical Studies with CIN-107

Five clinical pharmacology studies of CIN-107 have been conducted to date in healthy subjects: a single-ascending dose (SAD) study, a MAD study, a study to characterize the effect of food on the pharmacokinetics (PK) and to bridge the PK of the solution formulation of CIN-107 to the tablet formulation, a study to assess the effect of CIN-107 on PK of the multidrug and toxin extrusion (MATE) substrate metformin, and a PK study to evaluate the PK of CIN-107 in subjects with varying degrees of renal function.

Results of the SAD study which investigated the safety, tolerability, PK, and pharmacodynamics (PD) of CIN-107 in healthy male volunteers (Study WP28586 NCT01995383) 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 (CIN-107 IB Version).

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 (CIN-107 IB Version 4).

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 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 subjects 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 subjects under low-salt (2.5 and 5 mg) and normal-salt conditions (0.5, 1.5, and 2.5 mg). Specifically, there were no deaths, SAEs, or treatment-emergent adverse events (TEAEs) leading to withdrawal, and there were no clinically significant changes in electrocardiograms (ECGs), or vital signs. PK data from the MAD study indicate that exposure to CIN-107 (as assessed 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 subjects. As expected with a reduction in aldosterone levels, there were mild, dose-dependent increases in plasma potassium levels and reductions in plasma sodium levels.

Of note, the drug product used in the Phase 1 SAD and MAD studies was provided as an oral solution. As a replacement for the 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 (fed and fasted). Results of the relative bioavailability assessment indicate that exposure to CIN-107 and its primary metabolite following administration of the CIN-107 tablet formulation planned for use in future studies is equivalent to that observed following administration of the oral solution used in the SAD and MAD studies. Consumption of a high-fat, high-caloric 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 maximum plasma concentration occurred approximately 1 hour later (median of 4 hours) when CIN-107 was administered with the specified meal as compared to in a fasted state (median of 3 hours).

The metformin drug-drug interaction study demonstrated that systemic exposure to metformin is unchanged when administered with CIN-107. Specifically, the geometric mean ratio (associated 90% confidence interval [CI]) for C_{max} was 0.99 (0.91, 1.07) while the geometric mean ratios and

associated CI for AUC from time 0 to infinity ($AUC_{0\text{-}inf}$) and AUC from time 0 to the last measurable concentration ($AUC_{0\text{-}last}$) were 1.00 (0.94, 1.06) and 0.97 (0.91, 1.03), respectively. Consistent with the findings in plasma, CIN-107 did not affect renal clearance (CL_R) of metformin (CL_R = 27.99 L/h when metformin was administered alone and 26.48 L/h in the presence of CIN-107). Furthermore, the safety profile of metformin was similar in the presence and absence of CIN-107. Specifically, there were no deaths, SAEs, or TEAEs leading to withdrawal and there were no clinically significant changes in ECGs or vital signs.

Study CIN-107-113 investigated the PK of CIN-107 in individuals with varying degrees of renal impairment. The PK profiles of CIN-107 and its primary metabolite CIN107-M, following administration of a single 10 mg dose in individuals with renal impairment, were qualitatively and quantitatively similar to those measured in healthy subjects. Pairwise comparisons of plasma PK parameters for CIN107 in the moderate to severe renal impairment group confirmed the lack of noteworthy effect across groups with geometric mean ratios of 1.02, 1.21, and 1.17 for C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}last}$, respectively, as compared to the control group. Higher exposures to CIN-107 were not observed in the kidney failure group as compared to the control group with geometric mean ratios of 0.88, 0.68, and 0.68 for C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}last}$, respectively. The conclusions of these studies demonstrate that a single 10-mg dose of CIN-107 was well tolerated when administered to individuals with varying degrees of renal function, including those with moderate to severe renal impairment or kidney failure (on hemodialysis). There were no noteworthy increases in systemic exposure or decrease in clearance in individuals with impaired renal function. Dose adjustment of CIN-107 based on renal function was therefore not considered necessary.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of Study D6970C00001 are to evaluate:

- The safety and tolerability of CIN-107 in patients with PA at doses from 2 to 8 mg per day
- The reduction in systolic blood pressure (SBP) with CIN-107 in patients with PA after 12 weeks of treatment

2.2 Secondary Objectives

The secondary objectives of Study D6970C00001 are to evaluate:

- The reduction in diastolic blood pressure (DBP) as a function of dose in patients with PA after 12 weeks of treatment
- The change in serum potassium and requirement for potassium supplementation as a function of CIN-107 dose

2.3 Exploratory Objectives

Exploratory objectives are to evaluate:

- The correlation of serum aldosterone and plasma aldosterone-to-renin ratio (ARR) changes to drug dosage of CIN-107
- Relationship between BP reduction and changes in aldosterone and renin levels with CIN-107 dosages
- The changes in concentration in PD markers, including but not limited to:
    - plasma aldosterone and its relevant precursors (18-OH corticosterone, corticosterone, and 11-deoxycorticosterone)
    - plasma cortisol (free and total) and its relevant precursor
    - NT-pro (B-type natriuretic peptide)
    - plasma renin concentration and activity
    - 24-hour urine analytes sodium, potassium, creatinine, albumin, protein, and aldosterone

2.4 Pharmacokinetic-Pharmacodynamic Objectives

The PK-PD objectives are to evaluate:

- The exposure-response relationships of CIN-107 in patients with PA using measures of safety, effectiveness, and/or PD
- The relationship between plasma renin, aldosterone, and ARR to the SBP response to CIN-107

Extension Part (Part 2) Additional Objectives

To assess:

- The safety and tolerability of CIN-107 in patients with PA at doses from 2 to 8 mg per day for patients who elect to participate in the extension study for up to 74 weeks
- The management of blood pressure control for patients who elect to participate in the extension study for up to 74 weeks
- The CIN-107 long term treatment effects on PD markers

2.5 Benefit/Risk Assessment

2.5.1 Potential Risks

2.5.1.1 Cumulative Risk of Elevated Blood Pressure

Wash out of MRA drugs increases the cumulative risk of elevated BP for patients participating in the study. To minimize this risk, patients will monitor BP closely and can start taking CIN-107 if SBP is ≥ 160 mmHg or the SBP has increased by ≥ 20 mmHg from the measurement recorded at the Screening Visit, whichever occurs first.

2.5.1.2 Risk of Hyperkalemia and Hyponatremia

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

2.5.1.3 Risk of Adrenal Effects

While CIN-107 exhibits a highly selective CYP11B2 inhibition, CYP11B1 inhibition cannot be ruled out with repeat dosing and may result in reduction in cortisol levels, as seen with high doses in preclinical studies and in clinical studies of the non-selective CYP11B1/B2 inhibitor LCI699 (Calhoun 2011, Andersen 2001, Karns 2013). Preliminary data from the CIN-107-121 study indicate no clinically meaningful effect of baxdrostat on plasma cortisol.

2.5.1.4 Risk of Sex Hormone-Related Adverse Events

Known side effects of MRAs including gynecomastia, mastodynia, and abnormal vaginal bleeding were observed more frequently with spironolactone than with eplerenone. Occurrence of these events will be monitored in this study. A selective inhibitor of aldosterone synthase is not expected to interfere with sexual hormone pathways (NCT01995383) as the MRA effects are believed to work through their off-target inhibition of other steroid hormone receptors, which is not a property expected to be present in an aldosterone synthase inhibitor. Preliminary data from the CIN-107-121 study demonstrated no AEs such as those noted above that would indicate off target effects on sexual hormone pathways.

2.5.1.5 Risk of Allergic Reactions

Patients with known allergies to CIN-107 or its excipients should not receive CIN-107.

2.5.2 Potential Benefit

CIN-107, an ASI, is a new therapeutic option aimed at decreasing aldosterone concentrations in plasma and tissues, thus reducing both MR-dependent and MR-independent effects of aldosterone. Patients enrolled in this study could benefit from the BP-lowering effect of CIN-107. Patient participation in the study will enable the assessment of a new therapeutic agent for the treatment of PA, with the potential to affect the clinical course of a large segment of the PA population.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a multicenter, open-label clinical pharmacology study in adult patients with PA to evaluate the effectiveness and safety of CIN-107 after up to 12 weeks of treatment. Twelve to 18 patients with a confirmed diagnosis of PA will be enrolled at clinical sites in the United States. Patients will complete 8 visits over a period of approximately 19 weeks. Additional unscheduled visits may occur as per the Investigator's discretion to manage BP and electrolyte balance during the study.

The safety of CIN-107 will be assessed from the time of informed consent until the end of the Follow-Up Period. Patients will be followed for safety, effectiveness, and adherence throughout the study. PD variables analyzed during the study may include, but are not limited to, measures of aldosterone and its precursors, cortisol and its precursor, plasma renin activity (PRA), and calculation of ARR. PK variables analyzed during the study will include plasma concentrations of CIN-107 and any measured metabolite(s).

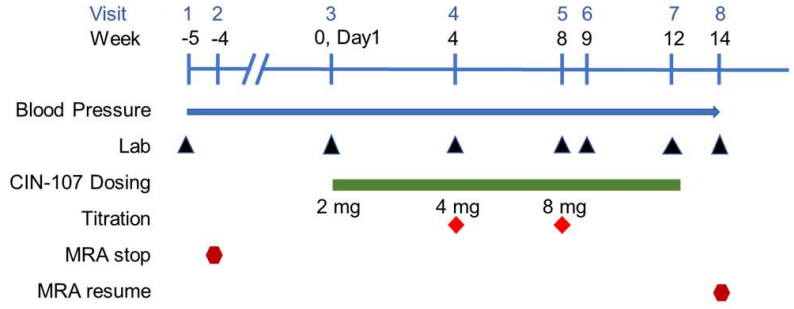
Patients will be instructed to bring their antihypertensive medications and/or study drug and the BP monitoring device to all clinical site visits. Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical site visit.

3.1.1 Study Visits

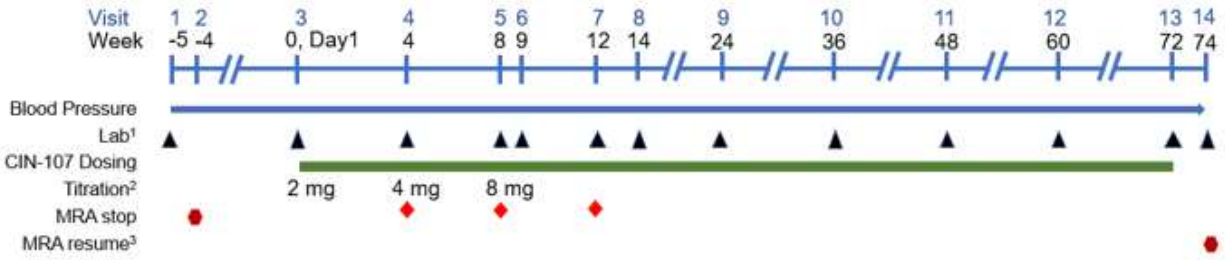
The study will consist of the following periods/visits detailed in Figure 1.

Figure 1 Schedule of Visits for Study D6970C00001

Top Panel (Part 1 only)



Bottom Panel Part 1 + Part 2 (Extension)



Abbreviations: MRA: mineralocorticoid receptor antagonist.
Specifics of the treatment extension (optional part 2):

1. Dose adjustment for baxdrostat allowed at week 12 and when clinically required during the treatment extension period
2. Additional anti-hypertensive agents made be added in the extension period per Investigator's judgment.
3. For patients consented to participate in the treatment extension, MRA will not be permitted until 2 weeks after the last dose of baxdrostat is administered.

3.1.1.1 Screening Period

Visit 1 (up to 5 weeks prior to date of first dose):

Patients who have been diagnosed with PA and have signed the informed consent form (ICF) may complete the screening procedures. During the Screening Period, all assessments, safety, and administrative events will be completed as detailed in Appendix A.

Visit 2 (up to 4 weeks prior to date of first dose):

The patient's eligibility will be confirmed and, if qualified, dosing with MRA (spironolactone or eplerenone) will be discontinued in those patients who are receiving an MRA. During the visit, an automated BP monitoring device will be provided to the patient. Training in the correct use of the BP device and daily BP measurements thereafter will be required. Patients who take an MRA will discontinue the MRA and monitor BP daily for up to 4 weeks.

Patients will be instructed to contact the Investigator and schedule Visit 3 as soon as possible (preferably within 1 week) if SBP is ≥ 160 mmHg or the SBP increases by ≥ 20 mmHg from the measurement recorded at the Screening Visit, whichever occurs first, or if symptoms of withdrawal (palpitations, chest pain, etc.) occur. Should patients observe a change in their blood pressure measurement that is cause for concern earlier than their planned, scheduled Visit 3, the patient should contact the investigative site as soon as possible to determine the appropriate course of action. This may include an up-titration of current antihypertensive non-MRA medication or an addition of a new antihypertensive non-MRA medication in the short term to address any acute blood pressure concerns (Appendix D of the protocol outlines concomitant antihypertensive medications that can be used during the course of the study). Investigators may also expedite the Visit 3 in order to evaluate the patient and dispense study medication per their discretion. However, for patients whose SBP > 180 mmHg or DBP > 110 mmHg or has 2 consecutive occurrences of mean seated SBP ≥ 160 mmHg or DBP ≥ 100 mmHg after stopping their MRA, they may undergo up titration of current antihypertensive medication or receive rescue antihypertensive medications (chosen at the discretion of the investigator, but which must not be MRAs) to control their blood pressure and have their BP reassessed for eligibility up to four weeks later.

Any safety parameters should be checked as soon as possible in an unscheduled visit at the investigational site or in a local laboratory. For patients taking more than 1 anti-hypertensive agent, the other non-MRA agents should be taken continuously. Potassium supplements may be prescribed if clinically indicated. Unscheduled local laboratory assessments of electrolytes (see

Table 2, footnote b for specific values to be reported) may be done at the Investigator's discretion to monitor the expected electrolyte level changes during the period after MRA discontinuation. These values should be entered in EDC.

If the SBP does not rise after 4 weeks, the patient will be considered a screen failure and will be advised to seek consultation with their physician for BP management.

For patients who are newly diagnosed with PA, have not taken any MRA in the past 12 weeks, and have SBP ≥ 150 mmHg, dosing with CIN-107 may start after all eligibility criteria are confirmed. Visit 2 is not required for these patients.

3.1.1.2 Treatment Period

The treatment period will consist of 12 weeks of CIN-107 dosing.

Visit 3 (Week 0, Day 1)

After eligibility is confirmed, pre-dose vital signs recorded, and safety and PD samples drawn, patients will be provided with an initial dose of CIN-107 and start once daily dosing of CIN-107 tablets at 2 mg QD.

Patients will be instructed to measure BP at least once every day prior to dosing with CIN-107 in the morning. The BP measurements should be the average of 3 readings. Patients should contact the Investigator if the BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or the BP is < 90/60 mmHg. Safety surveillance will be conducted if clinically indicated. Up titrated doses of antihypertensive medications started after Visit 2 or rescue antihypertensive medications, if started, should be down titrated to baseline dose levels (or stopped if possible for the rescue medications) following Visit 3 and ideally by before any up-titration of baxdrostat doses at Visit 4. Repeat and unscheduled testing for serum potassium may be measured at the clinical site or at local laboratory for a faster turn-around time to allow clinical assessment.

Visit 4 (Week 4, Day 28)

CIN-107 dose may be up-titrated to 4 mg QD if the patient tolerates dosing of CIN-107 at 2 mg (and if their background hypertensive medications are at the same doses as at screening) and the BP records indicate minimal hypotension risk. Blood and urine samples will be drawn for safety laboratory testing and for hormone level measurements including aldosterone and renin levels.

The Investigator will contact the patient by phone approximately 7 days after the dose is up-titrated and the laboratory results are available. CIN-107 dose may be down-titrated to 2 mg if the safety laboratory results indicate hyperkalemia, hyponatremia, or other abnormal safety laboratory findings suggesting that the patient is not tolerating CIN-107 4 mg dosing. An unscheduled visit may be conducted in the clinic or in local laboratory if clinically indicated or if samples cannot be processed.

Visit 5 (Week 8, Day 56)

CIN-107 dose may be up-titrated to 8 mg QD if the patient has tolerated dosing of CIN-107 at 4 mg. Up-titration should not proceed if the following occurs based on the most recent available laboratory results:

- Hyperkalemia (serum potassium ≥ 5.5 mEq/L)
- Hyponatremia (serum sodium < 130 mmol/L)
- Un-suppressed renin activity (plasma renin activity [PRA] ≥ 1.0 ng/mL/h) with systolic BP level < 120 mmHg
- Hypotension (with 3 measurements of BP < 90/60 mmHg or symptomatic)

CIN-107 dose may be down-titrated to the 2 mg initial dose or continued with 4 mg. The CIN-107 dose level will be determined by the Investigator based on the BP and safety laboratory values.

Visit 6 (Week 9, Day 63)

Patients will have blood samples drawn for safety laboratory testing at the clinic or in a local setting if a patient lives far from the study investigational site approximately 1 week after the 8 mg dose is initiated. The visit should be scheduled early in the morning for measurement of morning cortisol and ACTH to monitor possible cortisol suppression. If cortisol insufficiency is suspected, the Investigator may also conduct an ACTH stimulation test. At the Investigator's discretion, the dose may be down titrated to 4 mg or 2 mg if laboratory results indicate an electrolyte imbalance or other adverse reaction that is deemed related to CIN-107 treatment. Visit 6 is not required if a patient does not receive 8 mg dose of CIN-107.

Visit 7 (Week 12, Day 89)

For patients in Part 1 only, ie, not opting to continue in the extension part of the study, the patient will take the last dose at the clinic and return any unused study drug. Patients will be reminded that the BP must be measured daily, and the patient should contact the Investigator if the BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or if BP is < 90/60 mmHg.

The treatment duration for patients who complete all 3 dose levels, and who opt not to continue in the extension part of the study, is 12 weeks. For patients who do not complete up-titration, the treatment duration will include at least 4 weeks of dosing with the final dose level. If down-titration of CIN-107 dose is determined at Visit 6 (Week 9), the total treatment duration may be extended to 13 weeks to allow sufficient time for CIN-107 treatment effect at the final dose to be assessed. If the final dose of CIN-107 is reached before week 8 (Visit 5) and no up-titration occurs at Visit 5, the patients will be encouraged to continue CIN-107 treatment till Visit 7 for a total of 12 weeks of treatment. The patients who opt not to continue to Part 2 will not receive any study drug and will return for their safety follow up visit (Visit 8) in 2 weeks. They may also resume their MRA at this time, per Investigator's judgment.

For patients who opt to continue in the extension part (Part 2) of the study, criteria for extension study eligibility include the following: 1) achieving at least comparable BP control to historical treatment, e.g., with mineralocorticoid receptor antagonist, prior to starting baxdrostat and 2) requiring potassium replacement while on baxdrostat that is less than or comparable to

historical replacement in patients with a history of hypokalemia. Exclusion criteria for the extension study are the same as for the main study.

For eligible patients who opt to continue to the extension part of the study, patients will continue to receive their dose of baxdrostat and be instructed to measure BP at least once every week prior to dosing with CIN-107 in the morning, during the extension phase. The BP measurements should be the average of 3 readings. Patients should contact the Investigator if the BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or the BP is < 90/60 mmHg. Safety surveillance will be conducted if clinically indicated. Repeat and unscheduled testing for serum potassium may be measured at the investigator's clinical site--or at local laboratory for a faster turn-around time to allow clinical assessment. These patients entering part 2 will skip Visit 8 and their next visit will be Visit 9.

3.1.1.3 Safety Follow-Up Period

The safety Follow-Up Period will last for approximately 2 weeks after the last dose of CIN-107. Patients will continue taking the non-MRA agents but will not start an MRA during the Follow-Up Period so that the BP, safety data, and biomarker changes can be assessed after CIN-107 dosing is complete. MRA may be prescribed for safety reasons, if necessary, per Investigator's discretion but every effort should be made to bring the patient back to collect the follow up study assessments off CIN-107 treatment, before initiating the MRA.

Visit 8 (Week 14, Day 98)

For patients not opting to continue in the extension part of the study, the patient will complete the last clinical visit and data for BP, samples for safety, and biomarker assessment samples will be collected. Patients will be counseled to maintain a healthy diet and lifestyle and resume MRA if clinically indicated. Patients will receive a telephone call from the clinical site 1-week (± 3 days) following the last dose of CIN-107 to assess adverse events and concomitant medications.

For patients who opt to continue to the extension part of the study, Visit 8 can be skipped.

Visits 9-12 (Week 24, 36, 48, and 60)

For patients who opt to continue to the extension part of the study, patients will continue their dose of baxdrostat and be instructed to measure BP at least once every week prior to dosing with CIN-107 in the morning. The BP measurements should be the average of 3 readings. Patients should contact the Investigator if the BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or the BP is < 90/60 mmHg. Safety surveillance will be conducted if clinically indicated. Repeat and unscheduled testing for serum potassium may be measured at the clinical site or at local laboratory for a faster turn-around time to allow clinical assessment. At the Investigator's discretion, the dose may be up or down titrated to between 2 mg or 8 mg daily if laboratory results indicate an electrolyte imbalance or other adverse reaction that is deemed related to CIN-107 treatment.

Visit 13 (Week 72)

The patient in the extension phase of the study will take their last dose at the clinic and return any unused study drug. Patients will be reminded that the BP must be measured daily, and the patient should contact the Investigator if the BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or if BP is < 90/60 mmHg.

Visit 14 (Week 74) Safety Follow Up Period for Extension Part of the Study

For patients opting to continue in the extension part of the study, the patient will complete the last clinical visit and data for BP, samples for safety, and biomarker assessment samples will be collected. Patients will be counseled to maintain a healthy diet and lifestyle and resume MRA if clinically indicated. Patients will receive a telephone call from the clinical site 1-week (± 3 days) following the last dose of CIN-107 to assess adverse events and concomitant medications.

3.1.2 Rationale for Study Design

PA is characterized by autonomous secretion of aldosterone from the zona glomerulosa of the adrenal cortex. ASIs, by inhibiting aldosterone synthesis, provide a direct mechanism to address the primary pathogenesis of the disease. Reducing aldosterone levels has the potential to reduce BP, either alone or in combination with other antihypertensive agents, improve potassium levels, and reduce the risk of end organ damage. CIN-107 is a highly potent, selective, and competitive inhibitor of aldosterone synthase. Based on findings from nonclinical studies and SAD and MAD clinical studies, CIN-107 may be a novel treatment for the deleterious effects of inappropriately elevated aldosterone resulting in elevated BP in patients with PA. CIN-107 has the potential to offer a new therapeutic option aimed at decreasing aldosterone concentrations in plasma and tissues, thus reducing both the mineralocorticoid receptor-dependent and mineralocorticoid receptor-independent effects of aldosterone.

The diagnosis of PA as defined for this this study reflects current guidelines (Funder JW, 2016). A diagnosis of PA is supported by meeting all three of the criteria of elevated aldosterone level (> 20 ng/dL), depressed renin concentration or activity (PRC < lower limit of renin assay or PRA < 1 ng/mL/min) and a history of hypokalemia. Patients who meet these criteria do not require confirmatory testing to meet the diagnosis of PA. Alternatively a PA diagnosis may be made via an aldosterone to direct renin ratio (ADRR) of > 50 if aldosterone was measured in pmol/L and direct renin concentration (DRC) is measured in mU/L. A conversion factor for DRC of 1 mIU (or 1 mU)/L= 2.2 pg/mL and a conversion factor for aldosterone of 1 ng/dL to 27.7 pmol/L may be used. Plasma ARR of > 15 can be used as a component of the diagnosis of PA if the plasma renin activity was measured in ng/mL/hr and aldosterone in ng/dL. Exceeding the threshold of 15 for the ARR, or 50 for ADRR, still requires confirmatory testing by one of the methods outlined in the protocol.

3.1.2.1 Dose Selection

In a clinical study conducted in healthy subjects, administration of a single CIN-107 dose (1 to 360 mg) induced a dose-dependent blunting of plasma aldosterone levels with a maximum effect achieved at the 10 mg dose level (approximate 85% to 90% decrease as compared to baseline). This effect was observed both on the ACTH challenge readout and on the standing aldosterone peak study (WP28586 Clinical Study Report). The ability of CIN-107 to inhibit aldosterone synthesis was confirmed in a multiple dosing study CIN-107-111. Markedly decreased aldosterone levels were observed after the initial dose of CIN-107 and were sustained throughout the 10-day dosing period for doses ≥ 1.5 mg under both normal salt diet and low salt diet conditions (CIN-107-111 Clinical Study Report). Based on the dose-dependent decreases in plasma aldosterone levels, it is hypothesized that CIN-107 dose at 0.5 mg per day may be effective in lowering aldosterone. The extent of aldosterone synthase inhibition was comparable between CIN-107 at 2.5 mg and 5.0 mg in healthy subjects indicating the maximal treatment effect of CIN-107 is likely achieved in doses under 5 mg in subjects with regular or modestly elevated aldosterone. CIN-107 dose strengths of 0.5, 1, 2, and 4 mg are being evaluated in patients with hypertension in the current phase 2 trials that CinCor is conducting. It is hypothesized that a higher dose level may be required in patients diagnosed with PA to suppress potential more significantly elevated aldosterone levels. The planned regimen of an initial dose of 2 mg with an up-titration option to 4 mg and 8 mg will allow the safety, tolerability, and effectiveness of CIN-107 be assessed.

3.1.2.2 Number of Patients

A total of 12 to 18 patients with a confirmed diagnosis of PA, who consent to participate in the study and meet the eligibility criteria, will be enrolled. The study sample size is chosen empirically for the purpose of this study without considering any formal hypothesis testing. The selected sample size is considered adequate to meet the study objectives and support decision-making for future clinical studies.

3.1.2.3 Safety Measures

Safety surveillance will be conducted at specified clinic visits from the time of informed consent until the end of the Follow-Up Period. The Investigator will review the BP records and measure vital signs and perform ECG and physical examination at designated visits. Safety laboratory tests including serum potassium, sodium, blood urea nitrogen, creatinine, bicarbonate levels, and ARR will be measured at the clinical site visit (See Schedule of Events Appendix A).

Unscheduled assessments should be completed at the Investigator's discretion for acute management of the patient (e.g., follow-up from elevated serum potassium, acute changes in clinical condition, suspected dehydration, etc.) as recommended below:

- For serum potassium of ≥ 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 of ≥ 6 mEq/L, the patient should suspend study drug dosing and present to the clinical site immediately for repeat testing.
- For serum sodium of < 130 mmol/L, the patient should present to the clinical site for repeat testing. The Investigator may withhold dosing if sodium is < 125 mmol/L.
- For serum creatinine at 1.5 to 1.9 times the Screening levels or a ≥ 0.3 mg/dL increase from levels at Screening, the patient should suspend study drug dosing and present to the clinical site for repeat testing.

Repeat and unscheduled testing for serum potassium and sodium levels may be measured at the local laboratory. For a full description of study procedures, assessments and visits see Section 6.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

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

1. Are male or female patients ≥ 18 years of age
2. Have been diagnosed with PA. The diagnosis may be based on meeting all three of the criteria of 1) elevated aldosterone level > 20 ng/dL (555 pmol/L), 2) plasma renin concentration (PRC) < lower limit of renin assay or plasma renin activity (PRA) < 1 ng/mL/min, and 3) hypokalemia (no confirmatory testing is needed in these cases). Otherwise, the diagnosis of PA must include both:
    - Historical evidence of plasma aldosterone to renin activity ratio (ARR) of > 15 if the PRA was measured in ng/mL/hr or aldosterone to direct renin ratio (ADRR) > 50 if aldosterone was measured in pmol/L and direct renin concentration in mU/L (see protocol section 3.1.2 for conversion factors if needed to calculate ARR or ADRR), AND
    - Historical or newly conducted confirmatory testing by one of the following methods: the fludrocortisone-suppression test, the oral saline load test, the intravenous saline load test, or the captopril challenge test
3. Are taking MRA to control BP; or are newly diagnosed with PA and have not started MRA treatment

    Note: the MRAs can be taken with or without other antihypertensive agents including beta blockers, clonidine, methyldopa, minoxidil, angiotensin-converting enzyme inhibitors, diuretics, angiotensin receptor blockers, and/or dihydropyridine calcium channel blockers
4. Are willing and able to cease dosing of MRA for up to 4 weeks in patients taking MRA
5. Are willing to be compliant with the contraception and reproduction restrictions of the study as follows:
    a. Male patients must agree to abstain from sperm donation from Day 1 through 90 days after the final dose of study drug
    b. Postmenopausal women must not have had menstrual bleeding for at least 1 year before initial dosing and either be > 60 years or have an elevated follicle stimulating hormone level of > 40 mIU/mL at Screening
    c. Female patients of childbearing potential (i.e., ovulating, pre-menopausal, and not surgically sterile) must have a documented negative pregnancy test at Screening
    d. Female patients of childbearing potential must use a highly effective method of contraception (i.e., <1% failure rate) from Day 1 through 30 days after the last administration of study drug. Acceptable methods of contraception include:
        i. Surgical sterilization (tubal ligation)

ii. Intra-uterine device for at least 12 weeks prior to Screening Visit

iii. Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before the Screening Visit or

iv. Diaphragm used in combination with spermicide

6. Are willing and able to give informed consent for participation in the study
7. Have increased SBP by ≥ 20 mmHg or have SBP ≥ 160 mmHg after dosing of MRA is ceased, or have SBP ≥ 150 mmHg for patients who are newly diagnosed with PA and have not taken MRA in the past 12 weeks for managing hypertension

4.2 Exclusion Criteria

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

1. During the Screening, have a single occurrence of mean seated SBP > 180 mmHg or DBP > 110 mmHg if not taking an MRA; or have a mean seated SBP ≥ 160 mmHg or DBP ≥ 100 mmHg if currently taking an MRA

   Note: Mean seated BP is defined as the average of 3 measurements obtained at any 1 clinical site visit. If the patient missed regularly scheduled antihypertensive medication(s) prior to the visit, and in the opinion of the Investigator has been otherwise adherent to their antihypertensive regiment, 1 BP re-test is allowed ≥ 2 hours after taking medication(s)
2. Have a body mass index > 45 kg/m^2 at the Screening Visit
3. Have an upper arm circumference < 7 or > 17 inches at the Screening Visit
4. Have had a previous surgical intervention for an adrenal adenoma or have a planned adrenal carcinoma, adrenalectomy, renal nerve denervation, or adrenal ablative procedure during the course of the study

   Note: Patients who have had a procedure > 6 months prior to Screening but still have elevated PAC (> 15 ng/dL) and meet BP and other eligibly criteria may be considered
5. Have a documented estimated glomerular filtration rate < 45 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology equation at the Screening Visit
6. Have a planned dialysis or kidney transplantation during the course of the study
7. Have known documented New York Heart Association class III or IV chronic heart failure
8. Have had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure within 6 months before the Screening Visit
9. Have known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease, diagnosed from a prior echocardiogram

10. Have a planned coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) or any major surgical procedure during the study
11. Have had PCI, CABG, other major cardiac surgery (e.g., valve replacement), or peripheral arterial bypass surgery within 6 months before the Screening Visit
12. Have chronic, permanent atrial fibrillation
13. Have a history of, or currently experiencing, clinically significant arrhythmias as judged by the Investigator, including ventricular tachycardia, ventricular fibrillation, Torsades de points, and supraventricular arrhythmias. Patients with minor forms of ectopy (e.g., premature atrial contractions) are not excluded per Investigator discretion
14. Have had a prior solid organ transplant or cell transplant
15. Are expected to receive or are receiving any of the exclusionary drugs such as strong inducers of cytochrome P450 3A, drugs known to prolong QT, and/or chronic use of NSAIDs or steroids within 28 days or 5 half-lives, whichever is longer prior to the first dose of study drug until the end of treatment

    Note: patients who are using medication(s) noted above at Screening who are willing to come off during the course of the study are allowed to participate
16. Have a known hypersensitivity to CIN-107 or excipients in CIN-107
17. Are positive for HIV antibody, hepatitis C virus RNA, or hepatitis B surface antigen
18. Have typical consumption of > 14 alcoholic drinks weekly

    Note: One drink of alcohol is equivalent to ½ pint of beer (285 mL), 1 glass of spirits (25 mL), or 1 glass of wine (125 mL)
19. Have participated in another clinical study involving any investigational drug within 30 days prior to the Screening Visit, or plans to participate in another clinical study within 30 days of discontinuation of study drug
20. Have received experimental therapy with a small molecule within 30 days of the Screening Visit or 5 half-lives, whichever is longer, or received experimental therapy with a large molecule within 90 days of the Screening Visit or 5 half-lives, whichever is longer
21. Have been on night shifts at any time during the 4 weeks before the Screening Visit and/or plans to begin night shift at any time during Screening
22. Is pregnant, breastfeeding, or planning to become pregnant during the study
23. Is considered by the Investigator, after reviewing medical and psychiatric history, physical examination, and laboratory evaluations, 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

At Visit 2 prior to enrollment:

24. Mean seated SBP > 180 mmHg or DBP > 110 mmHg or has 2 consecutive occurrences of mean seated SBP ≥ 160 mmHg or DBP ≥ 100 mmHg. Note that for patients whose BP exceeds these values after stopping their MRA, they may receive rescue antihypertensive medications (which must not be an MRA) to control their blood pressure and have their BP reassessed for eligibility.

25. Have evidence of any of the following at Screening:

    a. White blood cell count > 15×10^9/L or absolute neutrophil count < 1×10^9/L
    b. Serum potassium < 2.5 mEq/L. Note: Patients with a serum potassium level below normal range may continue in the study if the Investigator elects to correct the serum potassium level with supplementation and offers to manage the condition
    c. Serum potassium >5.0 mEq/L
    d. Hemoglobin < 10.0 g/dL or anticipated initiation of erythropoietin-stimulating agents or planned transfusion within 2 months after the Screening Visit
    e. Serum aspartate aminotransferase or alanine aminotransferase >3 × upper limit of normal (ULN) or
    f. Total bilirubin >2 × ULN, unless due to Gilbert's syndrome
    g. Uncontrolled diabetes with glycosylated hemoglobin > 9.5% at the Screening Visit

4.3 Screen Failures

Screen Failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled in the study and do not receive the first dose of study drug at Visit 3.

Minimal information collected regarding Screen Failures includes, but is not limited to, demography, reason for screen failure, and any SAEs.

4.4 Withdrawal Criteria

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

1. The patient withdraws consent or requests discontinuation from the study for any reason
2. The patient has a single occurrence of mean seated SBP > 180 mmHg or DBP > 110 mmHg OR 2 consecutive occurrences of mean seated SBP ≥ 160 mmHg or DBP≥ 100 mmHg during the Treatment Period

   Note: If the patient missed the regularly scheduled antihypertensive medication(s) prior to the visit, 1 BP re-test is allowed ≥2 hours after taking the medication(s). Note the exception to this during the MRA washout period between Visit 2 and Visit 3 where rescue antihypertensive medications (that are not MRAs) can be used to reduce BP below these values.

3. The patient has an occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol
4. The patient has a requirement of any prohibited concomitant medication
5. The patient becomes pregnant
6. The study is terminated by the Sponsor or the regulatory authority

If a patient withdraws prematurely from the study due to the above criteria or any other reason, site staff should make every effort to complete the full panel of assessments scheduled for the End of Treatment (EOT) Visit. The reason for patient withdrawal must be documented in the electronic case report form (eCRF). Patients should still attend study visits after Early Termination for safety monitoring unless the patient withdraws consent or is lost to follow-up.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records.

Withdrawn patients may be replaced (see Section 4.4.1).

4.4.1 Procedures for Replacement of Withdrawn Patients

Patients who discontinue from participation for reasons unrelated to safety, tolerability or due to an AE that is not considered to be related to the study drug may be replaced at the discretion of the Investigator in consultation with the Sponsor.

Patients who discontinue for study drug-related safety or tolerability reasons will not be replaced.

4.5 Dose Suspension and Stopping Rules

The safety data of this open-label study will be monitored by the Investigators and the study Medical Monitor. In addition, a Data Review Committee (DRC) will evaluate emerging safety and efficacy data after approximately 6 and 12 patients complete the 12-week Treatment Period. Dosing of the study drug may be suspended temporarily for any of the following reasons. When one of the below criteria is met, the DRC will convene as soon as possible, preferably within 48 hours, after learning of the occurrence of a criteria in order to determine if all active subjects should suspend dosing.

1. Any SAE that is deemed related to the study drug, including death
2. A study drug-related adverse event (AE) deemed by the Investigator to be severe in intensity (severity) in ≥ 2 patients
3. A study drug-related AE from a single system organ class deemed to be of moderate intensity (severity) in ≥ 4 patients
4. Serum potassium ≥ 6 mEq/L; the patient should suspend study drug dosing and present to the clinical site immediately for repeat testing

Note: This criterion is specific only to the individual patient suspending dosing. Other enrolled patients do not need to suspend dosing unless determined necessary by the DRC.

This is not an exhaustive list, and each instance should be evaluated on a case-by-case basis by the Investigator and Sponsor for restarting or discontinuing the study drug.

The Investigator, Sponsor and/or DRC may also suspend dosing for any other reason based on emerging data from this study or other ongoing CIN-107 studies. The DRC may review and discuss all available safety, PK, and PD data from all patients participating in the study up until the time of the event.

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

- Dosing may be temporarily held in a patient who has evidence of hyponatremia (sodium concentrations < 130 mmol/L with repeat confirmation within 72 hours upon notification), or SBP ≤ 90 mmHg with symptoms consistent with postural hypotension until the respective hyponatremia or postural hypotension has resolved. The patient may restart study drug following consultation and approval from the Sponsor and/or Medical Monitor.

  Note: This criterion is specific only to the individual subject suspending dosing. Other enrolled subjects do not need to suspend dosing.

4.6 Dose Titration Criteria

The Investigator will assess the daily BP records and determine if up-titration of CIN-107 dose may proceed without significant risk of hypotension at Visit 4 (4 weeks after the first dose) and at Visit 5 (8 weeks after the first dose). CIN-107 dose level may be up-titrated from the initial dose of 2 mg to 4 mg and from 4 mg to 8 mg at those visits.

The Investigator or designated staff will contact the patient approximately 1 week after each dose adjustment by phone and assess if the BP changes are acceptable. The patient will be advised to have blood electrolytes or other safety laboratory tests performed locally for faster turn-around time if the patient experiences rapid BP change or symptoms suggesting other AEs. The dose may be reverted to a lower dose level if the patient experiences hyperkalemia, hyponatremia, or declining renal function based on laboratory testing or the SBP decreases rapidly to < 115 mmHg on 2 consecutive days.

As described in Section 3.1.1.2, up-titration to 8 mg dose should not proceed if any one or more of the following occurs based on the most recent available laboratory results:

- Hyperkalemia (serum potassium ≥ 5.5 mEq/L)
- Hyponatremia (serum sodium < 130 mmol/L)
- Un-suppressed renin activity (PRA] ≥ 1.0 ng/mL/h) with systolic BP level < 120 mmHg
- Hypotension (with 3 measurements of BP < 90/60 mmHg or symptomatic)

At Visit 6, approximately 1 week after the dosing of 8 mg is initiated, all patients will have blood samples drawn for safety laboratory testing at the clinic or in a local setting if a patient lives far from the study investigational site. At the Investigator's discretion, the dose may be titrated down to 4 mg or 2 mg if the laboratory results indicate an electrolyte imbalance. Any of the dose changes and reasons for the dose adjustment must be recorded in the eCRF.

5 STUDY TREATMENTS

5.1 CIN-107 Dose Strengths

The CIN-107 doses to be tested in this study are 2, 4, and 8 mg.

5.2 Blinding

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

5.3 Drug Supplies

5.3.1 Formulation and Packaging

CIN-107 tablets with 2 mg strength will be provided as white tablets in bottles containing 32 tablets per bottle. CIN-107 tablets will contain the active ingredient and lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate as inactive ingredients.

5.3.2 Study Drug Preparation and Dispensing

The study drug will be delivered from the Central Depot to the clinical site. Once a patient has enrolled, site staff who have been delegated the task of drug dispensing by the Investigator will dispense the study drug (CIN-107) at Visits 3 (Day 1, first day of dosing), Visit 4, and Visit 5.

5.3.3 Study Drug Administration

Patients will be instructed to take 1, 2, or 4 tablets, per day for dosing at 2, 4, or 8 mg, respectively, by mouth QD with or without food.

Patients will be allowed a normal diet the morning of study drug administration. At Visit 3, patients will self-administer the first single dose of study drug at the clinical site. Subsequent doses of the study drug are to be taken by the patient QD by mouth at approximately the same time each morning at home.

On days of clinical site visits, patients will take their morning dose of applicable antihypertensive drugs (including medications for other comorbidities, if any) at home prior to their scheduled visit and withhold the study drug. At the clinical site, patients will self-administer the study drug to be witnessed by site staff after completion of pre-dose evaluations and laboratory sampling.

A tablet administration guide outlining the best practices for administering study drug will be provided to clinical sites.

5.3.4 Adherence to Treatment and Home Blood Pressure Monitoring

Patients will self-administer the study drug at the clinical site to be witnessed by site staff after completion of pre-dose evaluations and laboratory sampling; the date and time of study drug administration will be recorded.

On days of clinical site visits, patients will bring their medications (study drug and all antihypertensive medications, if applicable) to the clinical site for assessment of treatment adherence. Site staff will assess treatment adherence based on pill counts. 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.

For all protocol-specified doses when the patient is not at the clinical site, patients will self-administer study drug at home and continue taking their background antihypertensive medications (if applicable). Patients will record whether the daily dose(s) of study drug and each background antihypertensive medication (if applicable) were self-administered in a patient diary. Between clinical site visits, site staff will utilize the information recorded in the diary to ensure patient's adherence to study drug and background antihypertensive regimen (if applicable).

Home BP measurements will also be recorded in the daily diary by the patient. Patients will be asked to bring their daily diary to all clinical site visits for review by the Investigator/site staff.

Site staff will counsel patients about the importance of adhering to their medications (antihypertensive regimen, if applicable, and/or study drug) with completion of diary entry every evening and from Visit 1, about home BP monitoring with entry of all BP measurements in their daily diary

5.3.5 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 (USP) references, excursions between 15°C to 30°C are allowed during storage. During transport, excursions up to 40°C permissible up to 1 week.

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

At the conclusion of the study and after final accountability, all unused study drug should be collected by site staff and 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. A certificate of return will be provided to the clinical sites by the Central Depot. If no study drug remains, this will be indicated in the drug accountability log.

5.4 Prior and Concomitant Medication

5.4.1 Excluded Medications and/or Procedures

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

- Strong inducers of CYP3A
- Products known to prolong QT
- Chronic use of NSAIDs
- Chronic use of steroids

Examples of the above excluded products are provided in Appendix D.

5.4.2 Allowed Medications

Non-RAAS-modifying antihypertensive drug(s), defined as mono- or combination therapy with a non-dihydropyridine calcium channel blocker (e.g., diltiazem, verapamil), hydralazine, an alpha blocker, or a thiazide diuretic are allowed for BP management. MRAs or potassium sparing diuretics are not allowed during the CIN-107 treatment period. Anti-anginal nitrates, including nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate are not considered antihypertensive agents.

Medications other than those excluded (see Section 5.5.1) are also allowed during the study period.

5.4.3 Documentation of Prior and Concomitant Medication Use

All medications used within 30 days of the Screening Visit will be recorded. All concomitant medications and concurrent therapies will be documented in the patient's eCRF as indicated in Appendix A. Dose, route, unit frequency of administration, indication for administration, and dates of medication administration will also be captured in source documents and on the appropriate eCRF.

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

6 STUDY PROCEDURES AND ASSESSMENTS

The activities at each clinic visit listed below are presented in Appendix A. The required laboratory tests scheduled at each visit are listed in Appendix B for the eligibility tests at screening and in Tables 1 and 2. Detailed laboratory assessments are described in Section 9.10.

Visit 3 is the day of first dose and the basis for the visit window. A visit window of ± 3 days is allowed for visits after Visit 3.

6.1 Informed Consent

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

Patients will be given the option to participate in a pharmacogenomic assessment during the consenting process. The written informed consent for pharmacogenomic sample collection will be included in the main ICF. For patients who provide written informed consent to participate in the optional pharmacogenomic assessment, a blood sample will be collected at any time during the Treatment Period. Section 12.3 provides additional details on informed consent.

6.2 Screening and Baseline Procedures and Assessments (Visits 1 and 2)

Screening procedures, including vital signs, BP measurements, and laboratory assessments, may be repeated no more than 2 times for eligibility purposes. A patient who is screened and does not meet the study Inclusion/Exclusion Criteria (Screen Failure) may be rescreened no less than 5 days after the last study visit, with Sponsor and/or Medical Monitor consultation and approval.

At Visit 2, eligible patients who take an MRA to manage BP will discontinue dosing with MRA and monitor their BP daily for up to 4 weeks using the provided BP monitor.

6.3 Treatment Period (Visit 3 through End of Treatment)

After washout of MRA and when SBP is ≥ 160 mmHg or increases ≥ 20 mmHg from the measurement recorded at the Screening Visit, patients who continue to meet all the inclusion criteria and none of the exclusion criteria will be eligible to initiate study drug treatment (2 mg CIN-107) at Visit 3. During the treatment period, patients should take and record BP daily with the provided BP monitor. Patients will be instructed to contact the Investigator if BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or if BP is < 90/60 mmHg. All assessments and safety monitoring will occur as detailed in Appendix A (Schedule of Events).

At Visit 4 (Week 4), the dose of CIN-107 may be increased to 4 mg if the patient tolerates dosing of CIN-107 at 2 mg. The Investigator will contact the patient in approximately 7 days, when laboratory testing results are available, if safety laboratory results indicate hyperkalemia or hyponatremia. The dose of CIN-107 may remain at 2 mg if an electrolyte imbalance or other safety laboratory results indicate the patient is not tolerating CIN-107 dosing.

At Visit 5 (Week 8), the dose of CIN-107 may be increased to 8 mg if the patient tolerates dosing of CIN-107 at 4 mg. The Investigator will contact the patient if safety laboratory results indicate hyperkalemia or hyponatremia. The dose of CIN-107 may remain at 4 mg or reduced to 2 mg if an electrolyte imbalance or other safety laboratory results indicate the patient is not tolerating CIN-107 dosing. Detailed dose titration guidance is described in Section 5.2.

At Visit 6 (Week 9), patients will have blood samples drawn for safety laboratory testing at the clinic or in a local setting if a patient lives far from the study investigational site approximately 1 week after the highest dose of 8 mg is initiated. At the Investigator's discretion, the dose may be down titrated to 4 mg or 2 mg if the laboratory results indicate an electrolyte imbalance. Visit 6 is not required if a patient does not receive 8 mg dose of CIN-107.

At the Visit 7 (Week 12), all assessments, safety monitoring, collection of unused study drug, evaluation of treatment adherence, and administrative requirements will occur as detailed in the Schedule of Events (Appendix A). At Visit 7, for patients in Part 1 only**,** ie, not opting to continue in the extension part of the study, the patient will take the last dose at the clinic and return any unused study drug. Patients will be reminded that the BP must be measured daily, and the patient should contact the Investigator if the BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or if BP is < 90/60 mmHg. The patients who opt not to continue to Part 2 will not receive any study drug and will return for their safety follow up visit (Visit 8) in 2 weeks. They may also resume their MRA at this time, per Investigator's judgment.

For patients who opt to continue in the extension part (Part 2) of the study, patients will continue to receive their dose of baxdrostat and be instructed to measure BP at least once every week prior to dosing with CIN-107 in the morning, during the extension phase. The BP measurements should be the average of 3 readings. Patients should contact the Investigator if the BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or the BP is < 90/60 mmHg. Safety surveillance will be conducted if clinically indicated. Repeat and unscheduled testing for serum potassium may be measured at the investigator's clinical site--or at local laboratory for a faster turn-around time to allow clinical assessment. These patients entering part 2 will skip Visit 8 and their next visit will be Visit 9.

6.4 Follow-Up Visit

At Visit 8 (Week 14), for patients not continuing in the extension (Part 2 of the study), all assessments, safety monitoring, collection of unused study drug, evaluation of treatment adherence, and administrative requirements will occur as detailed in the Schedule of Events (Appendix A).

At the Follow-Up Visit, concomitant medications will be recorded, and AEs will be recorded and assessed. Patients will be counseled to maintain a healthy diet and lifestyle and resume MRA at the same dose taken prior to washout if clinically indicated. For patients who have never taken an MRA, the dose may be titrated up based on Investigator's judgement. **For patients who opt to continue to the extension part of the study, Visit 8 can be skipped.**

Visits 9-12 (Week 24, 36, 48, and 60)

For patients who opt to continue to the extension part of the study, patients will continue their dose of baxdrostat and be instructed to measure BP at least once every week prior to dosing with CIN-107 in the morning. The BP measurements should be the average of 3 readings. Patients should contact the Investigator if the BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or the BP is < 90/60 mmHg. Safety surveillance will be conducted if clinically indicated. Repeat and unscheduled testing for serum potassium may be measured at the clinical site or at local laboratory for a faster turn-around time to allow clinical assessment. At the Investigator's discretion, the dose may be up or down titrated to between 2 mg or 8 mg daily if laboratory results indicate an electrolyte imbalance or other adverse reaction that is deemed related to CIN-107 treatment.

Visit 13 (Week 72)

The patient in the extension phase of the study will take their last dose at the clinic and return any unused study drug. Patients will be reminded that the BP must be measured daily, and the patient should contact the Investigator if the BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or if BP is < 90/60 mmHg.

Visit 14 (Week 74) Safety Follow Up Period for Extension Part of the Study

For patients opting to continue in the extension part of the study, the patient will complete the last clinical visit and data for BP, samples for safety, and biomarker assessment samples will be collected, as detailed in the Schedule of Events (Appendix A). Patients will be counseled to maintain a healthy diet and lifestyle and resume MRA if clinically indicated. Patients will receive a telephone call from the clinical site 1-week (± 3 days) following the last dose of CIN-107 to assess adverse events and concomitant medications.

7 EFFICACY ASSESSMENTS

7.1 Primary Endpoints

The primary endpoints include the following:

- Safety parameters measured by AEs, ECGs, hematology and chemistry laboratory values, vital signs, and physical examination
- Effectiveness measured by change in mean seated SBP after 12 weeks of treatment in patients with PA

7.2 Secondary Endpoints

The secondary efficacy endpoints include the following:

- Effectiveness measured by change in mean seated DBP, after 12 weeks of treatment in patients with PA
- The percentage of patients who achieve a seated BP response < 140/90 mmHg with CIN-107 after treatment at each dose
- The percentage of patients who achieve a seated BP response < 130/80 mmHg with CIN-107 after treatment at each dose

7.3 Exploratory Endpoints

The exploratory endpoints include the following:

The exploratory endpoints include the following:

- Changes in the concentrations from baseline to EOT in PD markers, including but not limited to, PAC, 11-deoxycorticosterone, PRA, direct renin concentration, calculated ARR, and 24-hour urinary aldosterone, NT-proBNP, sodium, and potassium with CIN-107 treatment
    - Relationship between BP reduction and changes in aldosterone, renin levels and ARR with CIN-107
- The percentage of patients who, after 12 weeks of treatment with CIN-107 for PA, achieve either:
    - a PAC < 15 ng/dL and a PRA ≥ 0.5 ng/mL/h; or
    - an ARR < 15; or
    - unsuppressed renin activity PRA ≥ 1.0 ng/mL/h
- Exploratory endpoints in extension study
    - The decline in systolic blood pressure at end of study versus baseline for patients who elect to participate in the extension study

- The decline in diastolic blood pressure at end of study versus baseline for patients who elect to participate in the extension study
- Change in the concentrations from baseline to end of the extension study participation in PD markers, including but not limited to, PAC, 11-deoxycorticosterone, PRA, direct renin concentration, calculated ARR, and 24-hour urinary aldosterone, NT-proBNP, sodium, and potassium with CIN-107 treatment
- Safety parameters measured by AEs, ECGs, hematology and chemistry laboratory values, vital signs, and physical examination throughout the extension study.

8 PHARMACOKINETIC, PHARMACODYNAMIC, AND PHARMACOGENOMIC ASSESSMENTS

8.1 Pharmacokinetic Assessments

Pre- and post-dose PK samples will be collected within 15 minutes before study drug dosing at Visits 3, 4, 5, and 7 and at approximately 2 hours ± 5 minutes after study drug dosing. The actual date and time of collection of each PK sample will be recorded.

Additional PK samples may also be collected in the event of an SAE, AE leading to withdrawal, or any other safety event at the discretion of the Investigator, DRC, and/or Sponsor, if needed for comparison with safety and tolerability data.

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

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

8.2 Pharmacodynamic Assessments

PD samplings, including blood at Visits 2, 3, 4, 5, 6, 7,8, 10 and 13 and 24-h urine collections at Visits 2, 4, 6,7, 10 and 13 will be performed. Site staff and patients will make every effort to time-match PD blood sampling at each visit. Variables analyzed will include measurement of aldosterone and relevant precursors, cortisol and relevant precursor, plasma renin activity, direct renin concentration, and calculated aldosterone to renin ratio (see Table 2). The 24-h urine samples will be collected for measurements of aldosterone, electrolytes (potassium and sodium), creatinine, albumin and protein. Additional PD samples may also be collected in the event of an SAE, AE leading to withdrawal, or any other safety event at the discretion of the Investigator and/or Sponsor. The actual date and time of collection of each PD sample will be recorded. Details regarding the PD sample collection, processing, and shipment can be found in the Laboratory Manual

Table 1 List of Pharmacodynamic Assessments

Blood Analytes	
Aldosterone and its relevant precursors (18 OH corticosterone, corticosterone, and 11-deoxycorticosterone)	Cortisol (free and total) and its relevant precursor, 11 deoxycortisol
Direct renin concentration	Plasma renin activity
NT-proBNP	ARR
24-hour Urine Collection Analytes	
Aldosterone	Potassium
Sodium	Creatinine
Albumin	Protein

8.3 Pharmacogenomic Assessments

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

Patients will be given the option to participate in the pharmacogenomic assessment during the consenting process. The written informed consent for pharmacogenomic sample collection will be included in the main ICF. For patients who provide written informed consent to participate in the optional pharmacogenomic assessment, a blood sample will be collected at any time during the patient's participation in the Treatment Period. The patient may withdraw consent to participate in the pharmacogenomic assessment at any time during the study without withdrawing consent to participate in the study. See Section 8.3.1 for details regarding sample and data destruction following withdrawal of consent.

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

If analysis of the pharmacogenomic samples is undertaken, details of sample and data analyses will be provided in a separate protocol and/or analysis plan. The results obtained from analysis of the pharmacogenomic samples will be accessible to the Sponsor, the party(ies) performing sample analysis and data analyses, and the party involved in maintenance of the Sponsor's database. The results may be disclosed to the Investigator but are not intended to be provided to the patient. The pharmacogenomic results will be reported or published without any of the patient's personal identification information. Blood samples for pharmacogenomic assessments will be stored and analyzed at Cincinnati Children's Hospital Medical Center.

8.3.1 Collection, Storage, and Destruction of Pharmacogenomic Samples

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

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

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

9 SAFETY ASSESSMENTS

9.1 Safety Endpoints

The safety of CIN-107 will be assessed from the time of informed consent until Visit 8 (Week 14). All safety endpoints will be summarized descriptively. The safety endpoints will include the following:

- Change from baseline in potassium levels and/or potassium supplementation requirements with CIN-107 after 12 weeks of treatment in patients with PA
- Vital signs (heart rate, respiratory rate, body temperature), mean SBP, mean DBP, orthostatic vitals (standing BP and heart rate), physical examinations, electrocardiography, weight measurement, and clinical laboratory evaluations including standard safety chemistry panel, hematology, coagulation, and urinalysis
- TEAEs
- Treatment-emergent SAEs
- TEAEs leading to premature discontinuation of the study drug
- Treatment-emergent marked laboratory abnormalities
- Change in standing SBP and DBP (measured at the clinical site prior to administration of study drug)

9.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation that occurs to a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is related to the study drug. 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 time of informed consent until the end of the Follow-up Period. Patients should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study drug. Beginning at Screening, Investigators should make an assessment for AEs at each visit and record the events on the appropriate AE eCRF.

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

Any medical condition already present at the Screening Visit should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline change 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 (e.g., ECG) findings that are detected during the study or are present at the Screening Visit 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 (e.g., 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
- Based on the clinical judgement of the Investigator

AEs will be monitored and documented from the time of informed consent through Visit 8. Patients will be instructed to report any AE that they experience to the Investigator, regardless of whether they think the event is due to study treatment. Beginning at Screening and after collection of informed consent, Investigators should make an assessment for AEs at each study visit and record the event in the appropriate AE eCRF.

9.2.1 Adverse (Drug) Reaction

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

9.2.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

9.2.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to the 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.

Assessment of Causality

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
- Underlying, concomitant, intercurrent diseases
- Concomitant drugs
- Known response pattern for this class of study drug
- Exposure to physical and/or mental stresses
- The pharmacology and PK of the study drug

9.2.4 Adverse Events of Special Interest

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

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

For this study, AESIs include the following:

- Hypotension events that require clinical intervention
- Abnormal potassium laboratory values that require clinical intervention
- Abnormal sodium laboratory values that require clinical intervention

During the course of the study, additional AESIs may be identified by the Sponsor. AESI must be recorded in the eCRF.

9.3 Serious Adverse Events

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

- Death
- A life-threatening AE
- Requires hospitalization or prolongation of existing hospitalization

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., 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
- 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.

9.4 Serious Adverse Event Reporting – Procedures for Investigators

Initial Reports

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

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an e-mail to Medpace Safety at **medpace-safetynotification@medpace.com** or call the Medpace SAE reporting line, and fax/email the completed paper SAE form to Medpace (contact information listed in Section 13.2.3) 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 (e.g., 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.

9.5 Overdose Reporting

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

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

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

9.6 Safety Surveillance and Management of Serum Potassium Levels

Patients who present during the Screening Period (Visits 1 and 2) with a serum potassium level outside of the normal range may continue in the study if the Investigator elects to correct the serum potassium level with supplementation and offers to manage the condition.

Serum potassium levels of patients will be monitored systematically throughout the study. In addition to the clinical laboratory tests predefined in the Schedule of Events (Appendix A), interim

assessments of serum potassium levels are recommended under certain situations (e.g., overdose of potassium supplements, vomiting and/or diarrhea for ≥ 1 day) that may impact the patient's electrolyte levels or fluid balance.

For serum potassium, ≥ 5.5 mEq/L and < 6 mEq/L, the patient should present to the clinical site immediately for repeat testing and the study drug dosing need not be suspended.

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.

9.7 Pregnancy Reporting

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

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

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

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

9.8 Expedited Reporting

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

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

Medpace will also inform all Investigators as required per local regulations. The requirements above refer to the requirements relating to the study drug.

Safety Contact Information: Medpace Clinical Safety

Medpace SAE hotline – United States:

Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3

Fax: +1-866-336-5320 or +1-513-570-5196

Email: **medpace-safetynotification@medpace.com**

9.9 Vital Signs and Blood Pressure Measurements

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

- Patients should not exercise, smoke, or consume caffeinated beverages or food 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
- Vital signs and BP measurements should be obtained prior to ECG recordings
- For measuring BP during clinical site visits, the following standardized procedures are recommended:
    - The patient should be seated for at least 5 minutes in the examination room 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 AOBPM device will be provided to each clinical site and must be used for all study-related measurements
    - An appropriately sized cuff should be used with the bladder centered over the brachial artery
    - The cuff size and arm used for the measurement should be recorded
    - The arm with the higher mean seated BP value at Screening should be used for Screening and subsequent BP measurements
    - All BP measurements should be obtained at approximately the same time of day as the Screening measurements are obtained
    - Three 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, additional readings should be performed

- Once the seated BP has been determined, the patient should be asked to stand, and a single standing BP measurement and heart rate (orthostatic vitals) will be obtained after 60 seconds, as required

9.10 Clinical Laboratory Evaluations

Safety laboratory tests include standard hematology, coagulation, and chemistry panel and urinalysis. Clinical laboratory testing will take place at the local laboratory. See Table 2 for a full list of analytes.

Table 2 Clinical Laboratory Analytes

Standard Safety Chemistry Panel	
Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate [b]
Blood urea nitrogen [b]	Calcium
Chloride [b]	Creatine kinase
Creatinine [b]	Estimated glomerular filtration rate [b]
Gamma-glutamyl transferase	Glucose [b]
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium [b]
Sodium [b]	Total bilirubin
Total protein	Uric acid
Additional Chemistry Parameters	
Glycosylated hemoglobin	
Hematology	
Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential [a]	
Coagulation	
Activated partial thromboplastin time	Prothrombin time
International normalized ratio	
Urinalysis	
Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [a]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	
Endocrinology	
β-human chorionic gonadotropin [b]	Follicle-stimulating hormone [c]

[a] Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range. [b] Values typically measured/reported at a minimum for unscheduled electrolyte determinations.
[b] Serum or point-of-care pregnancy tests will be performed only for female patients of childbearing potential (i.e., ovulating, pre-menopausal, and not surgically sterile).
[c] Follicle-stimulating hormone levels will be measured only for female patients ≤ 60 years of age who are postmenopausal for at least 1 year at Screening and are not surgically sterile.

9.11 Electrocardiograms

Standard 12-lead ECGs will be performed at Visits 1, 3, 4, 5, 6, 7, and 8 (or Early Termination) as indicated in Appendix A.

Every effort will be made to eliminate any sources of physical (including movement, eating, or drinking) or electrical interference. During these assessments, patients are not permitted to use cell phones, iPods, laptop computers, tablets, or any type of battery-operated or electrical device; all these devices must be turned off during the assessments.

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

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

- Heart rate
- QRS interval
- PR interval
- RR interval
- QT interval
- QTc (QTcF)

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

9.12 Physical Examination

A complete physical examination will be performed at Visit 2 and includes assessment of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system. A limited physical examination will consist of a minimum of general appearance, skin, heart, lungs, and abdomen and will be performed at Visits 1, 3, and 7 (see Appendix A).

9.13 Height and Weight

Height will be measured at Visit 1 only and be taken with patient's shoes off. Weight will be determined at the specified visits throughout the study.

10 STATISTICS

10.1 Analysis Populations

The following analysis populations are defined for the different types of data analyses, and additional analysis population(s) may be added in the Statistical Analysis Plan (SAP).

- Intent-to Treat Population (ITT): All patients enrolled in the study
- Per-Protocol Population: All patients in the ITT population who have a baseline value for the SBP assessment, have at least one post-dose value for the SBP assessment, and have no major protocol deviations that could potentially impact the primary efficacy endpoint
- Safety Population: All patients who receive at least 1 dose of study drug will be used for safety analysis
- PK Population: All patients in the ITT Population who have at least 1 quantifiable plasma concentration
- PD population: All patients in the ITT Population who have at least 1 quantifiable concentration of a PD variable

10.2 Statistical Methods

10.2.1 Efficacy Analysis

The SAP will be finalized before database lock. Any changes to the methods described in the final SAP will be described and justified as needed in the Clinical Study Report.

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

10.2.2 Safety Analysis

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

The assessment of safety will be based primarily on the frequency of AEs, clinical laboratory assessments, vital signs, and 12-lead ECGs. Other safety data will be summarized as appropriate.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs, defined as AEs that newly occur or worsen in severity during the treatment period, will be summarized by system organ class and preferred term. A list of patients with SAEs and those who discontinue from study treatment due to an AE will be provided.

Summary statistics at baseline, at each visit, and of changes from baseline to each visit for laboratory parameters, vital signs, and other safety measurements will be provided. The occurrence

of significant abnormalities in change from baseline of laboratory values will be summarized. Physical examination data will be listed.

10.2.3 Pharmacokinetic Analysis

Individual plasma concentration data for CIN-107 and any measured metabolite(s) will be listed and summarized by visit, timepoint, and CIN-107 dose level in the PK population.

10.2.4 Pharmacodynamic Analysis

All PD variables will be summarized descriptively in the PD population.

10.2.5 Pharmacokinetic/Pharmacodynamic Analysis

An attempt will be made to correlate plasma concentration data with measures of safety, PD, and/or efficacy.

10.2.6 Interim Analysis

No formal interim analysis is planned. A DRC will be formed in order to conduct data reviews to assess safety and tolerability as outlined in Section 4.5. Details related to the DRC responsibilities, authorities, and procedures will be documented in the DRC Charter.

11 DATA MANAGEMENT AND RECORD KEEPING

11.1 Data Management

11.1.1 Data Handling

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

11.1.2 Computer Systems

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

11.1.3 Data Entry

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

11.1.4 Medical Information Coding

For medical information, the following dictionaries will be used:

- MedDRA for medical history and AEs and
- World Health Organization Drug Dictionary for prior and concomitant medications

11.1.5 Data Validation

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

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

11.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the clinical site. Source data 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.

11.3 End of Study

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

12 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and 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.

12.2 Institutional Review Board

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

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

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

12.3 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 patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any protocol-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF 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.

12.4 Study Monitoring Requirements

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

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site 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 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 the site staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

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

12.5 Disclosure of Data

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

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

12.6 Retention of Records

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

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

12.7 Publication Policy

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

12.8 Financial Disclosure

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

13 STUDY ADMINISTRATIVE INFORMATION

13.1 Protocol Amendments

Any amendments to the 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.

13.2 Address List

13.2.1 Sponsor

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13.2.3 Serious Adverse Event Reporting

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13.2.4 Biological Specimens

13.2.4.1 Central Laboratory

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13.2.4.3 Pharmacogenomic Laboratory

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13.2.5 Central Depot

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13.2.6 Central Pharmacy

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14 References

Aldactone® (spironolactone) [package insert]. New York, NY. Pfizer, Inc. 2014.

Amar L, Azizi M, Menard J, et al. Aldosterone synthase inhibition with LCI699: a proof-of-concept study in patients with primary aldosteronism. Hypertension. 2010;56(5):831-838.

Andersen M, Bjerre P, Schrøder HD, et al. In vivo secretory potential and the effect of combination therapy with octreotide and cabergoline in patients with clinically non-functioning pituitary adenomas. Clin Endocrinol (Oxf). 2001;54(1):23-30.

Beygui F, Collet J-P, Benoliel J-J, et al. High plasma aldosterone levels on admission are associated with death in patients presenting with acute ST-elevation myocardial infarction. Circulation. 2006;114(24):2604-2610.

Bomback AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. *Nat* Clin Pract Nephrol. 2007;3(9):486-492.

Born-Frontsberg E, Reincke M, Rump LC, et al. Cardiovascular and cerebrovascular comorbidities of hypokalemic and normokalemic primary aldosteronism: results of the German Conn's Registry. J Clin Endocrinol Metab. 2009;94(4):1125-1130.

Calhoun DA, Nishizaka MK, Zaman MA, et al. Hyperaldosteronism among Black and White subjects with resistant hypertension. Hypertension. 2002;40(6):892-896.

Calhoun DA, White WB, Krum H, et al. Effects of a novel aldosterone synthase inhibitor for treatment of primary hypertension: results of a randomized, double-blind, placebo- and active-controlled phase 2 trial. Circulation. 2011;124(18):1945-1955.

Catena C, Colussi G, Nadalini E, et al. Cardiovascular outcomes in patients with primary aldosteronism after treatment. Arch Intern Med. 2008:168(1):80-85.

Duprez DA. Aldosterone and the vasculature: mechanisms mediating resistant hypertension. J Clin Hypertens (Greenwich). 2007;9(1 Suppl 1):13-18.

Fogari R, Preti P, Zoppi A, et al. Prevalence of primary aldosteronism among unselected hypertensive patients: a prospective study based on the use of an aldosterone/renin ratio above 25 as a screening test. Hypertens Res. 2007;30(2):111-117.

Funder JW. Reconsidering the roles of the mineralocorticoid receptor. Hypertension. 2009;53(2):286-290.

Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(5):1889-1916.

Güder G, Bauersachs J, Frantz S, et al. Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. Circulation. 2007;115(13):1754-1761.

Hundemer GL, Baudrand R, Brown JM, et al. Renin Phenotypes Characterize Vascular Disease, Autonomous Aldosteronism, and Mineralocorticoid Receptor Activity. J Clin Endocrinol Metab, June 2017;102(6):1835–1843.

Ivanes F, Susen S, Mouquet F, et al. Aldosterone, mortality, and acute ischaemic events in coronary artery disease patients outside the setting of acute myocardial infarction or heart failure. Eur Heart J. 2012;33(2):191-202.

Karns AD, Bral JM, Hartman D, et al. Study of aldosterone synthase inhibition as an add-on therapy in resistant hypertension. J Clin Hypertens (Greenwich). 2013;15(3):186-192.

Latini R, Masson S, Anand I, et al. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. Eur Heart J. 2004;25(4):292-299.

Manolis AA, Manolis TA, Melita H, et al. Eplerenone versus spironolactone in resistant hypertension: an efficacy and/or cost or just a men's issue? Curr Hypertens Rep. 2019;21(3):22.

Marney AM, Brown NJ. Aldosterone and end-organ damage. Clin Sci (Lond). 2007;113(6):267-278.

Milliez P, Girerd X, Plouin P-F, et al. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J Am Coll Cardiol. 2005;45(8):1243-1248.

Monticone S, D'Ascenzo F, Moretti C, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2018;6(1):41-50.

Mulatero P, Monticone S, Burrello J, et al. Guidelines for primary aldosteronism: uptake by primary care physicians in Europe. J Hypertens. 2016;34(11):2253-2257.

Mulatero P, Stowasser M, Loh K-C, et al. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. J Clin Endocrinol Metab. 2004;89(3):1045-1050.

Oelkers W. Adrenal insufficiency. N Engl J Med. 1996;335(16):1206-1212.

Rossi GP. Primary Aldosteronism: JACC state-of-the-art review. J Am Coll Cardiol. 2019;74(22):2799-2811.

Rossi GP, Bernini G, Caliumi C, et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J Am Coll Cardiol. 2006;48(11):2293-2300.

Sato A, Saruta T. Aldosterone-induced organ damage: plasma aldosterone level and inappropriate salt status. Hypertens Res. 2004;27(5):303-310.

Stowasser M, Sharman J, Leano R, et al. Evidence for abnormal left ventricular structure and function in normotensive individuals with familial hyperaldosteronism type I. J Clin Endocrinol Metab. 2005;90(9):5070-5076.

Swedberg K, Eneroth P, Kjekshus J, et al. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation. 1990;82(5):1730-1736.

US National Library of Medicine. A single ascending dose study investigating the safety, pharmacokinetics and pharmacodynamics of RO6836191 in healthy male volunteers. ClinicalTrails.gov. https://clinicaltrials.gov/ct2/show/NCT01995383. Accessed 09 July 2020.

Vantrimpont P, Rouleau JL, Ciampi A, et al. Two-year time course and significance of neurohumoral activation in the Survival and Ventricular Enlargement (SAVE) Study. Eur Heart J. 1998;19(10):1552-1563.

Vasan RS, Evans JC, Larson MG, et al. Serum aldosterone and the incidence of hypertension in nonhypertensive persons. N Engl J Med. 2004;351(1):33-41.

Wagner RL, White PF. Etomidate inhibits adrenocortical function in surgical patients. Anesthesiology. 1984;61(6):647-651.

Wagner RL, White PF, Kan PB, et al. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med. 1984;310(22):1415-1421.

Weldon SM, Brown NF. Inhibitors of aldosterone synthase. Vitam Horm. 2019;109:211-239.

Wrenn SM, Vaidya A, Lubitz CC. Primary aldosteronism. Gland Surg. 2020;9(1):14-24.

15 APPENDICES

APPENDIX A: SCHEDULE OF EVENTS: --WEEK -5 TO 14- NOTE: VISIT 8/WEEK 14 IS FOR PATIENTS ONLY IN PART 1, NOT IN THE EXTENSION PHASE (SEE FOLLOWING PAGES FOR THAT SCHEDULE)

	Screening		Treatment					Follow-up [n]
***Visit**	**1**	**2**	**3**	**4 [l]**	**5 [m]**	**6**	**7**	**8 [o]**
Study Day (visit window)	**up to Day -35 (+/- 3)**	**up to Day -28 (+/- 3)**	**1 (+/- 3)**	**28 (+/- 3)**	**56 (+/- 3)**	**63 (+/- 3)**	**89 (+/- 3)**	**98 (+/- 3)**
Week	**-5**	**-4**	**0**	**4**	**8**	**9**	**12**	**14**
Mineralocorticoid Receptor Antagonist (MRA)[a]								
MRA washout		X						
MRA treatment								X
CIN-107 **								
Dispense study drug			X	X	X			
CIN-107 treatment [b]			X	X	X	X	X	
Dose titration assessment				X	X			
Unused study drug collection							X	
Assess treatment adherence				X	X	X	X	
Administrative								
Informed consent	X							
Eligibility	X							
Demographics	X							
Medical/surgical history	X							
BP monitor dispensation and instructions [c]	X							
Review of home BP monitoring		X	X	X	X	X	X	X
Assessments								
Vital Signs [e]	X	X	X	X	X	X	X	X
Weight and Height (screening only)	X	X	X	X	X	X	X	X
Complete Physical Examination		X						
Limited Physical Examination	X		X				X	
12-Lead ECG	X		X	X	X	X	X	X

	Screening		Treatment					Follow-up [n]
***Visit**	**1**	**2**	**3**	**4 [l]**	**5 [m]**	**6**	**7**	**8 [o]**
Study Day (visit window)	**up to Day -35 (+/- 3)**	**up to Day -28 (+/- 3)**	**1 (+/- 3)**	**28 (+/- 3)**	**56 (+/- 3)**	**63 (+/- 3)**	**89 (+/- 3)**	**98 (+/- 3)**
Week	**-5**	**-4**	**0**	**4**	**8**	**9**	**12**	**14**
Safety laboratory testing including urinalysis [f, g]	X		X	X	X	X	X	X
PD blood sampling [h]		X	X	X	X	X	X	X
Provide 24-hour urine collection kit	X		X		X	X		
PD urine sampling [i]		X		X		X	X	
PK blood sampling [j]			X	X	X		X	
HIV, HbsAg, HCV screen	X							
Pregnancy test (WOCBP)	X							
Follicle-stimulating hormone [k]	X							
PGx sample (optional, once V3 to V7)					X			
Safety								
Adverse event monitoring	X	X			X			X
Prior/concomitant medications	X	X			X			X

Abbreviations: BP: blood pressure; ECG: electrocardiogram; HbsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; PD: pharmacodynamic; PGx: pharmacogenomic; PK: pharmacokinetic; SBP: systolic blood pressure; WOCBP: women of childbearing potential.

* Note: Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical study site visit. Additional unscheduled visits may occur at Investigator's discretion to manage BP and electrolyte balance.

** Note: If a patient is taking more than 1 anti-hypertensive agent, the other non-MRA agents should be taken continuously.

[a] Eligible patients that take an MRA to manage BP will discontinue MRA and monitor BP daily with provided BP monitor for up to 4 weeks before CIN-107 dosing starts. After the treatment period is complete, patients will resume the MRA after a 2-week Follow-Up Period is complete so that the BP, safety data, and biomarker changes can be assessed. The Follow-Up Period may be shortened and MRA may be prescribed, if necessary, due to safety concern per Investigator's discretion.

[b] Dosing with CIN-107 (2 mg once daily) will start after 4 weeks of MRA washout or when SBP is ≥ 160 mmHg or the SBP increases by ≥ 20 mmHg, whichever is sooner. For patients who are newly diagnosed with PA, have never taken MRA for managing hypertension, and have SBP ≥ 150 mmHg, dosing with CIN-107 may start after all eligibility criteria are confirmed. Visit 2 is not required for these patients.

[c] Patients will be instructed to measure BP daily and to contact the Investigator if BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or if BP is < 90/60 mmHg.

[d] 24-hour urine collection will be analyzed for aldosterone, electrolytes (including but not limited to sodium and potassium), and albumin, protein, and creatinine.

[e] Vital signs include heart rate (seated and standing), respiratory rate, body temperature, and BP (seated and standing).

[f] Safety laboratory tests include standard hematology, coagulation, chemistry panel and urinalysis. Full listing of laboratory analytes can be found in Table 2.

[g] Safety laboratory testing may take place at local laboratory.

[h] PD blood sample variables analyzed will include measurement of aldosterone and relevant precursors, cortisol and relevant precursor, plasma renin activity, direct renin concentration, calculated aldosterone to renin ratio and NT-proBNP. PD samples should be drawn prior to taking CIN-107.
[i] PD 24-hour urine samples will be collected for measurements of aldosterone, electrolytes (potassium and sodium), creatinine, albumin and protein.
[j] PK variables analyzed will include plasma concentration of CIN-107 and any additional metabolites. Pre- and post-dose PK samples will be collected within 15 minutes before study drug dosing at Visits 3, 4, 5, and 7 and 12 and at approximately 2 hours ± 5 minutes after study drug dosing.
[k] Follicle-stimulating hormone levels will be measured only for female patients ≤ 60 years of age who are postmenopausal for at least 1 year at Screening and are not surgically sterile
[l] At Visit 4 (Week 4), CIN-107 dose may be increased to 4 mg if the patient tolerates dosing of CIN-107 at 2 mg. The Investigator will contact the patient by phone approximately 7 days after the dose is up-titrated and the laboratory results are available. CIN-107 dose may be down-titrated to 2 mg if the safety laboratory results indicate hyperkalemia, hyponatremia, or other abnormal safety laboratory findings suggest that the patient does not tolerate CIN-107 4 mg dosing.
[m] At Visit 5 (Week 8), CIN-107 dose may be up-titrated to 8 mg QD if the patient tolerates dosing of CIN-107 at 4 mg. CIN-107 dose may be down-titrated to the 2 mg initial dose or continued with 4 mg if the patient experiences hyperkalemia, hyponatremia, or signs and symptoms of hypotension or un-suppressed renin activity (plasma renin activity [PRA] ≥ 1.0 ng/mL/h). The final CIN-107 dose level will be determined by the Investigator based on the BP and safety laboratory values.
[n] During the safety follow-up period (approximately 2 weeks after the last dose of CIN-107), patients will continue taking the non-MRA agents but will not start the MRA so that the BP, safety data, and biomarker changes can be assessed after CIN-107 dosing. MRA may be prescribed, if necessary, per Investigator's discretion. Patients will receive a telephone call from the clinical site 1-week (± 3 days) following the last dose of CIN-107 to assess adverse events and concomitant medications.
[o] At Visit 8 (Week 14) [Visit 13 (week 74) in the extension phase)], patients will complete the last clinical visit and data for BP, samples for safety, and biomarker assessment samples will be collected. Patients will be counseled to maintain a healthy diet and lifestyle and resume MRA if clinically indicated.

SCHEDULE OF EVENTS WEEKS 12-74 FOR PATIENTS IN THE PART 2 EXTENSION

	Extension Phase				Follow-up [n]	
***Visit**	**9**	**10**	**11**	**12**	**13**	**14**
Study Day (visit window)	**168 (+/- 7)**	**252(+/- 7)**	**336(+/-7)**	**420(+/-7)**	**504(+/-7)**	**532(+/-7)**
Week	**24**	**36**	**48**	**60**	**72**	**74**
Dispense study drug	X	X	X	X	X	
CIN-107 treatment [b]	X	X	X	X	X	
Dose titration assessment	X	X	X	X		
Unused study drug collection	X	X	X	X	X	
Assess treatment adherence	X	X	X	X	X	
Eligibility [p]	X					
Review of home BP monitoring	X	X	X	X	X	X
Vital Signs [e]	X	X	X	X	X	X
Weight	X	X	X	X	X	X
Complete Physical Examination					X	
Limited Physical Examination	X	X	X	X		X
12-Lead ECG	X				X	X
Safety laboratory testing including urinalysis [f, g]	X	X	X	X	X	X
PD blood sampling [h]		X			X	
Provide 24-hour urine collection kit	X			X		
PD urine sampling [i]		X			X	
PK blood sampling [j]					X	
Pregnancy test (WOCBP)						X
Safety						
Adverse event monitoring	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X
MRA treatment						X

Abbreviations: BP: blood pressure; ECG: electrocardiogram; HbsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; PD: pharmacodynamic; PGx: pharmacogenomic; PK: pharmacokinetic; SBP: systolic blood pressure; WOCBP: women of childbearing potential.
* Note: Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical study site visit. Additional unscheduled visits may occur at Investigator's discretion to manage BP and electrolyte balance.
** Note: If a patient is taking more than 1 anti-hypertensive agent, the other non-MRA agents should be taken continuously.

[a] Eligible patients that take an MRA to manage BP will discontinue MRA and monitor BP daily with provided BP monitor for up to 4 weeks before CIN-107 dosing starts. After the treatment period is complete, patients will resume the MRA after a 2-week Follow-Up Period is complete so that the BP, safety data, and biomarker changes can be assessed. The Follow-Up Period may be shortened and MRA may be prescribed, if necessary, due to safety concerns per Investigator's discretion.
[b] Dosing with CIN-107 (2 mg once daily) will start after 4 weeks of MRA washout or when SBP is ≥ 160 mmHg or the SBP increases by ≥ 20 mmHg, whichever is sooner. For patients who are newly diagnosed with PA, have never taken MRA for managing hypertension, and have SBP ≥ 150 mmHg, dosing with CIN-107 may start after all eligibility criteria are confirmed. Visit 2 is not required for these patients.
[c] Patients will be instructed to measure BP daily and to contact the Investigator if BP is ≥ 170/105 mmHg, if the patient experiences symptoms of hypotension, or if BP is < 90/60 mmHg.
[d] 24-hour urine collection will be analyzed for aldosterone, electrolytes (including but not limited to sodium and potassium), and albumin, protein, and creatinine.
[e] Vital signs include heart rate (seated and standing), respiratory rate, body temperature, and BP (seated and standing).
[f] Safety laboratory tests include standard hematology, coagulation, chemistry panel and urinalysis. Full listing of laboratory analytes can be found in Table 2.
[g] Safety laboratory testing may take place at local laboratory.
[h] PD blood sample variables analyzed will include measurement of aldosterone and relevant precursors, cortisol and relevant precursor, plasma renin activity, direct renin concentration, calculated aldosterone to renin ratio and NT-proBNP. PD samples should be drawn prior to taking CIN-107.
[i] PD 24-hour urine samples will be collected for measurements of aldosterone, electrolytes (potassium and sodium), creatinine, albumin and protein.
[j] PK variables analyzed will include plasma concentration of CIN-107 and any additional metabolites. Pre- and post-dose PK samples will be collected within 15 minutes before study drug dosing at Visits 3, 4, 5, and 7 and 12 and at approximately 2 hours ± 5 minutes after study drug dosing.
[k] Follicle-stimulating hormone levels will be measured only for female patients ≤ 60 years of age who are postmenopausal for at least 1 year at Screening and are not surgically sterile
[l] At Visit 4 (Week 4), CIN-107 dose may be increased to 4 mg if the patient tolerates dosing of CIN-107 at 2 mg. The Investigator will contact the patient by phone approximately 7 days after the dose is up-titrated and the laboratory results are available. CIN-107 dose may be down-titrated to 2 mg if the safety laboratory results indicate hyperkalemia, hyponatremia, or other abnormal safety laboratory findings suggest that the patient does not tolerate CIN-107 4 mg dosing.
[m] At Visit 5 (Week 8), CIN-107 dose may be up-titrated to 8 mg QD if the patient tolerates dosing of CIN-107 at 4 mg. CIN-107 dose may be down-titrated to the 2 mg initial dose or continued with 4 mg if the patient experiences hyperkalemia, hyponatremia, or signs and symptoms of hypotension or un-suppressed renin activity (plasma renin activity [PRA] ≥ 1.0 ng/mL/h). The final CIN-107 dose level will be determined by the Investigator based on the BP and safety laboratory values.
[n] During the safety follow-up period (approximately 2 weeks after the last dose of CIN-107), patients will continue taking the non-MRA agents but will not start the MRA so that the BP, safety data, and biomarker changes can be assessed after CIN-107 dosing. MRA may be prescribed, if necessary, per Investigator's discretion. Patients will receive a telephone call from the clinical site 1-week (± 3 days) following the last dose of CIN-107 to assess adverse events and concomitant medications.
[o] At Visit 8 (Week 14) [Visit 13 (week 74) in the extension phase)], patients will complete the last clinical visit and data for BP, samples for safety, and biomarker assessment samples will be collected. Patients will be counseled to maintain a healthy diet and lifestyle and resume MRA if clinically indicated.

[p] Eligibility for Part 2 will be determined based on the patient achieving at least comparable BP control to historical treatment and requiring potassium replacement while on baxdrostat that is less than or comparable to historical replacement in patients with a history of hypokalemia.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Viral Testing and Serology

Hepatitis B surface antigen
HIV antibody
Hepatitis C virus RNA

APPENDIX C: ELECTROCARDIOGRAM ALERT CRITERIA GUIDANCE

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

- QTcF ≥ 450 msec (males)
- QTcF ≥ 470 msec (females)
- A > 60 msec increase in QTcF from baseline
- A ≥ 6% increase in QTcF from baseline

New onset findings included but not limited to:

- 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
- Atrial fibrillation/atrial flutter (ventricular rate ≥ 150 bpm)

APPENDIX D: EXCLUDED MEDICATIONS

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

An extract of these websites is reflected in Table 3

Table 3 Examples of Excluded Medications

Group	Excluded Medication Examples
Strong inducers of CYP3A[a]	Apalutamide, carbamazepine[b], enzalutamide[c], mitotane, phenytoin[d], rifampin[e], St. John's wort[f]
Medications known to prolong QT	Amiodarone, azithromycin, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, dofetilide, domperidone, donepezil, erythromycin, escitalopram, fluconazole, hydroxychloroquine, levofloxacin, methadone, moxifloxacin, ondansetron, pentamidine, quinidine, sotalol, thioridazine, vandetanib

Sources: Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed 06 October 2020
Drugs with known TdP Risk. Available at www.CredibleMeds.org (registration required) Accessed 06 October 2020.
Abbreviations: AUC: area under the concentration time curve; CYP: cytochrome P450; DDI: drug-drug interaction.
[a] Examples of clinical inducers for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling [03 December 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.
[b] Strong inducer of CYP2B6 and CYP3A, and weak inducer of CYP2C9.
[c] Strong inducer of CYP3A and moderate inducer of CYP2C9 and CYP2C19.
[d] Strong inducer of CYP2C19 and CYP3A and moderate inducer of CYP1A2, CYP2B6, CYP2C8, and CYP2C9.
[e] Strong inducer of CYP3A and moderate inducer of CYP1A2 and CYP2C19.
[f] The effect of St John's wort varies widely and is preparation dependent.

Beginning at Visit 2, patients will be required to washout mineralocorticoid receptor antagonists (such as spironolactone) and remain off through Visit 8 (Follow-Up). During the course of the study, antihypertensives including beta blockers, clonidine, methyldopa, minoxidil, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and/or dihydropyridine calcium channel blockers may be continued to maintain blood pressure.