CLINICAL STUDY REPORT

A Randomized, Double-Blind Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of CIN-107 Following Multiple Oral Doses in Healthy Subjects

Investigational Product: CIN-107
Indication Studied: Hypertension
Protocol Number: CIN-107-111
Development Phase: 1
Initiation Date: 19 December 2019
Completion Date: 03 April 2020

Sponsor:
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Version Number: 1.0
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1 SIGNATURE PAGE

A Randomized, Double-Blind Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of CIN-107 Following Multiple Oral Doses in Healthy Subjects

I, the undersigned, have read this report and confirmed to the best of my knowledge it accurately describes the conduct and results of the study.

Signature

DocuSigned by:
[redacted]

CinCor Pharma, Inc.

Date

8/25/2020

2 SYNOPSIS

Name of Sponsor: CinCor Pharma, Inc.

Name of Finished Product: CIN-107

Name of Active Ingredient: CIN-107

Title of Study: A Randomized, Double-Blind Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of CIN-107 Following Multiple Oral Doses in Healthy Subjects

Investigator: Leela Vrishabhendra, MD

Study Site: 1 clinical site in the United States (Medpace Clinical Pharmacology Unit [Cincinnati, Ohio])

Publication (reference): None

Study Period: Approximately 15 weeks

Initiation Date: 19 December 2019

Completion Date: 03 April 2020

Phase of Development: 1

Indication: Hypertension

Study Objectives:

The objectives of this study were as follows:

- To assess the safety and tolerability of CIN-107 following oral dosing once daily for 10 days under normal and low salt conditions;
- To characterize the pharmacokinetics (PK) of CIN-107 following oral dosing once daily for 10 days under normal and low salt conditions; and
- To characterize the pharmacodynamic (PD) effects of CIN-107 following oral dosing once daily for 10 days under normal and low salt conditions.

Methodology:

This was a randomized, double-blind study to assess the safety, tolerability, PK, and PD of multiple oral doses of CIN-107 when administered to healthy adult subjects. The study consisted of 5 cohorts, with up to 12 subjects per cohort. Subjects were randomized in a 3:1 ratio to CIN-107 or placebo once daily for 10 days as follows:

- Cohort 1: 2.5 mg CIN-107 or matching placebo (low salt diet in 9 subjects receiving CIN-107 and 3 subjects receiving placebo);
- Cohort 2: 5.0 mg CIN-107 or matching placebo (low salt diet in 9 subjects receiving CIN-107 and 3 subjects receiving placebo);
- Cohort 3: 1.5 mg CIN-107 or matching placebo (normal salt diet in 9 subjects receiving CIN-107 and 3 subjects receiving placebo);

- Cohort 4: 2.5 mg CIN-107 or matching placebo (normal salt diet in 6 subjects receiving CIN-107 and 2 subjects receiving placebo); and
- Cohort 5: 0.5 mg CIN-107 or matching placebo (normal salt diet in 9 subjects receiving CIN-107 and 3 subjects receiving placebo).

Cohorts 1 and 2 dosed concurrently, with a minimum 5-day lag between the first dose for Cohort 2 and the first dose for Cohort 1. Cohorts 3 through 5 dosed concurrently. A Data Review Committee met between Cohorts 2 and 3 to review data from all prior cohorts.

For each subject, the study consisted of:

- A screening period of up to 28 days;
- A 5-day inpatient run-in period during which subjects adhered to a controlled, standardized diet and underwent baseline PD assessments;
- A 15-day inpatient treatment period, during which subjects received CIN-107 or placebo once daily for 10 days while adhering to a controlled, standardized diet, followed by PK and PD sampling over an additional 5 days; and
- A follow-up visit 3 days (±1 day) after discharge from the clinical unit.

A cortisol stimulation test (Cohorts 1 and 2 only) and standing aldosterone assessment (all cohorts) were performed on Days 1 and 10. Serial blood samples for PK and PD were obtained prior to and at specified time points over 24 hours after dosing on Day 1 as well as prior to and at specified time points over 120 hours after dosing on Day 10. In addition, blood samples for PK were collected prior to dosing on Days 8 and 9. Urine for PK and PD measurements was collected over 24 hours starting just prior to dosing on Day 1 as well as over 120 hours starting just prior to dosing on Day 10.

Subjects were discharged from the clinic following completion of discharge procedures 5 days after the final dose of CIN-107 or placebo and returned to the clinic for a follow-up visit 3 days (±1 day) after discharge from the clinic to collect a PK sample and to capture adverse events (AEs) and concomitant medications.

Safety was assessed throughout the study based on AEs, physical examinations, weight measurements, electrocardiograms (ECGs), orthostatic vital sign assessments, and clinical laboratory evaluations. In order to thoroughly assess any potential effect of CIN-107 on QT interval, continuous ECG recordings were also performed, starting approximately 1 hour before dosing and continuing for approximately 24 hours after dosing on Days 1 and 10.

Unscheduled procedures or visits and/or additional follow-up may have been required for subjects with clinically significant abnormal laboratory findings, unresolved treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) that required follow-up laboratories and review, and clinically significant AEs.

Duration of Treatment:

For each subject, study participation lasted up to 56 days. Treatment with CIN-107 or placebo lasted for 10 days (once daily dosing).

Number of Subjects:

Planned: 60 subjects planned (up to 12 subjects per cohort)

Screened: 130 subjects screened

Randomized: 56 subjects randomized

Completed: 54 subjects completed

Discontinued: 2 subjects discontinued from the study

Diagnosis and Main Criteria for Inclusion:

The population for this study included healthy subjects between the ages of 18 and 55 years, inclusive, who were in good health based on medical and psychiatric history, physical examination, ECG, orthostatic vital signs, and routine laboratory tests (blood chemistry, hematology, coagulation, and urinalysis); had a body mass index (BMI) between 18 and 30 kg/m^2, inclusive; who were nonsmokers; and who had an appropriate response to cortisol stimulation (Cohorts 1 and 2) or a normal cortisol level during the inpatient run-in period (Cohorts 3 through 5).

Investigational Product and Comparator Information:

Study subjects were dosed with CIN-107 oral drinking solution (CIN-107 Good Manufacturing Practice drug substance [anhydrate] lot number 208-027-3779-01) or matching placebo. The doses of CIN-107 administered were 2.5 and 5.0 mg with a low salt diet and 1.5, 2.5, and 0.5 mg with a normal salt diet.

Criteria for Evaluation:

Pharmacokinetics:

The following plasma PK parameters were determined for CIN-107 and its primary metabolite (CIN-107-M) following the first dose of CIN-107, as the data permitted:

- Maximum observed plasma concentration on Day 1 ($C_{max,D1}$), observed directly from data;
- Time to $C_{max,D1}$ ($T_{max,D1}$), observed directly from data; and
- Area under the plasma concentration-time curve (AUC) from time 0 to 24 hours postdose (AUC_{0-24h}).

The following plasma PK parameters were determined for CIN-107 and its primary metabolite (CIN-107-M) following the final dose of CIN-107 on Day 10, as the data permitted:

- Maximum observed plasma concentration on Day 10 ($C_{max,D10}$), observed directly from data;
- Time to $C_{max,D10}$ ($T_{max,D10}$), observed directly from data;
- AUC over a dosing interval (ie, tau) (AUC_{0-tau});
- AUC from time 0 to the time of the last quantifiable plasma concentration (C_{last}) (AUC_{0-t});
- AUC from time 0 to infinity (AUC_{0-inf});
- AUC extrapolated, the percent of AUC extrapolated, calculated as $100 \times (AUC_{0-inf} - AUC_{0-t})/AUC_{0-inf}$;

- Apparent first-order terminal elimination rate constant (λ_z);
- Terminal phase elimination half-life ($t_{½}$), calculated as $\ln(2)/\lambda_z$;
- Apparent plasma clearance (CL_{ss}/F), calculated as Dose/$AUC_{0\text{-}tau}$ (only for CIN-107); and
- Apparent volume of distribution (V_{ss}/F), calculated as Dose/[$\lambda_z \times AUC_{0\text{-}tau}$] (only for CIN-107).

Steady-state accumulation ratios were reported as follows:

- Accumulation ratio based on maximum observed plasma concentration (C_{max}) after the first dose and the final dose (R_{Cmax}), calculated as $C_{max,D10}/C_{max,D1}$; and
- Accumulation ratio based on AUC after the first dose and last dose (R_{AUC}), calculated as $AUC_{0\text{-}tau}/AUC_{0\text{-}24h}$.

The following urine PK parameters were determined for CIN-107 and its primary metabolite (CIN-107-M) following the first dose:

- Cumulative amount of drug excreted in urine on Day 1 ($A_{e,D1}$);
- Fraction of the dose excreted renally on Day 1 ($F_{e,D1}$), calculated as $100 \times A_{e,D1}$/Dose (only for CIN-107); and
- Renal clearance on Day 1 ($CL_{R,D1}$), calculated as $A_{e,D1}/AUC_{0\text{-}24h}$.

The following urine PK parameters were determined for CIN-107 and its primary metabolite (CIN-107-M) following the final dose:

- Cumulative amount of drug excreted in urine on Day 10 ($A_{e,D10}$);
- Fraction of the dose excreted renally on Day 10 ($F_{e,D10}$), calculated as $100 \times A_{e,D10}$/Dose (only for CIN-107); and
- Renal clearance on Day 10 ($CL_{R,D10}$), calculated as $A_{e,D10}/AUC_{0\text{-}inf}$.

Pharmacodynamics:

Plasma PD measures included concentrations of:

- Aldosterone and its precursors 18-hydroxycorticosterone, corticosterone, and 11-deoxycorticosterone;
- Cortisol (free and total) and its precursor 11-deoxycortisol;
- Plasma renin activity (PRA); and
- Adrenocorticotropic hormone (ACTH).

Plasma electrolyte measures included concentrations of:

- Sodium;
- Chloride; and
- Potassium.

For analysis, AUC values were calculated for aldosterone and cortisol (free and total) and all precursor parameters for the following time periods, when possible, using a non-compartmental method as appropriate:

- Area under the PD effect-time curve from time 0 to 4 hours postdose (AUC_{0-4h});
- Area under the PD effect-time curve from time 4 hours postdose to 12 hours postdose (AUC_{4-12h});
- Area under the PD effect-time curve from time 0 to 12 hours postdose (AUC_{0-12h}); and
- Area under the PD effect-time curve from time 0 to 24 hours postdose (AUC_{0-24h}).

The linear trapezoidal/linear interpolation method was used in the calculation of AUCs. Nominal time points were used in the AUC calculations.

Urine PD measures included concentrations of:

- Aldosterone;
- Cortisol (free and total); and
- Tetrahydroaldosterone.

For analysis, the urine PD concentrations were converted to total analyte amounts:

Total amount (unit) = concentration (unit/volume) × urine volume

(Note: Urine volume may have been converted from urine mass collected using 1 mg = 1 mL).

Urine electrolyte measures included concentrations of:

- Sodium;
- Chloride;
- Potassium;
- Creatinine; and
- Phosphorus.

For analysis, the urine sodium to potassium ratio was also calculated.

Safety:

Safety was assessed throughout the study based on AEs, physical examinations, weight measurements, ECGs, vital sign (including orthostatic) assessments, and clinical laboratory evaluations. In order to thoroughly assess any potential effect of CIN-107 on QT interval, continuous ECG recordings were also performed starting approximately 1 hour before dosing and continuing for approximately 24 hours after dosing on Days 1 and 10. If cardiodynamic analyses are undertaken, 12-lead ECGs will be extracted at predefined time points paired with PK samples, as outlined in the Schedules of Assessments.

Statistical Methods:

General considerations:

Placebo subjects were pooled into 2 treatment groups, when appropriate: placebo with low salt diet (Cohorts 1 and 2) and placebo with normal salt diet (Cohorts 3 through 5).

Descriptive statistics (arithmetic mean, standard deviation [SD], coefficient of variability [CV], median, minimum, and maximum) were calculated for quantitative safety data as well as for the difference from baseline (predose, Day 1) for safety measures, when appropriate. Baseline was defined as the last measurement prior to the first dose, except for parameters with time-matched collections. For these parameters (plasma aldosterone and cortisol [free and total] and all precursors), change and percentage change were based on the time-matched Day -1 time point value. Frequency counts were provided for the classification of qualitative safety data. Safety data were summarized by treatment group and point of time of collection, when appropriate. Summaries for a pooled CIN-107 group (either by diet type or overall) may have also been included, when appropriate.

Geometric mean (GM) and GM CV were also provided for PK parameters.

Analysis populations:

The Safety Population consisted of all randomized subjects who received any study drug (CIN-107 or placebo).

The PK Population included all subjects who received CIN-107 and had at least 1 quantifiable postdose plasma concentration for CIN-107 or CIN-107-M.

The PK Evaluable Population included subjects who received CIN-107 and had sufficient plasma concentration data to characterize at least 1 PK parameter for CIN-107 or CIN-107-M.

The PD Population included all subjects who received study drug (CIN-107 or placebo) and had at least 1 postdose PD measurement.

Pharmacokinetic analyses:

Individual plasma concentrations of CIN-107 and metabolite were summarized descriptively by treatment group and dosing day (Day 1 and Day 10) at each nominal time point for the PK Population. Individual plasma concentrations of CIN-107 and metabolite were also listed for the PK Population.

Individual concentrations of CIN-107 and metabolite were plotted by treatment group and dosing day (Day 1 and Day 10) on linear and semi-logarithmic scales against actual sampling time points relative to dosing time. Mean concentration was plotted on linear and semi-logarithmic scales against nominal time points by treatment group and by dosing day (Day 1 and Day 10) when available.

Individual and mean plasma trough concentrations of CIN-107 and metabolite (predose values on Days 8, 9, and 10 and the 24-hour postdose value relative to Day 10) were plotted similarly to demonstrate attainment of steady state.

PK parameters were listed and summarized descriptively by treatment group and day for the PK Evaluable Population.

For the first dose, $C_{max,D1}$ and $AUC_{0\text{-}24h}$ of CIN-107 were evaluated using a power model for the exploratory dose proportionality analysis for the PK Evaluable Population. The mean slope was estimated from the power model and the corresponding 90% confidence interval (CI) was calculated. For the final dose, $C_{max,D10}$, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ of CIN-107 were evaluated similarly.

Pharmacodynamic analyses:

Individual PD parameter values and derived AUC values were summarized descriptively by treatment group and point of time of collection for the PD Population. Descriptive statistics (arithmetic mean, SD, standard error [SE], CV, median, minimum, and maximum) were calculated for time point values as well as for the change and percentage change from baseline. GMs were also presented for the AUC summaries.

The plasma PD parameters of aldosterone and cortisol (free and total) and their precursors had the mean (with and without SE) absolute values and time-matched change and percentage change from baseline values plotted by treatment group across the available time points.

For urine PD and electrolyte parameters, each available collection's percentage change from baseline values was presented in boxplots by treatment group.

The effect of dose on plasma aldosterone and cortisol (free and total) and their precursors was investigated using an analysis of variance model on change in AUC from Day -1 to Day 1.

Least squares (LS) mean and corresponding 90% CI from this model were presented for exp (λ_k) for all *k*. This analysis was performed separately for Cohorts 1 and 2 and Cohorts 3 through 5 (due to the different salt diets) and repeated for the comparison of Day -1 to Day 10. The LS means and CIs were summarized in a table and also plotted.

For summary of the Cortrosyn® challenge, plasma cortisol (free and total) and 11-deoxycorticosterone were summarized descriptively (arithmetic mean, SD, minimum, and maximum) by treatment group for the time points before and after the challenge. Side-by-side plots of individual data and mean/SD of the 3 days were created by treatment group for the time points immediately before and at 1 hour after the challenge (corresponding to 1 hour after study drug administration and 2 hours after study drug administration, respectively).

Post hoc PD analyses of individual plasma PD parameter values and derived AUC values, urine PD and electrolyte parameters, and summary of the Cortrosyn challenge were repeated excluding outlier subjects.

All individual PD measurements and derived AUC values were listed for the PD Population.

Safety analyses:

Descriptive statistics (arithmetic mean, SD, CV, median, minimum, and maximum) were calculated for quantitative safety data as well as for the difference from baseline (predose, Day 1), when appropriate. Frequency counts were provided for the classification of qualitative safety data. Safety data were summarized by treatment group and time of collection, when appropriate.

An overview of AEs was provided by treatment group. TEAEs were summarized by treatment group at onset. Separate listings were prepared for death, SAEs, and AEs leading to study discontinuation as well as for all AEs.

Continuous safety laboratory data (observed values; change and percentage change from baseline, where appropriate) were summarized by treatment group at baseline and at each post-baseline time point using the Safety Population. Baseline was defined as the last value prior to dosing. Categorical data were summarized using frequency counts and percentages by treatment group.

Additional summaries for blood potassium and sodium were provided for the following changes:

- From Day 1 predose relative to the check-in visit;
- From Day 10 predose relative to the check-in visit;
- From Day 10 predose relative to Day 1 predose;
- From Day 11 24 hours postdose relative to the check-in visit; and
- From Day 11 24 hours postdose relative to Day 1 predose.

Post hoc analyses included the addition of summaries for blood sodium:potassium ratio, blood urea nitrogen, creatinine, and blood urea nitrogen:creatinine ratio.

The mean summaries of blood potassium and sodium were also plotted by treatment group. Plots of individual values for these parameters may also have been presented.

Shift tables describing post-baseline out-of-normal range shifts were provided for continuous laboratory results. Data were also listed using the Safety Population.

Vital signs, orthostatic BP and heart rate, and weight and BMI observed values and change from baseline at each scheduled time point were summarized by treatment group. For orthostatic BP and heart rate, additional summaries by treatment group were:

- Change by positions at visit Day -1 predose, Day 1 predose, and Day 10 predose:
  - From supine position to 1-minute standing position; and
  - From supine position to 3-minute standing position; and
- Change of change by positions at visit Day -1 predose, Day 1 predose, and Day 10 predose:
  - From supine position to 1-minute standing position; and
  - From supine position to 3-minute standing position.

Changes by treatment group for BP, weight, and orthostatic BP and heart rate were also summarized for:

- From Day 1 predose relative to the check-in visit;
- From Day 10 predose relative to the check-in visit;
- From Day 10 predose relative to Day 1 predose;
- From Day 11 24 hours postdose relative to the check-in visit; and
- From Day 11 24 hours postdose relative to Day 1 predose.

The mean summaries of the BP, weight, and orthostatic BP and heart rate parameters were also plotted by treatment group. Plots of individual values for these parameters may also have been presented. The correlation of change from Day 1 predose to Day 10 predose in supine BP and

plasma aldosterone were also plotted. Post hoc analyses of vital signs included the addition of an end of treatment visit summary. All vital signs data were listed for the Safety Population.

The ECG values were determined by the average of the triplicate ECGs captured. Baseline was defined as the average of the ECG values from the 3 Day 1 predose time points. Observed ECG parameters and change and percentage change from baseline at each scheduled time point were summarized by treatment group. All 12-lead ECG data were listed for the Safety Population.

Physical examination data were listed by treatment group for the Safety Population.

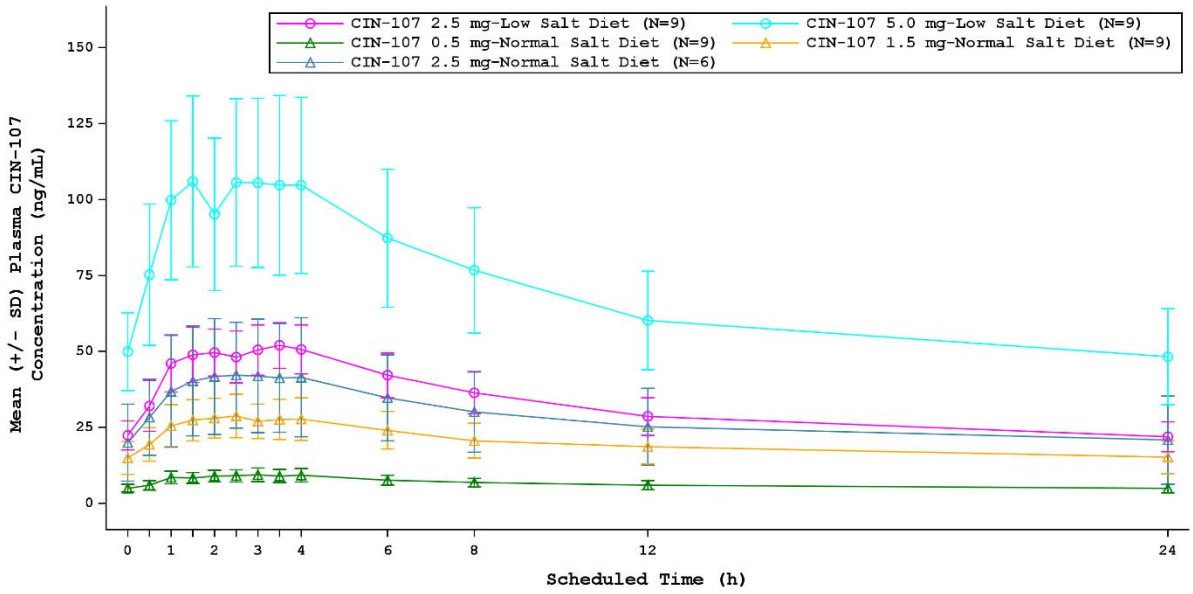
Fluid intake data were listed by treatment group for the Safety Population. A post hoc listing for urine weight and volume data and summaries of fluid intake and urine weight and volume by treatment and day were produced.

Summary of Results:

Pharmacokinetics:

After oral administration, CIN-107 was rapidly absorbed with peak concentrations typically observed within 4 hours after dosing (median time to maximum observed plasma concentration [T_{max}] ranged from 0.98 to 4 hours across treatment groups). Exposures declined from peak slowly in an apparent biphasic manner, with a long mean $t_{½}$ ranging from approximately 26 to 31 hours.

Figure S1. Plot of Mean (±Standard Deviation) Plasma CIN-107 Concentrations Versus Time (Day 10, 0-24 Hours) by Treatment on Linear Scale – Pharmacokinetic Population

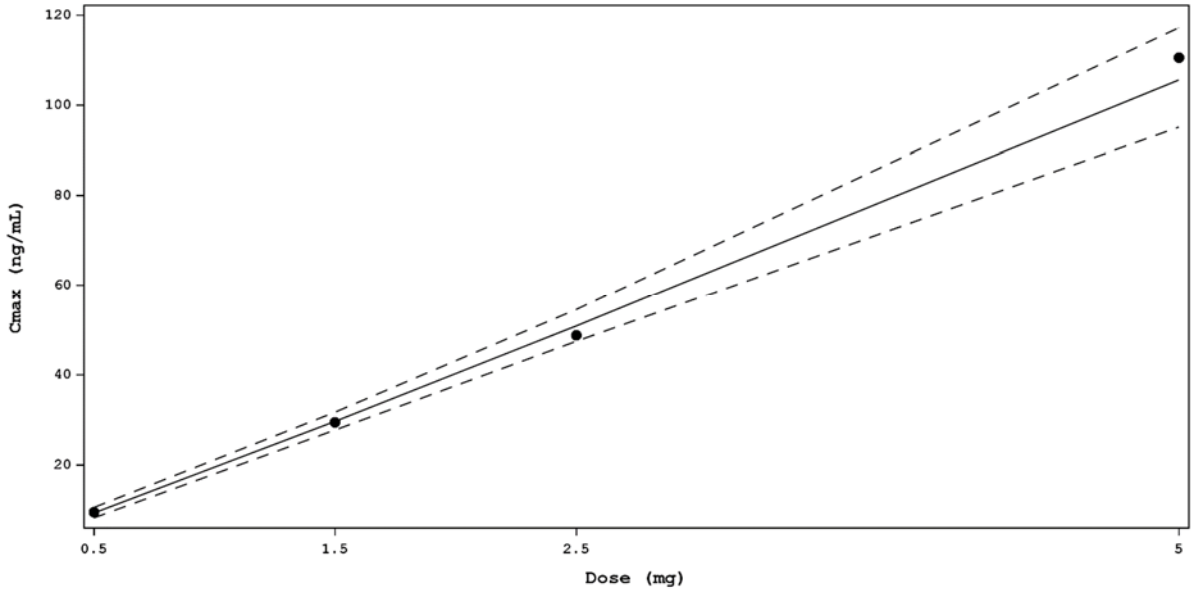


Lower limit of quantitation for CIN-107 = 0.05 ng/mL. Actual sampling times that were outside of the analysis sampling time window were excluded in the mean plot.
SD = standard deviation.
Source: Post-text Figure 14.2.1.1.5

At steady state, exposure was typically approximately 2- to 2.5-fold higher than after a single dose (mean R_{Cmax} values ranged from approximately 1.7 to 2.4 and mean R_{AUC} values ranged from 2 to 2.5 across treatment groups). Though the current study was not designed or powered to formally

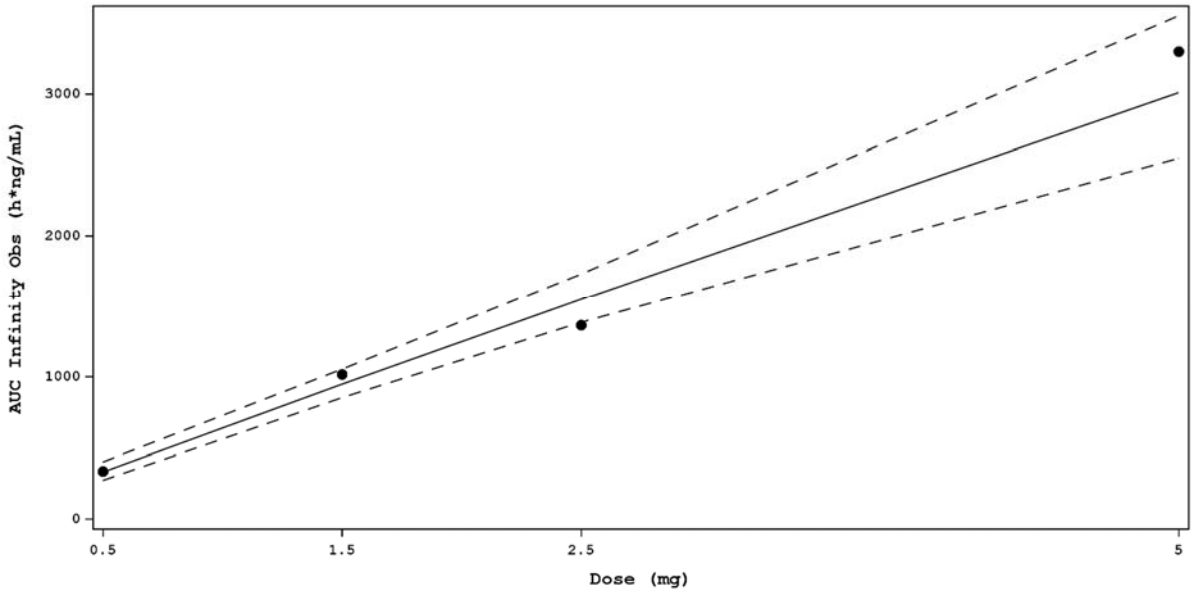
assess dose proportionality, the data were subjected to an exploratory dose proportionality assessment and CIN-107 is considered to be dose proportional over the dose range studied.

Figure S2. Plot of C_{max} Versus CIN-107 Dose (Day 10) – Pharmacokinetic Population



The solid line represents the predicted values. The dashed lines represent the 90% confidence intervals around the regression line. The black dots represent the geometric mean of the PK parameter.
C_{max} = maximum observed plasma concentration; PK = pharmacokinetic(s).
Source: Post-text Figure 14.2.1.1.17

Figure S3. Plot of $AUC_{0\text{-}inf}$ Versus CIN-107 Dose (Day 10) – Pharmacokinetic Population



The solid line represents the predicted values. The dashed lines represent the 90% confidence intervals around the regression line. The black dots represent the geometric mean of the PK parameter.
AUC = area under the plasma concentration-time curve; $AUC_{0\text{-}inf}$ = area under the plasma concentration-time curve from time 0 to infinity; Obs = observed; PK = pharmacokinetic(s).
Source: Post-text Figure 14.2.1.1.20

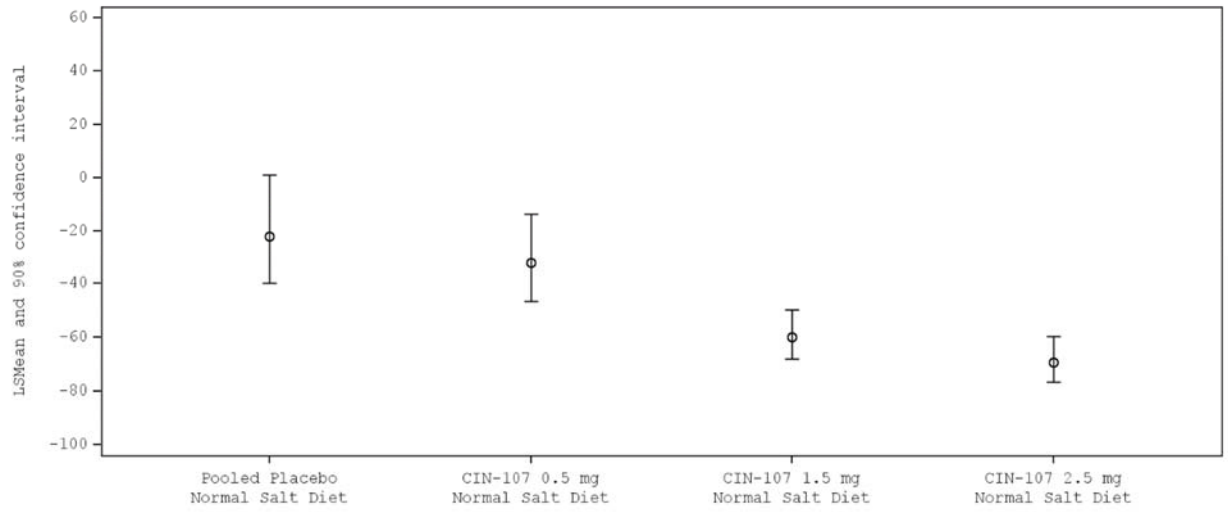
On average, approximately 7% (range of 6.3% to 10.8% across treatment groups) of the CIN-107 dose was recovered unchanged in the urine.

The primary metabolite of CIN-107 (CIN-107-M), which is not believed to contribute substantially to the effects of CIN-107, was formed slowly over time after the initial dose of CIN-107 (median T_{max} ranged from approximately 4 to 24 hours across treatment groups), with a steady-state (Day 10) median T_{max} observed within 4 hours (median T_{max} ranged from 3.5 to 4.0 hours across treatment groups). CIN-107-M levels increased with increasing dose. Plasma concentrations of CIN-107-M generally declined from peak slowly, with a long mean $t_{½}$ ranging from approximately 31 to 38 hours. At steady state, exposure (as assessed based on R_{Cmax} and R_{AUC} values) was approximately 2.4- to 3.5-fold higher than after a single dose. The metabolite CIN-107-M represents, on average, 8.0% to 11% of parent based on $C_{max,D10}$ and 10% to 22% of parent based on $AUC_{0\text{-}inf}$.

Pharmacodynamics:

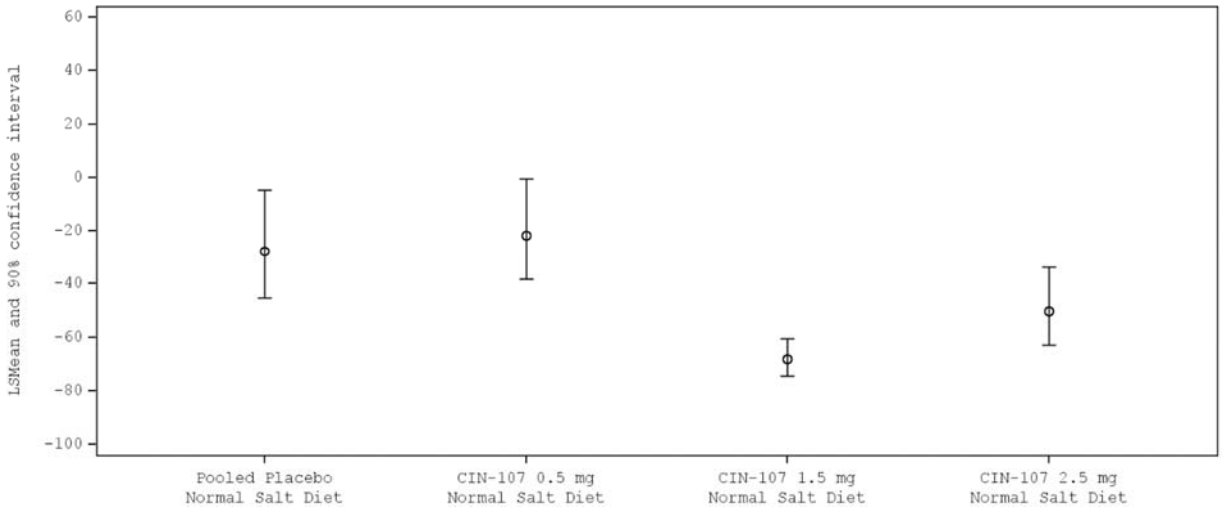
Marked inhibition of aldosterone synthesis was observed after the initial dose of CIN-107 and sustained throughout the 10-day dosing period under both normal salt diet and low salt diet conditions; however, the effect of 0.5 mg CIN-107 was similar to that of placebo.

Figure S4. Plot of Estimated Percent Change From Baseline in Plasma Aldosterone $AUC_{0\text{-}12h}$ by Treatment for Normal Salt Diet Treatment Groups on Day 1 – Pharmacodynamic Population (Excluding Outlier Subjects)



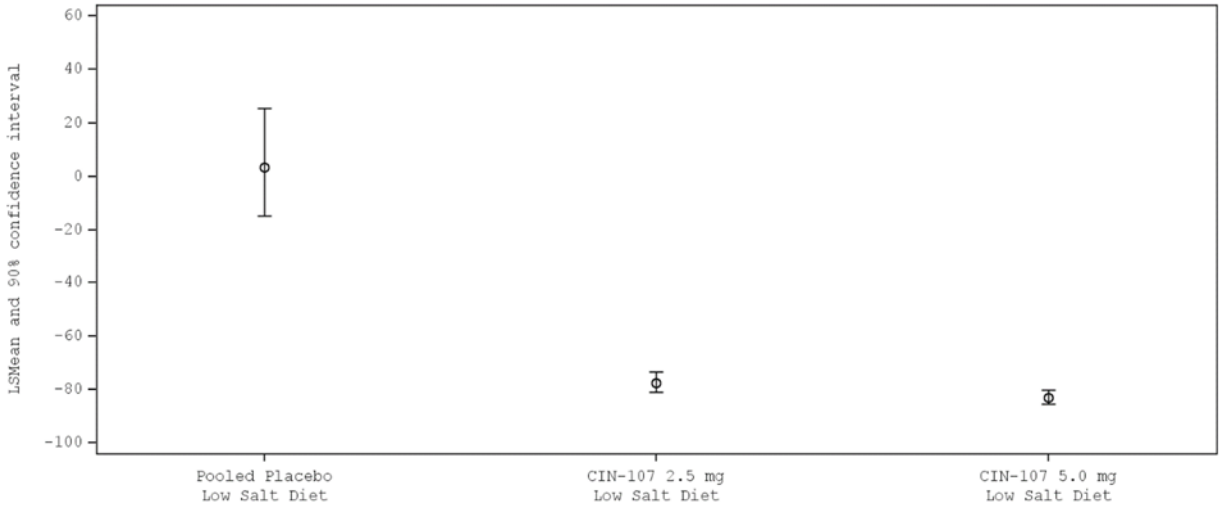
Measurements following a subject's early termination from study drug were excluded.
$AUC_{0\text{-}12h}$ = area under the pharmacodynamic effect-time curve from time 0 to 12 hours postdose; LS = least squares.
Source: Post-text Figure 14.2.3.1.19

Figure S5. Plot of Estimated Percent Change From Baseline in Plasma Aldosterone AUC_{0-12h} by Treatment for Normal Salt Diet Treatment Groups on Day 10 – Pharmacodynamic Population (Excluding Outlier Subjects)



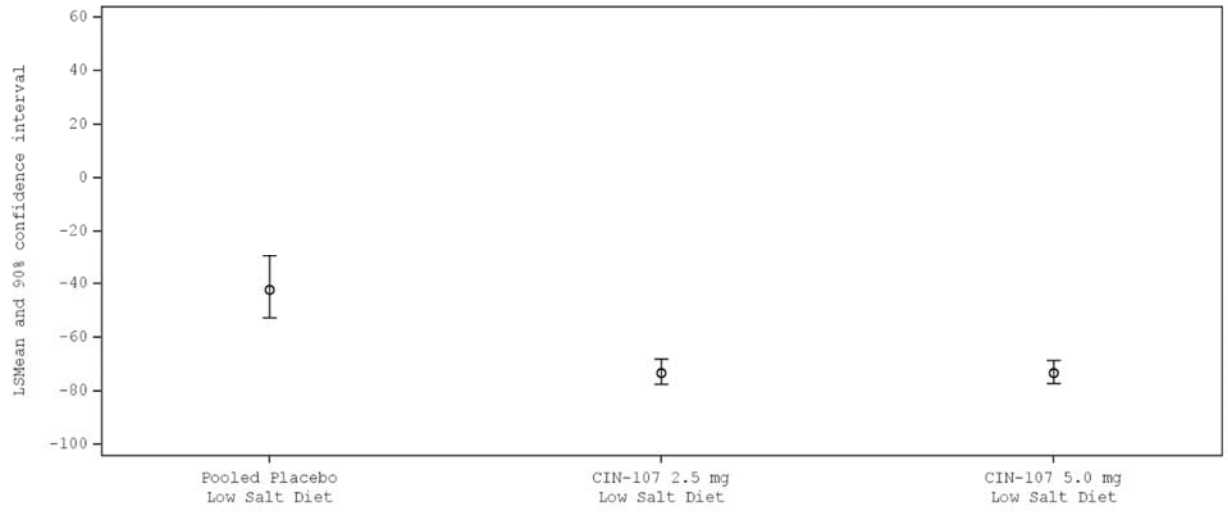
Measurements following a subject's early termination from study drug were excluded.
AUC_{0-12h} = area under the pharmacodynamic effect-time curve from time 0 to 12 hours postdose; LS = least squares.
Source: Post-text Figure 14.2.3.1.20

Figure S6. Plot of Estimated Percent Change From Baseline in Plasma Aldosterone AUC_{0-12h} by Treatment for Low Salt Diet Treatment Groups on Day 1 – Pharmacodynamic Population (Excluding Outlier Subjects)



Measurements following a subject's early termination from study drug were excluded.
AUC_{0-12h} = area under the pharmacodynamic effect-time curve from time 0 to 12 hours postdose; LS = least squares.
Source: Post-text Figure 14.2.3.1.21

Figure S7. Plot of Estimated Percent Change From Baseline in Plasma Aldosterone AUC_{0-12h} by Treatment for Low Salt Diet Treatment Groups on Day 10 – Pharmacodynamic Population (Excluding Outlier Subjects)

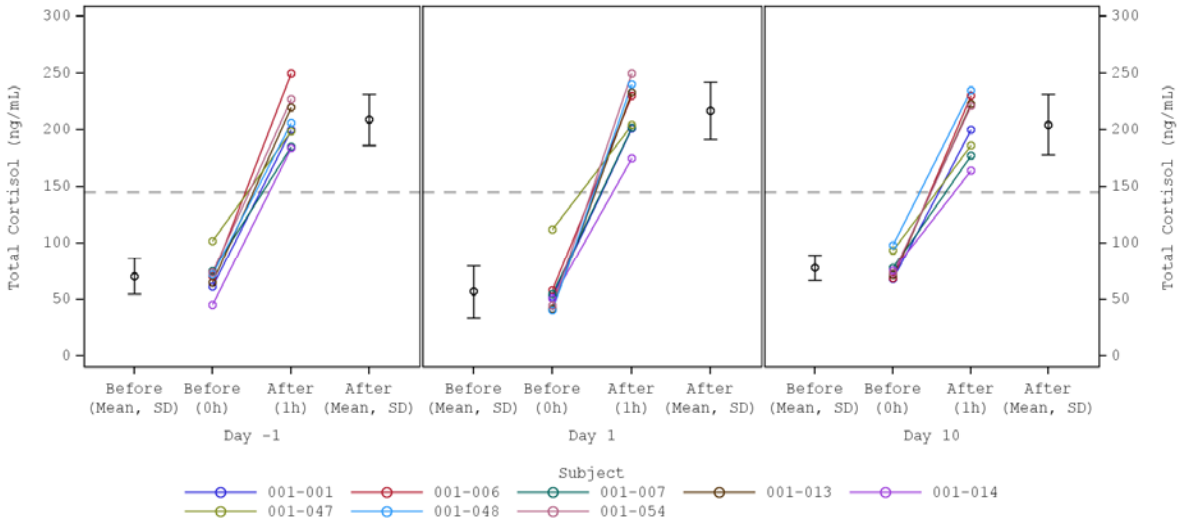


Measurements following a subject's early termination from study drug were excluded.
AUC_{0-12h} = area under the pharmacodynamic effect-time curve from time 0 to 12 hours postdose; LS = least squares.
Source: Post-text Figure 14.2.3.1.22

The effect of CIN-107 on aldosterone at doses ≥1.5 mg was observed both in the presence and absence of the Cortrosyn challenge, with an approximate 70% to 85% decrease in mean AUC_{0-12h} typically being observed as compared to baseline. Levels of the interim aldosterone precursors 18-hydroxycorticosterone and corticosterone demonstrated stepwise changes indicative of a progressive impact of cytochrome P450 11B2 inhibition on the pathway of aldosterone synthesis. Specifically, levels of 18-hydroxycorticosterone (the immediate precursor to aldosterone) were generally comparable to or decreased from baseline but to a lesser extent than observed decreases in aldosterone. Levels of corticosterone, which is further upstream from aldosterone, increased in an apparent dose-dependent manner. Finally, levels of 11-deoxycorticosterone, the initial aldosterone precursor, showed modest (approximately 2- to 3-fold) increases in predose values as compared to baseline, with changes being most apparent under low salt diet conditions in which subjects also underwent a cortisol stimulation test.

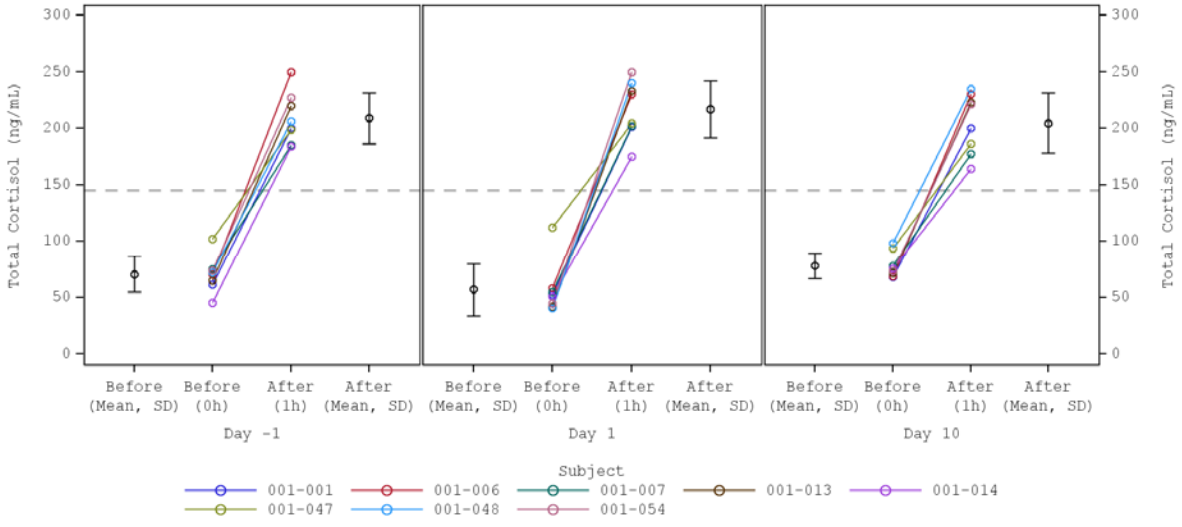
There were no apparent effects of CIN-107 on cortisol (total or free) or 11-deoxycortisol, including in the presence of Cortrosyn challenge (which occurred with the low salt diet treatment groups). Consistent with observations from the mean time course and AUC data for cortisol, CIN-107 had no apparent effect on response to the Cortrosyn challenge, with Day 1 and Day 10 responses in CIN-107-treated subjects being similar to their response at baseline and to the response in subjects receiving placebo.

Figure S8. Plot of Mean (±Standard Deviation) and Individual Plasma Total Cortisol Concentrations Relative to Cortrosyn Challenge for the 2.5 mg CIN-107 Low Salt Diet Treatment Group – Pharmacodynamic Population (Excluding Outlier Subjects)



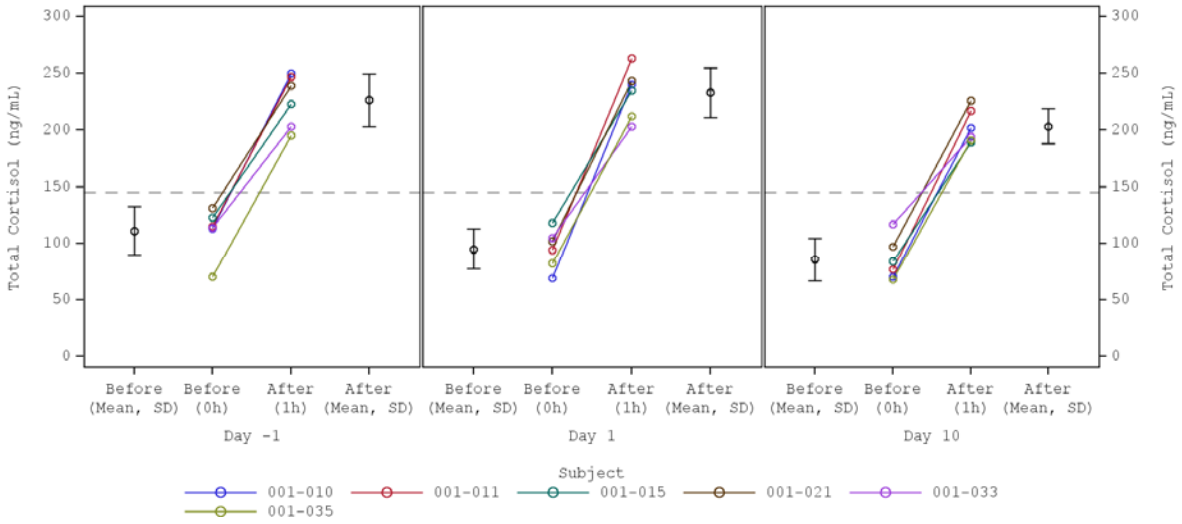
Measurements following a subject's early termination from study drug were excluded. The horizontal line represents the threshold for normal response (145 ng/mL) based on the LC-MS/MS method used for cortisol sample analysis at baseline and during the treatment period.
LC-MS/MS = liquid chromatography tandem mass spectrometry; SD = standard deviation squares.
Source: Post-text Figure 14.2.3.2.23

Figure S9. Plot of Mean (±Standard Deviation) and Individual Plasma Total Cortisol Concentrations Relative to Cortrosyn Challenge for the 5.0 mg CIN-107 Low Salt Diet Treatment Group – Pharmacodynamic Population (Excluding Outlier Subjects)



Measurements following a subject's early termination from study drug were excluded. The horizontal line represents the threshold for normal response (145 ng/mL) based on the LC-MS/MS method used for cortisol sample analysis at baseline and during the treatment period.
LC-MS/MS = liquid chromatography tandem mass spectrometry; SD = standard deviation squares.
Source: Post-text Figure 14.2.3.2.23

Figure S10. Plot of Mean (±Standard Deviation) and Individual Plasma Total Cortisol Concentrations Relative to Cortrosyn Challenge for the Pooled Placebo Low Salt Diet Treatment Group – Pharmacodynamic Population (Excluding Outlier Subjects)



Measurements following a subject's early termination from study drug were excluded. The horizontal line represents the threshold for normal response (145 ng/mL) based on the LC-MS/MS method used for cortisol sample analysis at baseline and during the treatment period.
LC-MS/MS = liquid chromatography tandem mass spectrometry; SD = standard deviation squares.
Source: Post-text Figure 14.2.3.2.23

The low salt diet conditions in Cohorts 1 and 2 resulted in an increase in ACTH. The increases were somewhat more pronounced in subjects receiving CIN-107 as compared to subjects receiving placebo. Following administration of CIN-107 under normal salt diet conditions, however, CIN-107 resulted in apparent dose-dependent decreases in ACTH.

There were no clinically significant changes in seated vital signs or dose-related trends. There was a slight decrease in seated BP for the overall CIN-107 treatment group compared to the overall pooled placebo group, although there was no clear dose dependency. Slight trends towards mild, drug-induced decreases in orthostatic BP and moderate increases in orthostatic heart rate were observed. As observed for the seated vital signs, these trends in orthostatic measurements were not consistently dose dependent. However, the most pronounced effects on heart rate were observed at the 5 mg CIN-107 dose level. Changes in BP when moving from supine to standing position were smaller on Day 10 as compared to baseline in all treatment groups (CIN-107 and placebo). However, the decreases were generally larger in subjects receiving CIN-107 as compared to subjects receiving placebo, particularly for systolic blood pressure (SBP). Likewise, increases in heart rate observed 1 minute after moving from a supine to a standing position were more pronounced in subjects receiving CIN-107 as compared to subjects receiving placebo. Although there were no clear and consistent dose-related trends, the most pronounced changes in 1-minute standing heart rate were typically noted at the 5 mg CIN-107 dose level.

Mild, dose-dependent decreases in plasma sodium levels and increases in plasma potassium levels were observed, as would be expected with a reduction in aldosterone levels. Urine sodium and potassium values corresponded to changes observed in plasma. Specifically, on Day 1 following the first dose of CIN-107, the sodium:potassium ratio was increased, with the sodium loss in urine

greater than the potassium retention. However, this effect had diminished by Day 10, suggesting that the balance between sodium excretion and potassium absorption was restored. The change in the sodium:potassium ratio appears to be mediated by a greater elimination of sodium in the urine on Day 1 as compared to sodium elimination in the urine on Day 10, as potassium appears not to change over the course of the 10-day treatment period.

There were mild increases in blood urea nitrogen, creatinine, and the blood urea nitrogen:creatinine ratio. A mild reduction in glomerular filtration rate (<15%) was also observed. The presence of increased blood urea nitrogen:creatinine ratio with reduced glomerular filtration rate suggests that CIN-107 is producing a mild diuretic effect.

Mean body weight and BMI decreased slightly from baseline during the treatment period in all groups, including placebo, under both low salt diet and normal salt diet conditions. However, the decrease in mean body weight and BMI in subjects receiving CIN-107 was more pronounced (-1.31 kg and -0.442 kg/m^2, respectively, in the overall CIN-107 group) as compared to that in subjects receiving placebo (-0.02 kg and -0.016 kg/m^2, respectively, in the pooled placebo group). There was no clear dose dependency in the observed decreases in the CIN-107 treatment groups. Values generally returned to baseline at the follow-up visit.

Safety:

Treatment with CIN-107 was safe and well tolerated. There were no deaths, SAEs, or discontinuations due to a TEAE, and there were no apparent increases in incidence or severity of AEs with increasing doses. The most common System Organ Class of TEAEs was nervous system disorders. All TEAEs were mild in severity except for 1, a moderate TEAE of ventricular tachycardia. Among subjects receiving CIN-107, 4 (9.5%) subjects experienced headache, 3 (7.1%) subjects experienced postural dizziness (preferred term of dizziness postural), and 2 (4.8%) subjects experienced dizziness. Generally, there were no clinically meaningful changes from baseline in laboratory parameters during the study; however, there were isolated abnormal sodium and potassium values, which were likely due to a combination of the protocol-specified dietary sodium requirements and the effects of CIN-107. There were no clinically meaningful changes in physical examination results or clinically significant changes in 12-lead ECG findings during the study, including no meaningful changes in QTcF.

Conclusions:

Administration of CIN-107 once daily for 10 days was safe and well tolerated by healthy subjects.

CIN-107 is rapidly absorbed and exhibits a long $t_{½}$ conducive to once daily dosing with predictable increases in exposure over the dose range studied. Accumulation of CIN-107 at steady-state is typically approximately 2- to 2.5-fold higher than after a single dose.

Treatment with CIN-107 resulted in marked, sustained, selective, and generally dose-dependent inhibition of aldosterone synthesis under both normal salt diet and low salt diet conditions without impact on cortisol or 11-deoxycortisol levels. The inhibition of aldosterone synthase associated with administration of CIN-107 produced expected changes in aldosterone precursors, with increases observed in corticosterone and 11-deoxycorticosterone while 18-hydroxycorticosterone remained comparable or decreased.

There were no clinically significant changes in BP with CIN-107 as compared to placebo. However, despite their normotensive status, there were slight reductions in SBP in subjects receiving CIN-107 as compared to subjects receiving placebo, particularly upon standing. Heart

rate increases upon standing were also greater following administration of CIN-107 versus placebo.

Consistent with what would be expected with an aldosterone synthase inhibitor, mild, dose-dependent decreases in plasma sodium levels and increases in plasma potassium levels were observed with corresponding changes in urine sodium and potassium levels. Mild increases in blood urea nitrogen:creatinine ratio and mild decreases in glomerular filtration rate were also observed following administration of CIN-107.

CIN-107 doses in the range of >0.5 mg to 5 mg or slightly higher may offer promise for treatment of hypertension in future studies.

Date of the Report: 13 August 2020