CLINICAL STUDY REPORT

A Randomized, Open Label, Crossover Study to Evaluate the Relative Bioavailability of a New Tablet Formulation of CIN-107 as Compared to Oral Solution and to Assess the Effect of Food on the CIN-107 Tablet Formulation in Healthy Subjects

Investigational Product: CIN-107
Indication Studied: Hypertension
Protocol Number: CIN-107-112
Development Phase: 1
Initiation Date: 11 March 2020
Completion Date: 29 April 2020

Sponsor:
CinCor Pharma, Inc.
5375 Medpace Way
Cincinnati, Ohio 45227
USA
[redacted]

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Date of Version: 13 August 2020

1 SIGNATURE PAGE

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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	Date
[redacted]	8/14/2020

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, Open Label, Crossover Study to Evaluate the Relative Bioavailability of a New Tablet Formulation of CIN-107 as Compared to Oral Solution and to Assess the Effect of Food on the CIN-107 Tablet Formulation in Healthy Subjects

Investigator: L. Vrishabhendra, MD

Study Site: 1 clinical site in the United States

Publication (reference): None

Study Period: Approximately 7 weeks

Initiation Date: 11 March 2020

Completion Date: 29 April 2020

Phase of Development: 1

Indication: Hypertension

Study Objectives:

The main objectives of this study were as follows:

- To assess the safety and tolerability of CIN-107 following single oral doses of CIN-107 tablet and oral solution;
- To determine the relative bioavailability of a tablet formulation of CIN-107 as compared to the oral solution; and
- To characterize the effect of food on the CIN-107 tablet.

The effects of single doses of CIN-107 on various measures associated with the renin-angiotensin-aldosterone system (RAAS) were also explored.

Methodology:

This was a randomized, open-label, crossover study primarily to assess the safety and tolerability of CIN-107 following single oral doses, to determine the relative bioavailability of a tablet formulation of CIN-107 as compared to the oral solution, and to characterize the effect of food on the CIN-107 tablet. Up to 15 subjects were planned to be enrolled in the study with the intent that 12 subjects would complete the treatment period. Subjects received each of the following treatments once during the study in a randomized crossover fashion:

- Treatment A: CIN-107 5 mg oral solution in a fasted state;
- Treatment B: CIN-107 5 mg tablet in a fasted state; and
- Treatment C: CIN-107 5 mg tablet in a fed state (standardized high fat meal).

For each subject, the study consisted of the following:

- A screening period of up to 28 days;
- 3 treatment periods, each consisting of a single dose of study drug followed by 5 days of pharmacokinetic (PK) sampling; and
- A follow-up phone call 3 days (±1 day) after discharge from the clinical unit.

There was a minimum 7-day washout between administration of study drug in each period. Subjects remained in the clinical unit from check-in on the day prior to dosing in treatment period 1 through completion of treatment period 3.

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 adverse events (AEs).

Duration of Treatment:

For each subject, study participation lasted for up to approximately 7 weeks (including screening).

Number of Subjects:

Planned: 15 subjects planned

Screened: 74 subjects screened

Randomized: 14 subjects randomized

Completed: 14 subjects completed

Discontinued: No 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, electrocardiogram (ECG), vital signs (seated and orthostatic), and routine laboratory tests (blood chemistry, hematology, coagulation, and urinalysis); had a body mass index between 18 and 30 kg/m^2, inclusive; and who were nonsmokers.

Investigational Product and Comparator Information: Study subjects were dosed with either CIN-107 oral drinking solution (CIN-107 Good Manufacturing Practice drug substance [anhydrate] lot number 208-027-3779-01) or CIN-107 tablet (bottled lot number 1912321A; bulk lot number 1912321) orally. The dose of CIN-107 administered was 5 mg.

Criteria for Evaluation:

Pharmacokinetics:

PK blood samples were collected and analyzed to measure the plasma concentrations of CIN-107 and its primary metabolite (CIN-107-M) using validated liquid chromatography mass spectrometry methods. The following plasma PK parameters were determined for CIN-107 and its primary metabolite (CIN-107-M) using non-compartmental methods as appropriate:

- Maximum plasma concentration (C_{max});
- Time to C_{max} (T_{max});

- Area under the plasma concentration versus time curve (AUC) from time 0 to the time of last quantifiable plasma concentration (AUC_{0-t});
- AUC from time 0 to infinity (AUC_{0-inf});
- Percent of AUC extrapolated;
- Terminal phase elimination half-life ($t_{1/2}$);
- Apparent terminal elimination rate constant;
- Apparent plasma clearance (CIN-107 only); and
- Apparent volume of distribution (CIN-107 only).

Pharmacodynamics:

Pharmacodynamic (PD) samples to support an exploratory assessment of the effect of CIN-107 on various measures associated with the RAAS including, but not limited to, angiotensin-converting enzyme (ACE), ACE2, angiotensin 1, angiotensin 2, and angiotensin 1-7, were collected.

Safety:

The safety of CIN-107 was assessed throughout the study based on AEs, physical examinations, ECGs, weight measurements, vital sign assessments (seated and orthostatic), and clinical laboratory evaluations.

Statistical Methods:

General considerations:

Categorical data were generally summarized with counts and percentages of subjects. The denominator used for the percentage calculation was clearly defined. Continuous data were generally summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, coefficient of variability (CV)%, minimum, and maximum. Geometric mean (GM), and GM CV% were also provided for PK parameters. The value of 0 was excluded from the calculation of GM and GM CV%.

Baseline was defined as the last measurement prior to the first dose of study drug unless otherwise specified.

Analysis populations:

The Safety Population consisted of all randomized subjects who received at least 1 dose of CIN-107.

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

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

Pharmacokinetic analyses:

Individual plasma concentrations of CIN-107 and any measured metabolite were summarized descriptively by treatment at each nominal time point for the PK Population. Individual plasma concentrations of CIN-107 and any measured metabolite were also listed for the PK Population.

Individual concentrations of CIN-107 and any measured metabolite were plotted by treatment 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, when available.

PK parameters were summarized by treatment using descriptive statistics for the PK Evaluable Population.

The relative bioavailability of the CIN-107 tablet (5 mg) to the CIN-107 oral solution (5 mg) was calculated. An analysis of variance (ANOVA) model using SAS Proc GLM was run on the natural logarithm (ln)-transformed PK parameters (C_{max}, AUC_{0-t}, AUC_{0-inf}) of the 2 treatments (Treatment B versus Treatment A). The ANOVA model included treatment, sequence, and period as fixed effects and subjects nested within sequence as a random effect. The estimates were back-transformed into original scale. The point estimates for ratios of central values (Treatment B versus Treatment A) and the corresponding 90% confidence intervals (CIs) were provided. These analyses were performed on the PK Evaluable Population. A subject must have had a calculable PK parameter for both treatments in order to be included in the analysis for that parameter.

An ANOVA model using SAS Proc GLM was performed on the ln-transformed PK parameters (C_{max}, AUC_{0-t}, AUC_{0-inf}) of the 2 treatments (fed state versus fasted state) including terms for sequence, dose, and period as fixed effects and subjects nested within a sequence as a random effect. The estimates were back-transformed into original scale. The point estimates for ratios of central values (Treatment C versus Treatment B) and the corresponding 90% CIs were provided. These analyses were performed on the PK Evaluable Population. A subject must have had a calculable PK parameter for both treatments in order to be included in the analysis for that parameter.

Pharmacodynamic analyses:

PD data analyses and results will be reported separately.

Safety analyses:

Safety data analyses were conducted on the Safety Population. Statistical analysis of the safety data was limited to descriptive summaries. AEs were coded and classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (Version 22.1).

An overview of AEs was provided by treatment. TEAEs were summarized by treatment at onset and overall. Separate listings were prepared for deaths, SAEs, and AEs leading to study withdrawal.

For chemistry, hematology, coagulation, and urinalysis clinical laboratory tests, all data were listed for individual subjects and values outside the reference ranges were flagged if appropriate. For each parameter, observed data and change from baseline were summarized descriptively at each scheduled time point by treatment. Shift tables describing out-of-normal range shifts were provided.

Vital signs (seated and orthostatic) data were listed for individual subjects. Observed data and change from baseline for each vital sign parameter were summarized descriptively at each scheduled time point by treatment.

Height and weight data were listed for individual subjects.

ECG results were listed for individual subjects. Observed data and change from baseline for each ECG parameter were summarized descriptively at each scheduled time point by treatment.

Physical examination data were listed for the Safety Population.

Summary of Results:

Pharmacokinetic results:

The geometric least-squares (LS) mean ratios (90% CI) of Treatment B (5 mg tablet in a fasted state) versus Treatment A (5 mg oral solution in a fasted state) for plasma CIN-107 C_{max}, AUC_{0-t}, and AUC_{0-inf} were 98.8 (93.10, 104.82), 97.8 (94.81, 100.91), and 97.8 (94.71, 101.06), respectively. The 90% CIs of all 3 PK parameters were wholly contained within the range of 80.00% to 125.00%, indicating there was no difference in the relative bioavailability of CIN-107 5 mg tablet as compared to CIN-107 5 mg oral solution, in a fasted state. Median T_{max} was comparable as a solution and tablet in a fasted state (2.5 and 3 hours postdose, respectively).

The geometric LS mean ratios (90% CI) of Treatment C (5 mg tablet in a fed state) versus Treatment B (5 mg tablet in a fasted state) for plasma CIN-107 C_{max}, AUC_{0-t}, and AUC_{0-inf} were 91.1 (85.28, 97.36), 97.8 (94.40, 101.35), and 98.1 (94.22, 102.07), respectively. The 90% CIs of all 3 PK parameters were wholly contained within the range of 80.00% to 125.00%, indicating that food did not affect the extent of absorption of CIN-107 5 mg tablet. Median T_{max} occurred 1 hour later (at 4 hours postdose) after administration of CIN-107 5 mg tablet in the fed state as compared to the fasted state (at 3 hours postdose).

The primary metabolite formed over time for each formulation tested and exhibited a long $t_{1/2}$. Formal statistical comparisons of CIN-107-M were not performed. However, the PK parameters of the primary metabolite were generally comparable across treatments.

Safety results:

There were no deaths, treatment-emergent SAEs, or TEAEs that led to withdrawal from the study or study drug.

In total, 3 (21.4%) subjects experienced an AE. Of those, 2 (14.3%) subjects experienced a TEAE: 1 (7.1%) subject following administration of the CIN-107 5 mg oral solution in a fasted state (skin abrasion) and 1 (7.1%) subject following administration of the CIN-107 5 mg tablet in a fasted state (postural dizziness [preferred term of dizziness postural]). Both TEAEs were mild in severity. The TEAE of postural dizziness was considered related to study drug by the Investigator.

No laboratory, vital signs, or ECG abnormalities were reported as SAEs or TEAEs that led to withdrawal from the study or study drug.

Conclusions:

Single doses of CIN-107 5 mg were well tolerated by healthy subjects as an oral solution (fasted state) and as a tablet (fasted and fed conditions).

Systemic exposure (as assessed by C_{max}, AUC_{0-t}, and AUC_{0-inf}) was equivalent following administration of the CIN-107 tablet planned for future use and the CIN-107 oral solution used in prior studies. As such, the PK and PD findings from the prior studies are considered relevant to the tablet formulation to be used in the future.

Food does not affect the extent of absorption of CIN-107 (as assessed by C_{max}, AUC_{0-t}, and AUC_{0-inf}) but does have a slight impact on the rate of absorption, which is characterized by a slight lag in early exposure and a delay of approximately 1 hour in T_{max}. Given that this drug is targeted to be used in a chronic manner where steady-state PK has been attained, this difference in T_{max} is not considered to be clinically meaningful. Therefore, CIN-107 may be administered with or without food in future studies.

Date of the Report: 13 August 2020