CLINICAL STUDY REPORT

A Phase 1, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Pharmacokinetics of CIN-107 in Subjects With Varying Degrees of Renal Function

Investigational Product: CIN-107
Indication Studied: Hypertension
Protocol Number: CIN-107-113
Development Phase: 1
Initiation Date: 12 January 2021
Completion Date: 30 April 2021

Sponsor:
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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.

[redacted]

04-Nov-2021

[redacted]

CinCor Pharma, Inc.

2 SYNOPSIS

Name of Sponsor: CinCor Pharma, Inc.

Name of Finished Product: CIN-107

Name of Active Ingredient: CIN-107

Title of Study: A Phase 1, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Pharmacokinetics of CIN-107 in Subjects With Varying Degrees of Renal Function

Investigators: T. Marbury, MD and J. Navarro, MD

Study Sites: 2 clinical sites in the United States

Publication (reference): None

Study Period: Approximately 15 weeks

Initiation Date: 12 January 2021

Completion Date: 30 April 2021

Phase of Development: 1

Indication: Hypertension

Study Objectives:

The primary objectives were the following:

- Assess the safety and tolerability of a single oral dose of CIN-107 administered to subjects with varying degrees of renal function; and
- Characterize the pharmacokinetics (PK) of a single oral dose of CIN-107 administered to subjects with varying degrees of renal function.

Methodology:

This was a Phase 1, open-label, parallel-group study in subjects with varying degrees of renal function to assess the safety, tolerability, and PK of a single 10 mg oral dose of CIN-107.

Subjects completing the study were enrolled for a period of up to approximately 38 days comprising a screening period of up to 28 days; a treatment period consisting of admission to the clinical site the day before study drug dosing, a single 10 mg CIN-107 dosing followed by 7 days of PK sampling; and a follow-up phone call 3 days (±1 day) after discharge from the clinical site.

Up to 12 subjects were planned to be enrolled into each of the following renal function groups defined based on estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration equation and further individualized based on calculated body surface area (BSA) to express in mL/min:

- Control (normal renal function or mild renal impairment): eGFR ≥60 mL/min;
- Moderate to severe renal impairment: eGFR 15 to 59 mL/min; and

- Kidney failure: eGFR <15 mL/min, including:
  - Subjects not on dialysis; and
  - Subjects on dialysis, with study drug administration on a non-dialysis day.

Enrollment in a given group ceased when 10 subjects in that group completed the treatment period (with adequate PK sampling to meet study objectives). Every effort was made to ensure that the continuum of renal function was represented within each group and that subjects in each group were comparable in terms of age, body mass index (BMI), race, gender, and smoking status. The following target criteria were provided for the protocol-specified matching between the renally impaired subjects and the control group:

- Age: approximately ±10 years based on average;
- Gender: comparable number of males and females;
- Race: comparable number of subjects who fell into the following categories:
  - "Black;"
  - "White;" or
  - "Other."
- BMI: approximately ±5 kg/m^2 of the average BMI; and
- Smoking status: no more than 70% smokers.

  Note: Deviation from these criteria may have been permitted with prior Sponsor approval.

In order to accomplish this efficiently, a minimum of 1 subject was planned to be enrolled into each of the renal impairment groups before each subject in the control group was enrolled, unless prior written Sponsor approval to deviate from this sequence was obtained.

Subjects remained in the clinic from Day -1 (check-in) on the day prior to dosing through completion of the treatment period.

Safety was assessed throughout the study based on adverse events (AEs), clinical laboratory evaluations, vital sign assessments (seated and orthostatic), electrocardiograms (ECGs), physical examinations, and weight measurements.

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), or clinically significant AEs that required follow-up laboratories and review.

Duration of Treatment:

There was one 8-day in-treatment period (from check-in through completion of treatment), consisting of a single dose of CIN-107.

Number of Subjects:

Planned: 30 subjects

Screened: 43 subjects

Enrolled: 33 subjects

Completed: 32 subjects

Discontinued: 1 subject

Diagnosis and Main Criteria for Inclusion:

The population for this study included subjects between the ages of 18 and 80 years, inclusive; who had a BMI between 18 and 40 kg/m^2, inclusive; and were in stable health based on medical and psychiatric history, physical examination, ECG, vital signs (seated and orthostatic), and routine laboratory tests (chemistry, hematology, coagulation, and urinalysis). Underlying medical conditions consistent with the population under study were acceptable if the subject's condition was considered stable by the Investigator. Subjects included those who did not use nicotine-containing products at all or smoked <10 cigarettes/day (approximately <half pack/day). For renally impaired subjects, their renal status must have been stable for a minimum of 3 months prior to screening. Additionally, subjects were not permitted to have had a history of prior or planned organ transplantation within 6 months of screening, history of clinically significant arrhythmias, or prolonged QTcF.

Investigational Product and Comparator Information:

Each enrolled subject received a single 10 mg dose of CIN-107 orally. CIN-107 tablets (lot number 2009264) were provided at a strength of 5 mg and packaged in high-density polyethylene bottles. No reference/placebo formulation was planned for this study.

Criteria for Evaluation:

Pharmacokinetics

The following PK parameters were determined for CIN-107, its primary metabolite (CIN-107-M), and any other measured metabolites using plasma concentration data:

- Maximum plasma concentration (C_{max});
- Time to C_{max};
- Area under the curve from time 0 to the time of last quantifiable plasma concentration ($AUC_{[0\text{-}last]}$);
- Area under the curve from time 0 to time infinity ($AUC_{[0\text{-}inf]}$);
- Percent of area under the concentration-time curve from time 0 to infinity extrapolated ($AUC_{\%extrap}$);
- Terminal phase elimination half-life ($t_{½}$);
- Apparent plasma clearance (CL/F) (for CIN-107 only); and
- Apparent volume of distribution (for CIN-107 only).

The following PK parameters were calculated using the urine concentrations of CIN-107 and its primary metabolite (CIN-107-M):

- The cumulative amount of CIN-107 and CIN-107-M excreted in the urine (Ae);
- Renal clearance (CL_R) (calculated as Ae/area under the curve [AUC]) of CIN-107 and CIN-107-M; and
- The fraction of the dose excreted renally (for CIN-107 only).

Safety

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

Statistical Methods:

General considerations

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

Categorical data were generally summarized with counts and percentages of subjects. The denominator used for the percentage calculation was clearly defined. The quantitative safety variables were generally summarized with descriptive statistics including n (ie, number of non-missing values), arithmetic mean, standard deviation (SD), median, minimum, and maximum, as well as for the difference from baseline, when appropriate.

Geometric mean (GM) and GM coefficient of variation (CV) were also provided for PK concentrations and parameters. The subjects with a 0 value were excluded from the calculation of GM and GM CV.

Analysis populations

The Safety Population included all subjects who received CIN-107.

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

The PK Evaluable Population included subjects who received CIN-107 and had sufficient plasma or urine concentration data to characterize at least 1 PK parameter for CIN-107 or any measured metabolite. For concentration data, sufficient was defined as at least 3 measurable post-dose concentrations in the PK profile.

Pharmacokinetic concentration

Individual plasma and urine concentrations of CIN-107 and CIN-107-M were summarized by renal function group at each nominal time point for the PK Population descriptively. Individual plasma and urine concentrations were also listed for the PK Population.

Individual plasma concentration was plotted by renal function group on linear and semi-logarithmic scales against actual sampling time points relative to dosing time. Mean (±SD) concentration was plotted on linear and semi-logarithmic scales against nominal time points by renal function group, when available. Lower limit of quantification was plotted as a reference line in both instances.

Cumulative amount of CIN-107 and metabolite(s) excreted in the urine over time was plotted (individual and mean per renal function group).

Pharmacokinetic parameters

The plasma and urine PK parameters of CIN-107 and CIN-107-M were listed and summarized descriptively by renal function group for the PK Evaluable Population. Actual collection times were used in PK parameter calculations. The Linear-Log Trapezoidal method (equivalent to the Linear Up/Log Down option in WinNonlin) was used in the computation of all AUC values. In order to estimate the apparent first-order terminal elimination constant (λz), linear regression of concentration in logarithm scale versus time was performed using at least 3 data points. Uniform weighting was selected to perform the regression analysis to estimate λz.

The constant λz and its derived parameters were listed but excluded from statistical analysis if one of the following occurred:

- The adjusted regression coefficient (R^2) was less than 0.8; or
- The $AUC_{\%extrap}$ exceeded 20%.

These λz values and λz-derived parameters were listed but excluded from statistical analysis.

Relationship between pharmacokinetic parameters and renal function category

Pair-wise comparisons for geometric least squares means of PK parameters in subjects with each renal impairment category versus matching controls were performed as follows for the PK Evaluable Population: moderate to severe renal impairment versus control and kidney failure versus control. Comparisons were performed for C_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$, $t_{½}$, CL/F, and CL_R (when possible) of CIN-107 and CIN-107-M. Logarithmic-transformation of PK parameters were performed prior to analysis. A statistical comparison of logarithmic-transformed primary PK parameters between groups was based on an analysis of variance model. A contrast statement was utilized for pair-wise comparisons. The difference (as ratio of the 2 groups) in least squares means between comparison groups and the associated 95% confidence intervals were calculated.

Within each renal function group, the possible effects of demographic and baseline conditions were explored. Scatter plots of C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ for CIN-107 by renal function group are presented for the following: smoking status, age, baseline BMI, gender, and race.

Safety analyses

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

Safety data were summarized for the Safety Population by renal function group and point of time of collection, when appropriate.

All AEs were coded to system organ class and preferred term by using the Medical Dictionary for Regulatory Activities (Version 23.1). TEAEs were defined as AEs that start after the first dose of study drug. An overview of AEs was provided, including counts and percentages of subjects (and event counts for any TEAEs) with the following:

- Subjects with any AEs;
- Subjects with any SAEs;

- Subjects with any TEAEs (overall and by maximum severity);
- Subjects with any study drug-related TEAEs (overall and by maximum severity);
- Subjects with any serious treatment-emergent adverse events (TESAEs);
- Subjects with any study drug-related TESAEs;
- Subjects with any adverse events of special interest (AESIs); and
- Subjects with any AEs leading to death.

Listings were presented specifically for SAEs and AESIs, as well as all AEs.

Continuous safety laboratory data (values and change from baseline) were summarized by renal function group at baseline and at each post-baseline time point. Categorical data were summarized using frequency counts and percentages by renal function group at baseline and post-baseline scheduled visits. Shift tables describing post-baseline out-of-normal range shifts were provided for continuous laboratory evaluations. Safety laboratory data, serology evaluations, pregnancy test evaluations, and urine drug screen and breath alcohol test evaluations were listed.

Vital signs values, including change from baseline, were summarized by renal function group at baseline and post-baseline scheduled visits were listed.

ECG parameters were summarized by renal function group at baseline and at each post-baseline visit. All ECG data were also listed.

All complete and limited physical examination findings, weight and height data, and BMI and BSA calculations were listed.

Summary of Results:

Pharmacokinetics

The plasma concentration-time curves of CIN-107 in each renal impairment group were qualitatively similar to the control group, with systemic exposures to CIN-107 generally as expected based on prior studies in healthy subjects.

There was a lack of noteworthy effect of renal impairment on the PK of CIN-107 based on pair-wise comparisons, and no strong linear or nonlinear relationships between eGFR and PK parameters were observed. Additionally, there was no meaningful impact of demographic characteristics on PK parameters.

Findings for CIN-107-M, the primary metabolite of CIN-107, were similar to those for the parent compound, with no clinically meaningful differences observed across renal function groups.

The percent of the dose excreted renally for CIN-107 was approximately 12% in the control group and the moderate to severe renal impairment group. Inadequate urine production in the kidney failure group resulted in negligible renal excretion of CIN-107 and CIN-107-M in these subjects.

Safety

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). Overall, there were no deaths, 1 (3.0%) subject experienced an SAE, and no subjects discontinued due to a TEAE. Overall, 2 (6.1%) subjects experienced a total of

3 TEAEs: 1 (10.0%) subject in the control group experienced a TEAE of mild diarrhoea following administration of CIN-107 that was considered related to the study drug; no subjects in the moderate to severe renal impairment group experienced a TEAE; and 1 (8.3%) subject in the kidney failure group experienced 2 TEAEs of moderate tremor and severe metabolic encephalopathy (recorded as an SAE) following administration of CIN-107 that were considered not related to the study drug. The SAE was thought to be secondary to the concomitant medications. As such, there was no apparent increase in incidence or severity of AEs with decreased renal function. There were no AEs related to laboratory parameters or trends or clinically meaningful changes in laboratory parameters. There were no AEs related to or clinically significant changes observed in vital signs, physical examinations, or 12-lead ECGs.

Conclusions:

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 CL_R in individuals with impaired renal function. Dose adjustment of CIN-107 based on renal function is not considered necessary.

Date of the Report: 14 October 2021