CLINICAL STUDY REPORT

A Randomized, Open-Label, Two-Period, Crossover Study to Evaluate the Effect of CIN-107 on the Pharmacokinetics of the MATE Substrate, Metformin, in Healthy Subjects

Investigational Product: CIN-107
Indication Studied: Not applicable
Protocol Number: CIN-107-114
Development Phase: 1
Initiation Date: 28 October 2020
Completion Date: 12 December 2020

Sponsor:
CinCor Pharma, Inc.
5375 Medpace Way
Cincinnati, OH 45227
United States
Telephone: [redacted]
Fax: [redacted]

Version Number: 1.0
Date of Version: 22 April 2021

1 SIGNATURE PAGE

A Randomized, Open-Label, Two-Period, Crossover Study to Evaluate the Effect of CIN-107 on the Pharmacokinetics of the MATE Substrate, Metformin, 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

[redacted]

CinCor Pharma, Inc.

Date

27-Apr-2021

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, Two-Period, Crossover Study to Evaluate the Effect of CIN-107 on the Pharmacokinetics of the MATE Substrate, Metformin, in Healthy Subjects

Investigator: Leela Vrishabhendra, MD

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

Publication (reference): None

Study Period: Approximately 6 weeks

Initiation Date: 28 October 2020

Completion Date: 12 December 2020

Phase of Development: 1

Indication: Not applicable

Study Objectives:

The objectives of this study were as follows:

- To assess the impact of CIN-107 on the pharmacokinetics (PK) of immediate-release metformin; and
- To assess the safety and tolerability of coadministration of CIN-107 and metformin as compared to that of metformin alone.

Methodology:

This was a randomized, open-label, two-period, crossover, Phase 1 study to assess the impact of CIN-107 on the PK of metformin and the safety and tolerability of coadministration of CIN-107 and metformin as compared to that of metformin alone. Up to 32 subjects were to be enrolled in the study with the intent that a minimum of 24 subjects would complete both treatment periods. Subjects were randomly assigned to 1 of 2 treatment sequences (AB or BA) below on Day 1 of Treatment Period 1:

- Treatment A: a single 1000 mg dose of immediate-release metformin; and
- Treatment B: a single 1000 mg dose of immediate-release metformin coadministered with a 10 mg dose of CIN-107.

  Note: Metformin was administered 2 hours after a single 10 mg dose of CIN-107.

Subjects were administered study drug on the morning of Day 1 of each treatment period.

For each subject, the study consisted of the following:

- A screening period of up to 26 days;
- Two 4-day inpatient periods (from Check-In through completion of treatment), each consisting of a single dose of study drug (metformin alone or coadministered with CIN-107) followed by 3 days of PK sampling; and
- A follow-up phone call 3 days (±1 day) after completion of Treatment Period 2.

There was a minimum 10-day washout between administration of study drug in each treatment period. Subjects were confined from Check-In on the day prior to dosing in each treatment period through collection of the final PK sample in each treatment period.

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

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

Duration of Treatment:

There were two 4-day inpatient periods (from Check-In through the completion of treatment), each consisting of a single dose of study drug (metformin alone or coadministered with CIN-107). There was a minimum 10-day washout between administration of study drug in each treatment period.

Number of Subjects:

Planned: up to 32 subjects planned

Screened: 51 subjects screened

Randomized: 27 subjects randomized

Completed: 26 subjects completed

Discontinued: 1 subject 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 had a body mass index (BMI) between 18 and 30 kg/m^2, inclusive; were in good health based on medical/surgical and psychiatric history, physical examination, ECG, vital signs (seated and orthostatic), and routine laboratory tests (serum chemistry, hematology, and urinalysis); had normal renal function; and were nonsmokers.

Investigational Product and Comparator Information:

CIN-107 [redacted] was supplied as 5 mg oral tablets. Immediate-release metformin [redacted] was obtained from a commercial supplier as 500 mg oral tablets.

Criteria for Evaluation:

Pharmacokinetics:

The following plasma PK parameters were determined for CIN-107 and its primary metabolite (CIN-107-M):

- Maximum observed plasma concentration (C_{max}), determined directly from the concentration-time profile;
- Time to C_{max} (T_{max}), defined as the first time point with the maximum value, if the maximum value occurred at more than 1 time point;
- Apparent first-order terminal elimination rate constant calculated from a semi-logarithmic plot of the plasma concentration versus time curve (λ_z), calculated by linear least squares (LS) regression analysis using points in the terminal logarithmic-linear phase;
- Area under the concentration-time curve (AUC) from time 0 to 24 hours (AUC_{0-24});
- AUC from time 0 to 72 hours;
- AUC from time 0 to infinity (AUC_{0-inf}) (CIN-107 only), calculated as AUC from time 0 to the time of the last quantifiable plasma concentration (AUC_{0-t}) + last quantifiable plasma concentration (C_{last})/λ_z; and
- Percent of AUC_{0-inf} extrapolated ($AUC_{\%extrap}$) (CIN-107 only), represented as $(1 - AUC_{0-t}/AUC_{0-inf}) \times 100$.

The following plasma PK parameters were determined for metformin:

- C_{max}, determined directly from the concentration-time profile;
- T_{max}, defined as the first time point with the maximum value, if the maximum value occurred at more than 1 time point;
- λ_z, calculated by linear LS regression analysis using points in the terminal logarithmic-linear phase;
- AUC_{0-24};
- AUC_{0-t};
- AUC_{0-inf}, calculated as $(AUC_{0-t} + C_{last}/\lambda_z)$;
- $AUC_{\%extrap}$, represented as $(1 - AUC_{0-t}/AUC_{0-inf}) \times 100$; and
- Terminal phase elimination half-life, calculated as $\ln(2)/\lambda_z$.

The following urine PK parameters were determined for metformin:

- Cumulative amount of metformin excreted in the urine (cumulative amount of drug excreted in the urine [Ae]);
- Renal clearance, calculated as Ae/AUC; and
- Fraction of the dose excreted renally, calculated as 100 × Ae/Dose.

Safety:

The following safety assessments were performed:

- AEs and SAEs;
- Clinical laboratory test assessments;
- Vital signs including heart rate, blood pressure (BP) (including orthostatic BP when indicated), respiration rate, and temperature;
- 12-lead ECGs;
- Physical examinations; and
- Height, weight, and BMI.

Statistical Methods:

General considerations:

Continuous data were summarized using descriptive statistics (number of subjects, mean, standard deviation, percent coefficient of variation [CV], median, minimum, and maximum). Geometric mean and geometric mean CV were also provided for the summary of concentrations and PK parameters. Subjects with a 0 value were excluded from the calculation of geometric mean and geometric mean CV. Categorical data were summarized using frequency counts and percentages of subjects. The denominators used for the percentage calculations were clearly defined. Summaries presented by treatment sequence were also presented by treatment group, if necessary, due to early withdrawals from the study.

Analysis populations:

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

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

The PK Evaluable Population included all subjects who received any study drug (CIN-107 or metformin) and had sufficient plasma concentration data to characterize at least 1 PK parameter of CIN-107, metformin, or any measured metabolite.

Pharmacokinetic analyses:

Plasma concentrations of CIN-107, its primary metabolite (CIN-107-M), and metformin were listed by individual subject and summarized by treatment using descriptive statistics for the PK Evaluable Population. CIN-107, CIN-107-M, and metformin plasma concentrations were plotted against time points by treatment (mean and individual). Mean concentrations were plotted against nominal sampling times, while individual concentrations were plotted against actual sampling times.

Urine concentrations of metformin were listed by individual subject and summarized by treatment using descriptive statistics for the PK Evaluable Population. Plots of Ae by time point and treatment (individual and mean) were also presented.

Plasma and urine PK parameters were determined using non-compartmental methods as appropriate. Parameters were listed by individual subject and summarized by treatment using descriptive statistics for the PK Population.

Logarithmic transformations of PK parameters of metformin were analyzed using a mixed model including terms for sequence, treatment group, and period as fixed effects, and subject nested within sequence as a random effect.

The PK parameters analyses were based on the PK Population.

Safety:

Safety analyses were performed throughout the study based on the Safety Population. Safety was evaluated through assessments of AEs, physical examinations, ECGs, weight measurements, vital signs assessments (seated and orthostatic), and clinical laboratory evaluations.

TEAEs were summarized by Medical Dictionary for Regulatory Activities system organ class (SOC) and preferred term (PT) for each treatment and overall.

The Safety Population was used for all the safety analyses. The following summaries of AEs were presented for each part:

- Overall summary of TEAEs by treatment and overall with a breakdown by AE maximum severity;
- TEAEs by SOC and PT by treatment;
- TEAEs by SOC, PT, and relationship to study drug or metformin by treatment;
- TEAEs by SOC, PT, and maximum severity by treatment; and
- TEAEs by SOC, PT, maximum severity, and the relationship to the study drug by treatment.

Separate listings were prepared for SAEs, AEs leading to death, and AEs leading to study discontinuation.

Safety laboratory values and changes from baseline were summarized descriptively by treatment group at each time point of collection, when appropriate. Shift tables describing out-of-normal range shifts were provided for clinical laboratory results. All safety laboratory data were provided in data listings.

Pregnancy test results, drug and alcohol testing results, and viral serology results were listed.

Vital signs; continuous ECG parameters; height, weight, and BMI values and changes form baseline were summarized descriptively by treatment group at each time point of collection. All data were listed.

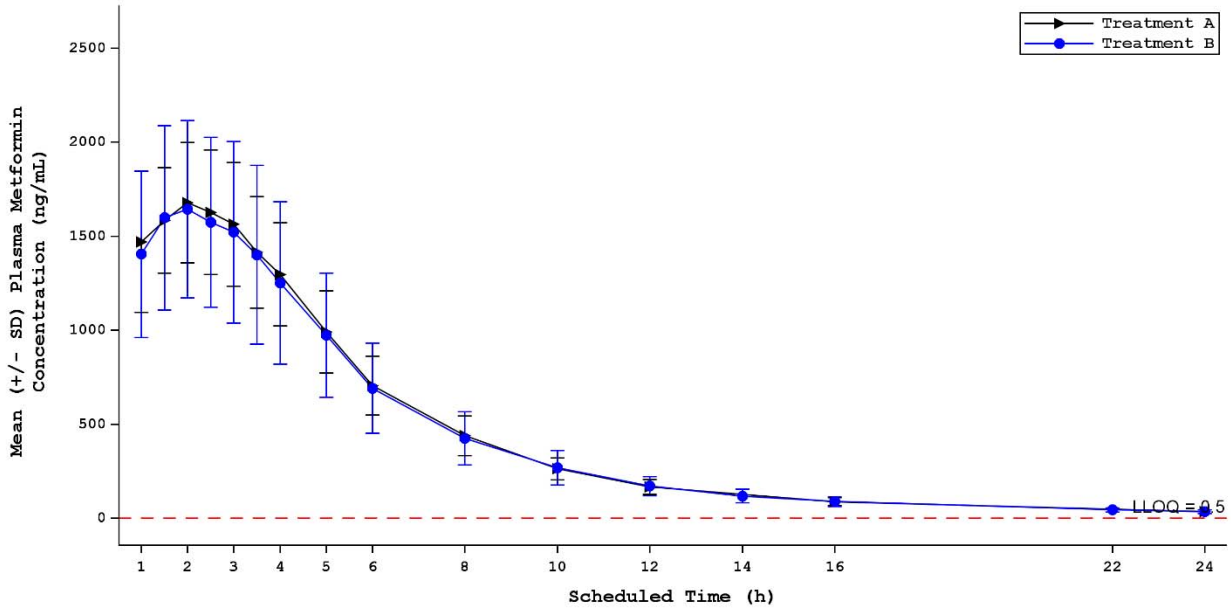
Physical examination results by body system were summarized at each time point of collection by treatment group and findings were listed.

Summary of Results:

Pharmacokinetics:

The plasma concentration-time course curves for metformin were nearly identical in the presence and absence of CIN-107.

Figure 1S. Plot of Mean (±SD) Plasma Metformin Concentrations by Treatment on a Linear Scale to Hour 24 – PK Population

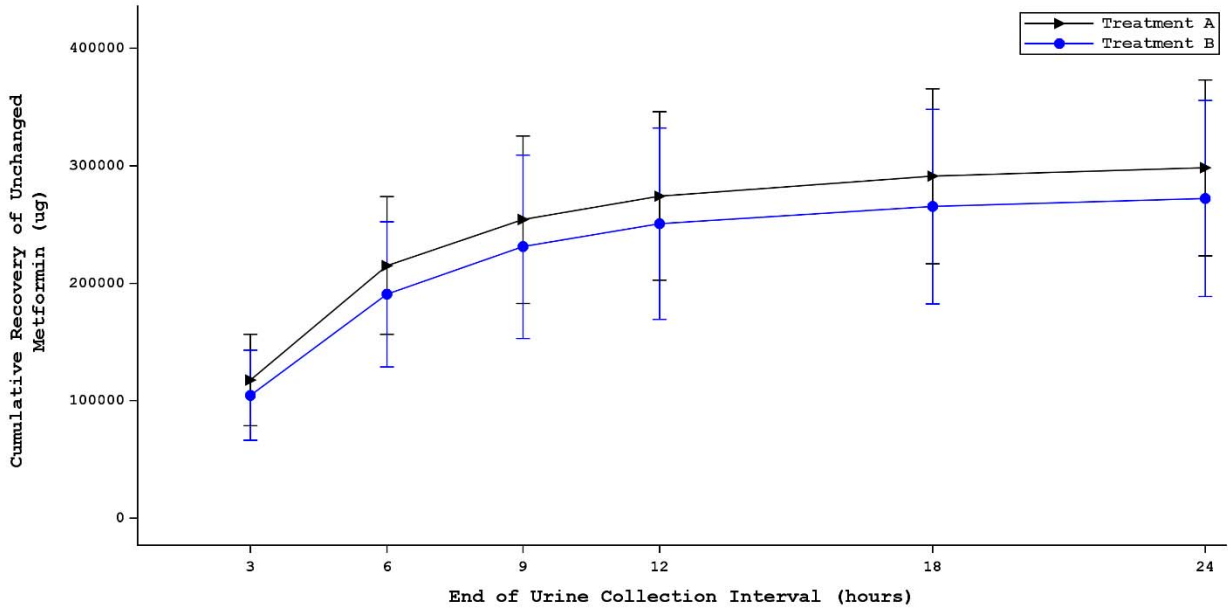


Note 1: LLOQ for metformin = 0.5 ng/mL.
Note 2: Treatment A: a single 1000 mg dose of immediate-release metformin, Treatment B: a single 1000 mg dose of immediate-release metformin coadministered with a 10 mg dose of CIN-107.
Scheduled time point is shown as relative to metformin dosing.
LLOQ = lower limit of quantification; PK = pharmacokinetic(s); SD = standard deviation.
Source: Post-text Figure 14.2.1.1.1

The ratios of geometric LS mean for Treatment B:Treatment A for metformin plasma C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$ all approximated 100%, with 90% confidence interval values falling within the acceptance range of 80% to 125%, indicating that systemic exposure to metformin was not affected by CIN-107.

Consistent with the lack of observed effect of CIN-107, urinary excretion of metformin was qualitatively and quantitatively similar in the presence and absence of CIN-107.

Figure 2S. Plot of Mean (±SD) Ae of Metformin by Treatment on a Linear Scale to Hour 24 – PK Population



Note 1: Treatment A: a single 1000 mg dose of immediate-release metformin, Treatment B: a single 1000 mg dose of immediate-release metformin coadministered with a 10 mg dose of CIN-107.
Ae = cumulative amount of drug excreted in the urine; PK = pharmacokinetic(s); SD = standard deviation.
Source: Post-text Figure 14.2.2.1

Safety:

The safety results of the current study indicate that metformin was well tolerated when administered alone or 2 hours after a single 10 mg dose of CIN-107. There were no deaths, SAEs, or discontinuations due to a TEAE, and there was no noteworthy increase in the incidence of AEs when metformin and CIN-107 were coadministered versus metformin administered alone. All TEAEs experienced by subjects were mild in severity. The most frequent TEAEs were gastrointestinal-related, as one would expect with a single high dose of metformin. There were no trends or clinically meaningful changes in laboratory parameters or physical examination results. There were no clinically significant changes observed in vital signs or 12-lead ECG findings, including no meaningful changes in QTcF.

Conclusions:

Metformin was well tolerated when administered alone or 2 hours after a dose of CIN-107. CIN-107 did not result in an increase in metformin plasma concentrations or a decrease in metformin renal clearance when compared with administration of metformin alone. Based on the results from this study, dose adjustment of metformin is not considered necessary when metformin is coadministered with CIN-107.

Date of the Report: 22 April 2021