2. SYNOPSIS

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 Hepatic Function

Investigational product: CIN-107

Sponsor: CinCor Pharma, Inc.

Investigator: Thomas C. Marbury, MD, Kimberly S. Cruz, MD, William B. Smith, MD, Zeid Kayali, MD, MBA, and Eric Lawitz, MD. This study was conducted at 5 sites in the United States

Publications: None

Period of study: 10 August 2021 (date of first informed consent) to 15 April 2022 (date as defined in protocol).

Phase of development: Clinical Phase 1

Objectives:

The study objectives were:

- To assess the safety and tolerability of CIN-107 following administration of a single oral dose of CIN-107 to subjects with varying degrees of hepatic function; and
- To characterize the pharmacokinetics (PK) of CIN-107 following administration of a single oral dose of CIN-107 to subjects with varying degrees of hepatic function.

Methodology:

This was a Phase 1, open-label, nonrandomized, multi-center, single-dose, parallel-group study in subjects with varying degrees of hepatic function to assess the safety, tolerability, and PK of a single 10-mg oral dose (two 5-mg tablets) of CIN-107. Hepatic function was classified based on the Child-Pugh classification of hepatic impairment in the protocol.

The total duration of study participation for each subject (from screening through follow-up phone call) was approximately 6 weeks.

Number of subjects (planned and analyzed):

It was planned to study a total of up to 20 subjects in 2 groups based on the Child-Pugh classification in the protocol at screening: up to 10 subjects in the normal hepatic function group and up to 10 subjects in the moderate hepatic impairment group. Twenty subjects entered and completed the study.

Diagnosis and main criteria for inclusion:

Subjects in stable health of any ethnic origin, aged between 18 and 80 years, inclusive, and with a BMI between 18 and 42 kg/m^2, inclusive were eligible.

Underlying medical conditions consistent with the population under study (including, but not limited to, hepatic function and renal function) were acceptable if the subject's condition was considered stable by the investigator. However, impaired hepatic function must have been the cause of the subject's Child-Pugh classification as opposed to other underlying disease (eg, autoimmune disease and renal impairment). For hepatically impaired subjects, their hepatic function category must have been stable for a minimum of 3 months prior to screening.

Test product, dose and mode of administration, batch/lot number:

Each subject was administered a single 10-mg oral dose (two 5 mg tablets) of CIN-107 in the fasted state the morning of Day 1. The batch number used for all 5 sites is 2009264.

Reference therapy, dose and mode of administration, batch/lot number:

Not applicable.

Duration of treatment:

A single oral dose of 10 mg (two 5-mg tablets) of CIN-107 was administered to each subject on Day 1.

Endpoints:

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

- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (T_{max})
- Area under the curve (AUC) from time 0 to the time of the last quantifiable plasma concentration ($AUC_{(0\text{-}last)}$)
- Area under the concentration-time curve from time 0 to infinity ($AU_{(0\text{-}inf)}$)
- Percentage of area under the concentration-time curve extrapolated ($\%AUC_{extrap}$)
- Terminal phase elimination half-life ($t_{1/2}$)
- Apparent total plasma clearance (CL/F, CIN-107 only)
- Apparent volume of distribution during the terminal phase (V_z/F, CIN-107 only).

The following PK parameters were calculated using the urine concentration data of CIN-107 and its primary metabolite (CIN-107-M), as the data permit:

- The cumulative amount of CIN-107 and CIN-107-M excreted in the urine;

- Renal clearance (CL_R) and non-renal clearance (CL_{NR}) of CIN-107 and CIN-107-M; and
- The fraction of the dose excreted renally (for CIN-107 only).

The safety of CIN-107 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.

Statistical methods:

Analysis populations:

The all subjects population included all subjects who signed the informed consent form and had any study assessment recorded in the database per the protocol.

The PK population included all subjects who received at least one dose of study treatment (CIN-107) and had at least 1 quantifiable postdose concentration for CIN-107 or any measured metabolite.

The safety population included all subjects who received at least 1 dose of study treatment (CIN-107).

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 any measured metabolite. Sufficient concentration data are defined as at least 3 measurable postdose plasma concentrations in the PK profile.

Pharmacokinetic analysis:

Blood and urine samples were collected at specific times during the study for the measurement of plasma and urinary concentrations of CIN-107 and its primary metabolite (CIN-107-M).

All PK concentrations and parameters were listed for the PK population. Inferential analyses were performed to compare the PK parameters (AUCs and C_{max}) between the hepatic impairment groups and the control group.

Safety analysis:

Safety assessments included adverse events, vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory evaluations, and physical examinations.

Determination of sample size:

No formal statistical assessment of sample size was conducted. Approximately 10 subjects were to be enrolled into each hepatic impairment group with the intent that up to 8 subjects per group complete the treatment period with adequate PK sampling to meet the study objectives. The control group could have enrolled up to 12 subjects.

Summary - Conclusions:

Subject disposition:

Twenty subjects enrolled and completed the study. There were 10 subjects in the normal hepatic function group and 10 subjects in the moderate hepatic impairment group. All subjects were included in the PK and safety populations. All subjects received a single planned 10-mg oral dose (two 5-mg tablets) of CIN-107.

Pharmacokinetic results:

- Geometric mean C_{max} and AUC values were similar between the normal and moderate hepatic impairment group for CIN-107.

- Geometric mean exposure for the metabolite CIN-107-M was increased by 2.4-fold for C_{max}, 3.5-fold for $AUC_{(0\text{-}last)}$, and 3.7-fold for $AUC_{(0\text{-}inf)}$ in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. However, given the comparatively low exposures of CIN-107-M compared to that of the parent drug CIN-107, these changes may be considered to be clinically insignificant.

- Geometric mean $t_{1/2}$ values for CIN-107 and CIN-107-M appeared similar for subjects with normal hepatic function and subjects with moderate hepatic impairment with no apparent trend related to hepatic impairment.The CL/F for CIN-107 was 2.64 and 2.80 L/h and V_z/F was 128 and 117 L in subjects with normal hepatic function and moderate hepatic impairment, respectively.The CL_R for CIN-107 and CIN-107-M was similar between subjects with normal hepatic function and moderate hepatic impairment. The non-renal clearance (CL_{NR}) for CIN-107 was similar between subjects with normal hepatic function and moderate hepatic impairment.The between-subject variability (geometric CV%) for C_{max}, $AUC_{(0\text{-}last)}$, and $AUC_{(0\text{-}inf)}$ values for CIN-107 in plasma were similar to each other for subjects in both hepatic function and moderate hepatic impairment groups, and values for the metabolite CIN-107-M in plasma were similar to each other for subjects in both hepatic groups.

Safety results:

A single oral dose of 10 mg CIN-107 was well tolerated in subjects with normal hepatic function and in subjects with moderate hepatic impairment. There were no SAEs or severe TEAEs, and no TEAEs led to the premature discontinuation of a subject from the study. Only 1 treatment-related TEAE (headache) was reported during the study and this event was considered by the investigator to be related to CIN-107. The event resolved by the end of the study.

Conclusions:

- Following a single 10-mg oral dose, CIN-107 appeared rapidly in plasma, with a median T_{max} of 2.25 and 2.75 hours for subjects in the moderate hepatic function group and normal hepatic function group and, respectively, and was eliminated with a geometric mean $t_{1/2}$ of approximately 33.5 and 28.9 hours for subjects in the normal hepatic function group and moderate hepatic impairment n group, respectively. Geometric mean C_{max} and

AUC values were similar between the normal and moderate hepatic impairment group for CIN-107.

- Urinary excretion of CIN-107 was minimal following single 10-mg oral dose and appeared to be similar between subjects with normal hepatic function and moderate hepatic impairment.
- A single oral dose of 10 mg CIN-107 was safe and well tolerated by both the normal hepatic function and moderate hepatic impairment groups in this study.
- The majority of TEAEs were mild, not considered by the investigator to be related to investigational medicinal product. Of the 4 TEAEs, 2 were treated with concomitant medications and the other two resolved without treatment. None of the subjects had a severe TEAE or SAE during the study, and no subjects were discontinued due to a TEAE.
- The most common TEAEs were hyperkalaemia and hypoglycaemia in the moderate hepatic impairment group; diarrhea and headache were most common in the normal hepatic function group.
- There were no treatment or dose-related trends and no clinically significant findings in the clinical laboratory evaluations, vital signs data, 12-lead ECG data, or physical examination findings during the study.