2. SYNOPSIS

Title of Study: A Phase 1, Open-label Study of the Absorption, Metabolism, and Excretion of [^{14}C]-baxdrostat Following a Single Oral Dose in Healthy Male Subjects

Investigational Product: Baxdrostat (Formerly, CIN-107)

Sponsor: CinCor Pharma, Inc.

Investigator: Nicholas Siebers, MD. This study was conducted at a single site in the United States.

Publications: None

Period of Study: 18 November 2021 (Date of First Informed Consent) to 15 January 2022 (Date of Final Poststudy Observation).

Phase of Development: Clinical Phase 1

Objectives and Endpoints:

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Primary: • to determine the routes, rates of elimination, and mass balance of total radioactivity from [^{14}C]-baxdrostat • to characterize the PK of baxdrostat and its primary metabolite (CIN-107M) following administration of [^{14}C]-baxdrostat to healthy male subjects • to characterize total radioactivity following administration of [^{14}C]-baxdrostat to healthy subjects	• total radioactivity recovery (fe_{t1-t2}) in urine and feces • PK parameters including, but not limited to, $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, t_{max}, and $t_{1/2}$ for baxdrostat and CIN-107M in plasma • cumulative amount of baxdrostat and CIN-107M excreted in urine (A_e), CL_R of baxdrostat and CIN-107M, fraction of dose excreted renally (baxdrostat only; fe_{t1-t2}) • PK parameters including, but not limited to, $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, t_{max}, and $t_{1/2}$ for total radioactivity in plasma and whole blood
Secondary: • to determine, where possible, the quantitative metabolite profiles in plasma, urine, and feces after [^{14}C]-baxdrostat • to determine, where possible, the chemical structure of major metabolites in plasma, urine, and feces after [^{14}C]-baxdrostat • to assess the safety and tolerability of [^{14}C]-baxdrostat when administered to healthy subjects	• quantitative metabolic profiles of baxdrostat in plasma and excreta • identification of baxdrostat metabolites in plasma and excreta • incidence and severity of AEs • incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results • 12-lead ECG parameters • vital signs measurements • physical examinations

Abbreviations: AE = adverse event; $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0-tlast}$ = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; CL_R = renal clearance; C_{max} = maximum observed concentration; ECG = electrocardiogram; fe_{t1-t2} = percentage of the dose administered recovered over the time interval t1 to t2; PK = pharmacokinetics; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time of the maximum observed concentration.

Methodology:

This was a Phase 1, open-label, nonrandomized, single dose study in healthy male subjects. Potential subjects were screened to assess their eligibility to enter the study within 28 days prior to the dose administration. Subjects were admitted to the study site on Day -1. On the morning of Day 1, all eligible subjects received a single oral dose of 10 mg containing approximately 100 μCi of [^{14}C]-baxdrostat.

Subjects were to be confined to the study site until at least Day 9. Subjects were to be discharged from the study site on Day 9 if the following discharge criteria were met:

- plasma radioactivity levels below the limit of quantitation for 2 consecutive collections, and
- ≥90% mass balance recovery, and
- ≤1% of the total radioactive dose was recovered in combined excreta (urine and feces) in 2 consecutive 24-hour periods.

If these criteria were not met by Day 9, subjects remained in the study site until all discharge criteria were met up to a maximum of Day 15 to continue 24-hour blood, urine, and feces collections. The study site contacted subjects through a phone call 3 days (±1 day) after discharge from the study site.

Number of Subjects (Planned and Analyzed):

Up to 8 subjects were planned to be studied in a single group to ensure that 6 subjects completed the study. A total of 8 subjects were enrolled in the study.

Diagnosis and Main Criteria for Inclusion:

Healthy male subjects of any race, between 18 and 55 years of age, inclusive, and with a body mass index between 18.0 and 32.0 kg/m^2 (inclusive) were selected according to inclusion and exclusion criteria.

Test Product, Dose and Mode of Administration, Batch Number:

A single oral dose of 10 mg containing approximately 100 µCi of [^{14}C]-baxdrostat (batch number: 11911PHC002-3) was administered to all subjects on Day 1 with 240 mL of room temperature water after an overnight fast of at least 10 hours.

Reference Therapy, Dose and Mode of Administration, Batch/Lot Number:

Not applicable.

Duration of Treatment:

Single oral dose was administered to all subjects on Day 1.

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 safety population included all subjects who received a dose of radiolabeled study treatment ([^{14}C]-baxdrostat). The pharmacokinetic (PK) population included all subjects who received the dose of radiolabeled study treatment ([^{14}C]-baxdrostat) and had at least 1 valid PK concentration.

Statistical methodology:

Pharmacokinetics

All plasma, whole blood, and nonradioactive urine PK concentrations and parameters were listed for the all subjects population.

Summary tables, arithmetic mean (+ standard deviation) figures, overlaying individual figures, and individual figures by time postdose were provided for plasma and whole blood PK concentrations.

Summary tables were provided for all PK parameters, except for diagnostic regression-related PK parameters. Separate summary tables by time interval were provided for nonradioactive excretion parameters and cumulative excretion parameters.

No inferential statistical analyses were performed.

Safety

Safety data were presented using descriptive statistics. No inferential statistical analyses were performed.

Determination of sample size:

No formal statistical assessment of sample size was conducted. The sample size chosen for this study is common in human radiolabeled studies and was considered sufficient to achieve the objectives of the study. Up to 8 subjects were to be enrolled and studied as a single group in order that 6 subjects complete the study.

Summary - Conclusions:

Subject disposition:

All 8 subjects enrolled in the study were dosed and completed the study in accordance with the protocol.

Pharmacokinetic results:

- Following oral administration of [^{14}C]-baxdrostat, baxdrostat was rapidly absorbed (median time of the maximum observed concentration (t_{max}): 1.50 hours) and characterized by relatively slow formation of metabolite CIN-107M (median t_{max}: 24.0 hours). Geometric mean apparent terminal elimination half-life ($t_{1/2}$) was 29.0 hours for baxdrostat and 30.6 hours for CIN-107M.
- Systemic exposure (area under the concentration-time curve from time 0 extrapolated to infinity [$AUC_{0-\infty}$]) to CIN-107M was 10.3% of the systemic exposure to baxdrostat.
- Following oral administration of [^{14}C]-baxdrostat, plasma and whole blood total radioactivity were characterized by a median t_{max} of 1.50 hours for both matrices and geometric mean $t_{1/2}$ of 33.2 hours and 34.6 hours, respectively.

- Systemic exposure ($AUC_{0-\infty}$) to baxdrostat and CIN-107M represented 71.2% and 6.24%, respectively, of the circulating total radioactivity in plasma.
- The geometric mean $AUC_{0-\infty}$ blood/plasma total radioactivity ratio was 0.917 suggesting a low association of radioactivity with red blood cells.
- The overall mean recovery of radioactivity in urine and feces samples was 84.7% of the administered dose over the 336-hour study (individual range: 79.5% to 86.8%) with urinary excretion as the principal route of elimination of radioactivity with a mean of 69.4% of the dose recovered in urine and 15.3% of the dose recovered in feces.
- The geometric mean cumulative fraction of the dose excreted as unchanged baxdrostat in urine was 16.6%, while there was negligible urinary excretion of CIN-107M (geometric mean cumulative amount of 0.0231 mg). The geometric mean renal clearance (CL_R) for baxdrostat and CIN-107M was 0.499 and 0.0791 L/h, respectively.
- Baxdrostat underwent extensive metabolism after a single oral dose of [^{14}C]-baxdrostat in human subjects. Metabolism was predominately mediated by oxidation, and, to a lesser extent, *N*-dealkylation, amide hydrolysis, *N*-demethylation, and *N*-acetylglucosaminidation. Notable secondary biotransformation pathways included reduction, glucuronidation, and oxidation.
- CIN-107M (M2), oxy-CIN-107 (M71), and *N*-desproprionony-CIN-107 (M3) were the most abundant, albeit minor, circulating metabolites.

Safety results:

- Overall, 3 subjects (37.5%) reported 5 treatment-emergent adverse events (TEAEs; diarrhoea, eye irritation, skin abrasion, flatulence, and noncardiac chest pain) following administration of a single dose of 10 mg (100 μCi) [^{14}C]-baxdrostat.
- All TEAEs were mild in intensity and were reported as recovered or resolved at the end of study.
- There were no serious adverse events reported during the study and no subject discontinued the study due to TEAE.
- One subject reported an event of flatulence that was considered by the investigator as mild in intensity and possibly related to baxdrostat.
- There were no other trends in mean or individual subject clinical chemistry, hematology, or urinalysis parameters, vital signs measurements, and electrocardiogram parameters; and none of the changes were reported as TEAEs.

Conclusions:

- The overall mean recovery of radioactivity in urine and feces samples was 84.7% of the administered dose over the 336-hour study, with recovery in individual subjects that ranged from 79.5% to 86.8% with urinary excretion as the principal route of elimination of radioactivity, with mean of 69.4% of the dose recovered in urine and 15.3% of the dose recovered in feces.
- Following oral administration of [^{14}C]-baxdrostat, baxdrostat was rapidly absorbed (median t_{max} of 1.50 hours) and slowly eliminated (geometric mean $t_{1/2}$ of 29.0 hours).

The metabolite CIN-107M slowly appeared in plasma and then was slowly eliminated (median t_{max} of 24.0 hours and geometric mean $t_{1/2}$ of 30.6 hours).

- Following oral administration of [^{14}C]-baxdrostat, plasma and whole blood total radioactivity were characterized by a median t_{max} of 1.50 hours for both matrices and geometric mean $t_{1/2}$ of 33.2 hours and 34.6 hours, respectively.
- Systemic exposure ($AUC_{0-\infty}$) to baxdrostat and CIN-107M represented 71.2% and 6.24%, respectively, of the circulating total radioactivity in plasma.
- The geometric mean $AUC_{0-\infty}$ blood/plasma total radioactivity ratio was 0.917 suggesting low association of radioactivity with red blood cells.
- Baxdrostat underwent extensive metabolism after a single oral dose of ^{14}C-baxdrostat to human subjects. Metabolism was predominately mediated by oxidation, and, to a lesser extent, *N*-dealkylation, amide hydrolysis, *N*-demethylation, and *N*-acetylglucosaminidation. Notable secondary biotransformation pathways included reduction, glucuronidation, and oxidation.
- CIN-107M (M2), oxy-CIN-107 (M71), and *N*-desproprionony-CIN-107 (M3) were the most abundant, albeit minor, circulating metabolites.
- The incidence of TEAEs was low with 3 subjects (37.5%) reporting a total of 5 TEAEs in this study.
- There were no other trends in mean or individual subject clinical chemistry, hematology, or urinalysis parameters, vital signs measurements, and ECG parameters; and none of the changes were reported as TEAEs.
- Overall, single dose of 10 mg single oral dose of [^{14}C]-baxdrostat was safe and well tolerated by healthy male subjects in this study.