2 SYNOPSIS

Name of Sponsor/Company: CinCor Pharma, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not applicable		
Name of Active Ingredient: Baxdrostat		

Title of Study: A Phase 1 Single and Multiple Dose Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of Baxdrostat in Healthy Japanese and Caucasian Subjects

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Phase of Development: 1

Study Period:
Date of first enrollment: 05 July 2022
Date of last completed: 20 September 2022

Objectives: The objectives of this single and multiple dose study were as follows:

- To assess the safety and tolerability of single and multiple oral doses of baxdrostat in healthy Japanese subjects.
- To assess pharmacokinetics (PK) of baxdrostat and CIN-107-M after single and multiple oral doses of baxdrostat in healthy Japanese subjects.
- To assess pharmacodynamic (PD) effects of single and multiple oral doses of baxdrostat in healthy Japanese subjects.
- To compare the PK and PD of baxdrostat and CIN-107-M after single and multiple oral doses of baxdrostat between Japanese and Caucasian subjects.

Methodology: This was a Phase 1, single and multiple oral dose study of the safety/tolerability, PK, and PD in healthy Japanese subjects with a cohort of healthy Caucasian subjects.

Subjects were admitted to the clinical site on Day -2. On Day -1, subjects had assessments and procedures (eg, vital signs, electrocardiograms (ECGs), PD samples, cosyntropin test) time-matched to the Day 10 assessments. Subjects received a single oral dose of baxdrostat on Day 1 and multiple oral doses once daily on Days 6 – 10. Safety, PK, and PD assessments were performed. On Day -1 and Day 10, subjects were supine for at least 30 minutes prior to sampling of the pre baxdrostat dose PD sample and remained in a supine position until at least the 4-hour post baxdrostat dose PD sample.

On Day -1, Day 1, and Day 10, subjects had an overnight fast of at least 8 h and continued to fast for 4 h postdose (time-matched for Day -1).

On all other days, subjects fasted overnight and remained fasting until 1 hour after dosing and assessments in the morning.

A total of 41 subjects were enrolled in this study: 31 Japanese subjects and 10 Caucasian subjects. The study included 4 cohorts and each cohort consisted of 10 subjects, randomized 4:1 (active:placebo). The Japanese cohorts (Cohorts 1, 2, and 4) were performed in parallel. The Caucasian cohort (Cohort 3) was performed after Cohort 2 was complete so that the Caucasian subjects could be matched by sex and Day -1 body mass index

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([BMI] ± 20%) to the Japanese subjects in Cohort 2. A minimum of 4 subjects of each sex was enrolled into each cohort (ie, at least 4 female and 4 male subjects).

The 4 cohorts were dosed as follows:

- Cohort 1: Oral tablet dose of baxdrostat 1 mg or placebo, administered as a single dose (Day 1) and multiple doses (once daily [QD] for 5 days, Days 6 – 10) to Japanese subjects
- Cohort 2: Oral tablet dose of baxdrostat 3 mg or placebo, administered as a single dose (Day 1) and multiple doses (QD for 5 days, Days 6 – 10) to Japanese subjects
- Cohort 3: Oral tablet dose of baxdrostat 3 mg or placebo, administered as a single dose (Day 1) and multiple doses (QD for 5 days, Days 6 – 10) to Caucasian subjects
- Cohort 4: Oral tablet dose of baxdrostat 10 mg or placebo, administered as a single dose (Day 1) and multiple doses (QD for 5 days, Days 6 – 10) to Japanese subjects

Subjects remained domiciled in the clinical unit until 24 h (morning of Day 2) after the single oral dose administration and returned for 4 additional ambulatory visits (mornings of Day 3, Day 4, Day 5, and Day 6) to complete blood draws and safety assessments, as applicable.

Subjects initiated multiple dosing starting on the morning of Day 6. The subjects had an ambulatory visit to the clinic on the morning of each of Days 6 – 9 to receive their daily dose of baxdrostat.

On the evening of Day 9, subjects were readmitted to the clinical unit and received their final dose of baxdrostat on the morning of Day 10. Subjects were released from the clinical unit ~ 24 h after the Day 10 dose administration and returned for 4 additional ambulatory visits (mornings of Days 12 – 15) with a final Follow-up visit on Day 19.

Subjects had safety/tolerability, PK, and PD assessments and procedures performed per the Schedules of Assessments.

Number of Subjects (Planned and Analyzed): A total of 40 subjects were to be enrolled, 30 Japanese subjects and 10 Caucasian subjects. A total of 41 subjects were enrolled and analyzed, 31 Japanese subjects and 10 Caucasian subjects.

Diagnosis and Main Criteria for Inclusion: Subjects were healthy males or females, aged 18 to 55 years, with a BMI between 18 – 30 kg/m^2, and of Japanese descent (as defined by the protocol, Cohorts 1, 2, and 4) or Caucasian (Cohort 3).

Test Product, Dose and Mode of Administration, Batch Numbers: Subjects assigned to active treatment received baxdrostat (1, 3, or 10 mg) as a single oral dose (Day 1) and multiple oral doses (Days 6 – 10, QD). Batch Numbers: 1 mg tablet = [redacted] 2 mg tablet = [redacted]

Reference Therapy, Dose and Mode of Administration, Batch Number: Subjects assigned to placebo treatment received placebo matched to the baxdrostat dose as a single oral dose (Day 1) and multiple oral doses (Days 6 – 10, QD). Batch Numbers: 0 mg tablet = [redacted]

Duration of Treatment: Subject participation lasted up to 47 days, including a 26-day screening period, 2-day prestudy preparation period, and a 19-day on study period (consisting of 2 treatment periods, a single dose period [Days 1 – 5], a multiple dose period [Days 6 – 19]), and the end-of-study visit.

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Criteria for Evaluation:

The following endpoints will be assessed during the study:

Safety:

- Incidence of adverse events (AEs), serious adverse events (SAEs), clinical laboratory values, vital signs, ECGs, and physical examinations

Pharmacokinetic:

The following PK parameters for baxdrostat and CIN-107-M were estimated using non-compartmental methods, as appropriate:

- Single Dose (Day 1):
  - maximum plasma concentration (C_{max})
  - Area under the concentration-time curve (AUC) from time 0 to 24 hours (AUC_{0-24})
  - AUC from time 0 to the time of the last quantifiable concentration (AUC_{last})
  - AUC from time 0 extrapolated to infinity (AUC_{inf})
  - time at which C_{max} was observed (T_{max})
  - terminal elimination half-life ($t_{1/2}$)
  - apparent oral clearance (CL/F)
  - apparent volume of distribution (V_d/F)
- Multiple Dose (Day 10):
  - maximum plasma concentration at steady state ($C_{max,ss}$)
  - AUC from time 0 to 24 hours at steady state ($AUC_{0-24,ss}$)
  - time at which C_{max} was observed at steady state ($T_{max,ss}$)
  - terminal elimination half-life at steady state ($t_{1/2,ss}$)
  - apparent oral clearance at steady state (CL_{ss}/F)
- apparent volume of distribution at steady state (Dose/[CL_{ss}/F])
- C_{max} (single and multiple dose) and AUC_{inf} (single dose) or $AUC_{0-24,ss}$ (multiple dose) were dose-normalized.
- Additional PK parameters would have been reported as appropriate.

Pharmacodynamic:

The following PD parameters were analyzed using plasma concentrations from blood samples collected on Day -1 (baseline) and Day 10 for aldosterone, total cortisol, and electrolytes (sodium, chloride, and potassium):

- C_{max}
- Area under the concentration-time curve from time 0 to 3 hours (AUC_{0-3})
- T_{max}

Statistical Methods:

Analysis Populations:

The **Safety Population** consists of subjects who received at least one dose of study drug, whether prematurely discontinued from the study or not. The Safety Population was for the safety data summaries and baseline characteristic summaries. The Safety Population was analyzed as treated.

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Subjects were excluded from the **PK Population** if they did not receive treatment or otherwise significantly deviated from the protocol, violated inclusion or exclusion criteria, or if data were unavailable or incomplete, which may have influenced the PK analysis. Excluded cases were documented along with the reason for exclusion. The PK Population was used for the PK concentration and parameter summaries and primary analysis. The PK Population was analyzed as treated.

Subjects were excluded from the **PD Population** if they did not receive treatment or otherwise significantly deviated from the protocol, violated inclusion or exclusion criteria, or if data were unavailable or incomplete, which may have influenced the PD analyses. Excluded cases were documented along with the reason for exclusion. The PD Population was analyzed as treated.

Note: Neither the PK nor PD Population was sized appropriately for definitive statistical comparisons. The 90% confidence intervals (CIs)were calculated and displayed for information purposes only.

Safety Data Analysis:

A summary of number and percentage of subjects reporting TEAEs, TEAEs by severity and relationship, SAEs, and subjects who discontinued study drug due to an AE is provided.

A summary of the number and percentage of subjects reporting each TEAE, categorized by SOC and PT coded according to MedDRA, is presented by cohort and overall. Counting was done by subject only, not by event; subjects were counted only once within each SOC or PT.

A summary of the number and percentage of subjects reporting each TEAE is presented by relationship to study drug (as recorded on the eCRF) and by cohort and overall. Subjects with multiple events within an SOC or PT were counted under the category of their most drug-related event within that SOC or PT.

A summary of the number and percentage of subjects reporting each TEAE is presented by severity (as recorded on the eCRF) and by cohort and overall. Subjects with multiple events within an SOC or PT are counted under the category of their most severe event within that SOC or PT.

All AEs (including non-treatment-emergent events) recorded on the eCRF are listed by subject.

A separate listing of AEs leading to study drug discontinuation is provided.

A listing of deaths and other SAEs is presented by subject.

Descriptive statistics summarizing continuous laboratory results of clinical chemistry, hematology, and urinalysis (and changes from baseline) by cohort and scheduled time are provided.

Descriptive statistics summarizing vital signs (and changes from baseline) by cohort and scheduled visit are provided.

Descriptive statistics summarizing mean ECG parameters (and changes from baseline) by cohort and scheduled visit are provided. The overall interpretation of the ECG results at each scheduled time is summarized by the number and percentage of subjects in each category (Normal, Abnormal – Not Clinically Significant, and Abnormal – Clinically Significant).

Pharmacokinetic Data Analysis:

Descriptive statistics were used to summarize the plasma concentrations by treatment at each scheduled timepoint.

Linear (± standard deviation [SD]) and semi-logarithmic (+SD) plots of the arithmetic mean plasma concentration by scheduled sampling time are presented by treatment.

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Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time are presented by subject.

Plasma PK parameters for baxdrostat and its metabolite CIN-107-M were estimated using noncompartmental methods with WinNonlin using best fit regression. The PK parameters were estimated from the concentration-time profiles, and AUCs were calculated using linear up/log down method.

Descriptive statistics were used to summarize the calculated PK parameters by dose group and by study day (Day 1 single dose and Day 10 multiple doses).

A scatter plot of individual (plus mean and median) PK parameters C_{max}, AUC_{last}, and AUC_{inf} for Day 1 single dose, and $C_{max,ss}$ and $AUC_{0-24,ss}$ for Day 10 multiple doses by dose group for baxdrostat and CIN-107-M is provided.

The plasma PK parameters C_{max}, AUC_{last}, AUC_{inf} (single dose only) for baxdrostat were compared across each dose level to assess dose proportionality (i.e., proportionality of a change in systemic exposure with a change in dose) for Japanese subjects. For Day 1 single dose, PK parameters C_{max}, AUC_{inf}, AUC_{last}, and AUC_{0-24} were analyzed. For Day 10 multiple doses, the PK parameters $C_{max,ss}$ and $AUC_{0-24,ss}$ were analyzed. Statistical analyses were done using a power model.

Scatterplots of the assessed PK parameters C_{max}, AUC_{last}, AUC_{inf}, and AUC_{0-24} for single dose and $C_{max,ss}$ and $AUC_{0-24,ss}$ for multiple doses on the log scale are presented by cohort and study day to visually review dose proportionality.

The effect of dose level on the PK of baxdrostat was assessed using an analysis of variance (ANOVA) model with the ratio and 90% CIs of the geometric least squares (LS) means of the dose normalized PK parameters: C_{max}/D, AUC_{last}/D, and AUC_{inf}/D for baxdrostat and CIN-107-M at Day 1 single dose phase; $C_{max,ss}/D$ and $AUC_{0-24,ss}/D$ for baxdrostat and CIN-107-M for Day 10 multiple doses. An ANOVA model with fixed effects for dose level and a random effect for subject was performed using the natural log-transformed dose-normalized parameters. Estimates on the original scale of measurement were obtained by exponentiating point estimates on the natural log scale. Geometric LS means are provided for each dose level. In all comparisons, the 1 mg dose was used as the reference.

The effect of ethnicity on the PK of baxdrostat was assessed using a linear mixed model with the ratio and 90% CIs of the geometric LS means of the plasma PK parameters: C_{max}, AUC_{last}, and AUC_{inf} for baxdrostat and CIN-107-M at Day 1 single dose; $C_{max,ss}$ and $AUC_{0-24,ss}$ for baxdrostat and CIN-107-M for Day 10 multiple doses. A linear mixed effects model with fixed effects for ethnicity and a random effect for subject were performed using the natural log-transformed parameters. Estimates on the original scale of measurement was obtained by exponentiating point estimates on the natural log scale. Geometric LS means were provided for each treatment. In all comparisons, Caucasian subjects were used as the reference.

Pharmacodynamic Data Analysis:

Descriptive statistics were used to summarize the PD parameters by dose group at each scheduled time point. For aldosterone and total cortisol levels, time-matched levels change from baseline (Day -1) were summarized by dose group at each scheduled time point.

Figures plotting mean PD parameters (aldosterone and total cortisol levels) by study phase, dose group, and scheduled time point are presented.

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Descriptive statistics were used to summarize C_{max}, AUC_{0-3}, and T_{max} by dose group at each scheduled time point for aldosterone and total cortisol levels.

The effect of dose level on the plasma aldosterone levels was assessed using an ANOVA model with the ratio and 90% CIs for change from baseline AUC_{0-3} and C_{max}. This model was only performed for Japanese subjects with active drug. An ANOVA model with fixed effects for dose and a random effect for subject was performed using the natural log-transformed parameters. Estimates on the original scale of measurement were obtained by exponentiating point estimates on the natural log scale. Geometric LS means ratio were provided for comparisons between dose groups. In all comparisons, the 1 mg baxdrostat dose group was used as the reference group.

Results:

Safety Results:

A total of 15 TEAEs were reported with 14 of the TEAEs occurring in subjects administered baxdrostat and 1 TEAE occurring in the placebo group. Overall, 8 subjects (19.5%) had at least 1 TEAE with 7 of those subjects in the baxdrostat dosing groups and 1 subject in the placebo group.

All TEAEs were of mild severity.

The majority of the TEAEs were not related (2 subjects, 4.9%) or unlikely related (3 subjects, 7.3%). Three subjects (7.3%) had TEAEs that were possibly related: 2 subjects (25.0%) in the baxdrostat 1 mg dose group and 1 subject (12.5%) in the baxdrostat 3 mg (CAU) dose group.

The SOC with the most reported TEAEs was Nervous System Disorders with a total of 4 subjects (9.8%) reporting TEAEs of headache (n = 2), dizziness (n = 1), presyncope (n = 1), and somnolence (n = 1). The most common TEAE reported was headache in 2 subjects (4.9%): 1 subject (12.5%) in the baxdrostat 1 mg cohort and 1 subject (12.5%) in the baxdrostat 3 mg (CAU) cohort. All other TEAEs were reported in 1 subject each.

There were no SAEs reported and 1 subject in the baxdrostat 10 mg dose group was discontinued due to a mild, unrelated AE (SARS-CoV-2 test positive).

There were no clinically meaningful findings in the laboratory results, vital signs measurements, 12-lead safety ECGs, or physical examination assessments in this study.

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Pharmacokinetic Results:

Baxdrostat PK: Following single and multiple oral dosing in Japanese subjects, there was an increase in primary PK parameter estimates of baxdrostat with increasing dose over the dosing range of 1 mg to 10 mg. Baxdrostat appeared rapidly in systemic circulation and reached peak levels within 1.00 to 3.50 h in each cohort. Baxdrostat showed dose-proportional PK at the tested dosing range for all primary PK parameters as evidenced by the 90% CIs for the slope of the power model that lay wholly within the standard criteria of 80% to 125% for both single and multiple dosing (Table 1).

Table 1 Statistical Analysis of Dose Proportionality of Baxdrostat in Japanese Subjects (PK Population)

Study Day	Parameter	n	Intercept	Slope	90% CI
Day 1 Single Dose	C_{max} (ng/mL)	25	2.541	1.048	(0.975, 1.120)
	AUC_{last} (h*ng/mL)	25	5.735	1.068	(0.962, 1.175)
	AUC_{inf} (h*ng/mL)	25	5.755	1.070	(0.960, 1.180)
Day 10 Multiple Doses	$C_{max,ss}$ (ng/mL)	24	3.060	1.045	(0.950, 1.141)
	$AUC_{0-24,ss}$ (h*ng/mL)	24	5.736	1.051	(0.940, 1.161)

Abbreviations: AUC = area under the concentration-time curve; $AUC_{0-24,ss}$ = AUC from time 0 to 24 hours at steady state; AUC_{inf} = AUC from time 0 extrapolated to infinity; AUC_{last} = AUC from time 0 to the time of the last quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; $C_{max,ss}$ = C_{max} at steady state; ln = natural logarithm; n = number; PK = pharmacokinetic

Notes: The dose proportionality analyses were performed using the power model:
ln(PK) = intercept + slope*ln(dose) + e, where PK is the PK parameter and e is the error term. A value of slope = 1 indicates dose proportionality.

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The geometric LS-means (GLSM) ratio and 90% CI of dose-normalized PK parameters of baxdrostat following single (C_{max}/D and AUC_{inf}/D) and multiple ($C_{max,ss}$/D and $AUC_{0-24,ss}$/D) dosing are listed in the table below. These results provide evidence to indicate that the dose-normalized PK parameters of baxdrostat were similar between the three cohorts (Cohort 2 vs Cohort 1 [Table 2] and Cohort 4 vs Cohort 1 [Table 3]) of Japanese subjects.

Table 2 Dose Normalized Treatment Comparison of Baxdrostat in Japanese Cohort 2 (3 mg) and Cohort 1 (1 mg) (PK Population)

		Geometric LS Mean					
		Cohort 2 3 mg (JPN) (Test)		Cohort 1 1 mg (JPN) (Reference)		Geometric LS Mean Ratio (Test/Reference)	
Study Day	**Parameter**	**n**	**Result**	**n**	**Result**	**Estimate**	**90% CI**
Day 1 Single Dose	C_{max}/D (ng/mL/mg)	8	12.733	8	13.018	0.978	(0.822, 1.163)
	AUC_{inf}/D (h*ng/mL/mg)	8	321.911	8	325.712	0.988	(0.759, 1.287)
Day 10 Multiple Doses	$C_{max,ss}$/D (ng/mL/mg)	8	22.175	8	21.445	1.034	(0.826, 1.295)
	$AUC_{0-24,ss}$/D (h*ng/mL/mg)	8	318.148	8	314.818	1.011	(0.779, 1.312)

Abbreviations: /D = dose normalized; ANOVA = analysis of variance; AUC = area under the concentration-time curve; $AUC_{0-24,ss}$ = AUC from time 0 to 24 hours at steady state; AUC_{inf} = AUC from time 0 extrapolated to infinity; CI = confidence interval; C_{max} = maximum plasma concentration; $C_{max,ss}$ = C_{max} at steady state; JPN = Japanese; ln = natural logarithm; LS = least squares; n = number; PK = pharmacokinetic

Notes: The C_{max} and AUC analyses were performed on ln-transformed dose normalized parameters using an ANOVA model with dose level as a fixed effect and subject as a random effect.

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Table 3 Dose Normalized Treatment Comparison of Baxdrostat in Japanese Cohort 4 (10 mg) and Cohort 1 (1 mg) (PK Population)

		Geometric LS Mean					
		Cohort 4 10 mg (JPN) (Test)		Cohort 1 1 mg (JPN) (Reference)		Geometric LS Mean Ratio (Test/Reference)	
Study Day	**Parameter**	**n**	**Result**	**n**	**Result**	**Estimate**	**90% CI**
Day 1 Single Dose	C_{max}/D (ng/mL/mg)	9	14.464	8	13.018	1.111	(0.939, 1.315)
	AUC_{inf}/D (h*ng/mL/mg)	9	380.677	8	325.712	1.169	(0.904, 1.511)
Day 10 Multiple Doses	$C_{max,ss}$/D (ng/mL/mg)	8	23.790	8	21.445	1.109	(0.886, 1.390)
	$AUC_{0-24,ss}$/D (h*ng/mL/mg)	8	353.312	8	314.818	1.122	(0.865, 1.457)

Abbreviations: /D = dose normalized; ANOVA = analysis of variance; AUC = area under the concentration-time curve; $AUC_{0-24,ss}$ = AUC from time 0 to 24 hours at steady state; AUC_{inf} = AUC from time 0 extrapolated to infinity; CI = confidence interval; C_{max} = maximum plasma concentration; $C_{max,ss}$ = C_{max} at steady state; JPN = Japanese; ln = natural logarithm; LS = least squares; n = number; PK = pharmacokinetic

Notes: The C_{max} and AUC analyses were performed on ln-transformed dose normalized parameters using an ANOVA model with dose level as a fixed effect and subject as a random effect.

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The GLSM ratio and 90% CI of PK parameters of baxdrostat following single (C_{max}, AUC_{last} and AUC_{inf}) and multiple ($C_{max,ss}$ and $AUC_{0-24,ss}$) baxdrostat dosing in Caucasian and Japanese subjects are given in Table 4. These results suggest that the effect of ethnicity on baxdrostat PK was mild at most and did not appear to be clinically significant.

Table 4 Statistical Analysis of the Effect of Ethnicity on Baxdrostat (PK Population)

		Geometric LS Mean					
		Cohort 3 3 mg (JPN) (Test)		Cohort 2 3 mg (CAU) (Reference)		Geometric LS Mean Ratio (Test/Reference)	
Study Day	**Parameter**	**n**	**Result**	**n**	**Result**	**Estimate**	**90% CI**
Day 1 Single Dose	C_{max} (ng/mL)	8	38.200	8	37.011	1.032	(0.848, 1.257)
	AUC_{last} (h*ng/mL)	8	948.518	8	1086.906	0.873	(0.695, 1.096)
	AUC_{inf} (h*ng/mL)	8	965.734	8	1129.066	0.855	(0.675, 1.084)
Day 10 Multiple Doses	$C_{max,ss}$ (ng/mL)	8	66.525	8	69.660	0.955	(0.754, 1.209)
	$AUC_{0-24,ss}$ (h*ng/mL)	8	954.443	8	1080.409	0.883	(0.693, 1.127)

Abbreviations: AUC = area under the concentration-time curve; $AUC_{0-24,ss}$ = AUC from time 0 to 24 hours at steady state; AUC_{inf} = AUC from time 0 extrapolated to infinity; AUC_{last} = AUC from time 0 to the time of the last quantifiable concentration; CAU = Caucasian; CI = confidence interval; C_{max} = maximum plasma concentration; $C_{max,ss}$ = C_{max} at steady state; JPN = Japanese; ln = natural logarithm; LS = least squares; n = number; PK = pharmacokinetic

Notes: The C_{max} and AUC analyses were performed on ln-transformed parameters using a linear mixed effects model with ethnicity as fixed effects and subject as a random effect.

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CIN-107-M PK: Following single and multiple oral dosing of baxdrostat, there was an increase in primary PK parameter estimates of CIN-107-M with increasing dose over the dosing range of 1 mg to 10 mg in Japanese subjects. CIN-107-M appeared steadily in systemic circulation reaching peak levels by 24.00 h (single dose) and 4.00 h (multiple dose) in each cohort. Both single- and multiple-dose PK parameters appeared to increase in an approximately dose-proportional manner (Table 5).

Table 5 Statistical Analysis of Dose Proportionality of CIN-107-M in Japanese Subjects (PK Population)

Study Day	Parameter	n	Intercept	Slope	90% CI
Day 1 Single Dose	C_{max} (ng/mL)	25	-0.292	1.028	(0.863, 1.194)
	AUC_{last} (h*ng/mL)	25	3.721	1.044	(0.816, 1.273)
	AUC_{inf} (h*ng/mL)	23	3.962	0.917	(0.680, 1.154)
Day 10 Multiple Doses	$C_{max,ss}$ (ng/mL)	24	0.714	1.002	(0.758, 1.245)
	$AUC_{0-24,ss}$ (h*ng/mL)	24	3.583	1.027	(0.779, 1.275)

Abbreviations: AUC = area under the concentration-time curve; $AUC_{0-24,ss}$ = AUC from time 0 to 24 hours at steady state; AUC_{inf} = AUC from time 0 extrapolated to infinity; AUC_{last} = AUC from time 0 to the time of the last quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; $C_{max,ss}$ = C_{max} at steady state; ln = natural logarithm; n = number; PK = pharmacokinetic

Notes: The dose proportionality analyses were performed using the power model: ln(PK) = intercept + slope*ln(dose) + e, where PK is the PK parameter and e is the error term. A value of slope = 1 indicates dose proportionality.

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The GLSM ratio and 90% CI of PK parameters of CIN-107-M following single (C_{max}/D and AUC_{inf}/D) and multiple ($C_{max,ss}$/D and $AUC_{0-24,ss}$/D) baxdrostat dosing are listed in the table below. These results provide evidence to indicate that the dose-normalized PK parameters of CIN-107-M were similar between the three cohorts (Cohort 2 vs Cohort 1 [Table 6] and Cohort 4 vs Cohort 1 [Table 7]) of Japanese subjects. The 90% CI of the GLSM ratio were wider for CIN-107-M suggesting higher variability in PK parameter estimates compared to baxdrostat.

Table 6 Dose Normalized Treatment Comparison of CIN-107-M in Japanese Cohort 2 (3 mg) and Cohort 1 (1 mg) (PK Population)

		Geometric LS Mean					
		Cohort 2 3 mg (JPN) (Test)		Cohort 1 1 mg (JPN) (Reference)		Geometric LS Mean Ratio (Test/Reference)	
Study Day	**Parameter**	**n**	**Result**	**n**	**Result**	**Estimate**	**90% CI**
Day 1 Single Dose	C_{max}/D (ng/mL/mg)	8	0.903	8	0.688	1.313	(0.889, 1.938)
	AUC_{inf}/D (h*ng/mL/mg)	8	50.689	7	50.824	0.997	(0.569, 1.748)
Day 10 Multiple Doses	$C_{max,ss}$/D (ng/mL/mg)	8	2.146	8	1.991	1.078	(0.606, 1.916)
	$AUC_{0-24,ss}$/D (h*ng/mL/mg)	8	39.153	8	34.945	1.120	(0.624, 2.011)

Abbreviations: /D = dose normalized; ANOVA = analysis of variance; AUC = area under the concentration-time curve; $AUC_{0-24,ss}$ = AUC from time 0 to 24 hours at steady state; AUC_{inf} = AUC from time 0 extrapolated to infinity; CI = confidence interval; C_{max} = maximum plasma concentration; $C_{max,ss}$ = C_{max} at steady state; JPN = Japanese; ln = natural logarithm; LS = least squares; n = number; PK = pharmacokinetic

Notes: The C_{max} and AUC analyses were performed on ln-transformed dose normalized parameters using an ANOVA model with dose level as a fixed effect and subject as a random effect.

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Table 7 Dose Normalized Treatment Comparison of CIN-107-M in Japanese Cohort 4 (10 mg) and Cohort 1 (1 mg) (PK Population)

		Geometric LS Mean					
		Cohort 4 10 mg (JPN) (Test)		Cohort 1 1 mg (JPN) (Reference)		Geometric LS Mean Ratio (Test/Reference)	
Study Day	**Parameter**	**n**	**Result**	**n**	**Result**	**Estimate**	**90% CI**
Day 1 Single Dose	C_{max}/D (ng/mL/mg)	9	0.746	8	0.688	1.084	(0.742, 1.584)
	AUC_{inf}/D (h*ng/mL/mg)	8	42.256	7	50.824	0.831	(0.474, 1.457)
Day 10 Multiple Doses	$C_{max,ss}$/D (ng/mL/mg)	8	2.003	8	1.991	1.006	(0.566, 1.788)
	$AUC_{0-24,ss}$/D (h*ng/mL/mg)	8	37.288	8	34.945	1.067	(0.594, 1.916)

Abbreviations: /D = dose normalized; ANOVA = analysis of variance; AUC = area under the concentration-time curve; $AUC_{0-24,ss}$ = AUC from time 0 to 24 hours at steady state; AUC_{inf} = AUC from time 0 extrapolated to infinity; CI = confidence interval; C_{max} = maximum plasma concentration; $C_{max,ss}$ = C_{max} at steady state; JPN = Japanese; ln = natural logarithm; LS = least squares; n = number; PK = pharmacokinetic

Notes: The C_{max} and AUC analyses were performed on ln-transformed dose normalized parameters using an ANOVA model with dose level as a fixed effect and subject as a random effect.

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The GLSM ratio and 90% CI of dose-normalized PK parameters of CIN-107-M following single (C_{max}, AUC_{last}, and AUC_{inf}) and multiple ($C_{max,ss}$ and $AUC_{0-24,ss}$) baxdrostat dosing in Caucasian and Japanese subjects are given in the table below. The GLSM estimates were slightly lower in Caucasians compared to Japanese subjects suggesting that ethnicity had a mild effect on CIN-107-M PK (Table 8). The slightly higher exposure of CIN-107-M in Japanese subjects is not expected to have a clinically meaningful impact on the PD of baxdrostat since the metabolite represents < 10% of the total AUC for drug-related material.

Table 8 Statistical Analysis of the Effect of Ethnicity on CIN-107-M (PK Population)

		Geometric LS Mean					
		Cohort 3 3 mg (JPN) (Test)		Cohort 2 3 mg (CAU) (Reference)		Geometric LS Mean Ratio (Test/Reference)	
Study Day	**Parameter**	**n**	**Result**	**n**	**Result**	**Estimate**	**90% CI**
Day 1 Single Dose	C_{max} (ng/mL)	8	2.708	8	1.602	1.690	(1.152, 2.479)
	AUC_{last} (h*ng/mL)	8	141.224	8	83.595	1.689	(1.031, 2.767)
	AUC_{inf} (h*ng/mL)	8	152.066	8	88.473	1.719	(1.034, 2.857)
Day 10 Multiple Doses	$C_{max,ss}$ (ng/mL)	8	6.438	8	4.697	1.371	(0.790, 2.380)
	$AUC_{0-24,ss}$ (h*ng/mL)	8	117.460	8	81.962	1.433	(0.838, 2.452)

Abbreviations: AUC = area under the concentration-time curve; $AUC_{0-24,ss}$ = AUC from time 0 to 24 hours at steady state; AUC_{inf} = AUC from time 0 extrapolated to infinity; AUC_{last} = AUC from time 0 to the time of the last quantifiable concentration; CAU = Caucasian; CI = confidence interval; C_{max} = maximum plasma concentration; $C_{max,ss}$ = C_{max} at steady state; JPN = Japanese; ln = natural logarithm; LS = least squares; n = number; PK = pharmacokinetic

Notes: The C_{max} and AUC analyses were performed on ln-transformed parameters using a linear mixed effects model with ethnicity as fixed effects and subject as a random effect.

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Pharmacodynamic Results:

A marked inhibition of aldosterone synthesis was observed after the multiple dosing period of baxdrostat for all dose levels.

The effect of baxdrostat on aldosterone for C_{max} and AUC_{0-3} was observed for each dose level, with an approximate 70% to 90% decrease in mean C_{max} and AUC_{0-3} typically being observed on Day 10 as compared to Day -1. No marked effect on aldosterone T_{max} was observed.

Comparing Cohort 2 (3 mg) vs Cohort 1 (1 mg) following multiple dosing, the ratio (%) of Day 10/Baseline for AUC_{0-3} and C_{max} were lower in Cohort 2 in comparison to Cohort 1. The GLSM ratio and corresponding 90% CI of C_{max} and AUC_{0-3} provide evidence to indicate that the change of AUC_{0-3} and C_{max} from Day 1 to Day 10 is larger in Cohort 2 compared to Cohort 1.

Comparing Cohort 4 (10 mg) vs Cohort 1 (1 mg) following multiple dosing, the ratio (%) of Day 10/Baseline for AUC_{0-3} and C_{max} were lower in Cohort 4 in comparison to Cohort 1. The GLSM ratio and corresponding 90% CI of C_{max} and AUC_{0-3} provide evidence to indicate that the change of AUC_{0-3} and C_{max} from Day 1 to Day 10 is larger in Cohort 4 compared to Cohort 1.

Inhibition of aldosterone was similar in Japanese and Caucasian subjects when comparing the Japanese Cohort 2 (3 mg baxdrostat) to Caucasian Cohort 3 (3 mg baxdrostat).

There were no changes in total cortisol concentrations after the multiple dosing period of baxdrostat for all dose levels compared to placebo groups. No effect of baxdrostat on total cortisol for C_{max}, AUC_{0-3}, and T_{max} was observed for each dose level.

No clear dose-dependent increases or decreases were observed for plasma sodium, chloride, and potassium levels or blood pressure changes over time.

Conclusions:

- Single and multiple doses of baxdrostat were safe and well tolerated in this group of Japanese and Caucasian subjects.
- Baxdrostat was readily absorbed into systemic circulation with a median T_{max} ranging from 1.00 to 3.50 h following single and multiple dosing. CIN-107-M appeared steadily in systemic circulation and peak levels were attained by 24.00 h (single dosing) and 4.00 h (multiple dosing) in each cohort.
- Single and multiple ascending doses of baxdrostat in Japanese subjects from 1 mg to 10 mg showed an increase in primary PK parameters of baxdrostat and CIN-107-M with increasing dose on Day 1 (single dose) and Day 10 (multiple dose).
- A dose-proportional increase in single dose (C_{max}, AUC_{last}, AUC_{inf}) and multiple dose ($C_{max,ss}$ and $AUC_{0-24,ss}$) primary PK parameters of baxdrostat was observed between the 1 mg to 10 mg dose range in Japanese subjects. For CIN-107-M, C_{max} and AUC values increased in an approximately dose-proportional manner following single and multiple baxdrostat dosing.
- Dose-normalized primary PK parameters for baxdrostat and CIN-107-M were generally similar between the 3 Japanese cohorts (Cohort 2 vs Cohort 1 and Cohort 4 vs Cohort 1) following single and multiple oral doses.

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- Ethnicity had no clinically meaningful impact on the PK of baxdrostat. The effect of ethnicity on CIN-107-M PK was mild. The slightly higher exposure of CIN-107-M in Japanese subjects is not expected to have a clinically meaningful impact on the PD of baxdrostat since the metabolite represents < 10% of the total AUC for drug-related material.
- Treatment with baxdrostat resulted in marked, selective, and generally dose-dependent inhibition of aldosterone synthesis without impact on total cortisol levels for both Japanese and Caucasian subjects.
- No clear dose-dependent increases or decreases were observed for plasma potassium, sodium, and chloride levels over time nor were there any clinically meaningful changes in blood pressure.
- In general, both single- and multiple-dose PK parameters of baxdrostat were similar between Japanese and Caucasian subjects. Baxdrostat also caused a dose-dependent decrease in serum aldosterone levels with no effect on serum cortisol levels. There is no evidence that any baxdrostat dose adjustment is necessary in the Japanese population.

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