Effect of Hepatic Impairment on the Pharmacokinetics, Safety, and Tolerability of Oral Paltusotine, A Non-Peptide, Selective Somatostatin Receptor Subtype 2 Agonist

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BACKGROUND AND OBJECTIVES

- Paltusotine is a once-daily, oral, small molecule, selective somatostatin receptor type 2 (SST2) agonist in clinical development for the treatment of acromegaly and carcinoid syndrome caused by a neuroendocrine tumor[1-3]
- Paltusotine was discovered via a medicinal chemistry process that focused on potency and selectivity at the SST2 receptor, sufficient bioavailability after oral administration, and low potential for drug-drug interactions[1]
- Ongoing studies of paltusotine include phase 3 trials in patients with acromegaly and a phase 2 trial in patients with carcinoid syndrome associated with neuroendocrine tumors
- The objective of this study was to assess the effects of varying degrees of hepatic impairment on the PK, safety, and tolerability of paltusotine

STUDY DESIGN AND METHODS

- This multicenter, open-label, phase 1 study enrolled participants with mild, moderate, and severe hepatic impairment (based on Child-Pugh classification) and matched healthy participants
- All participants received a single 20-mg oral dose of paltusotine (one 20-mg tablet) after an overnight fast of at least 10 hours and remained fasted for 4 hours after dosing
- Analysis of paltusotine in plasma was performed using a validated liquid chromatography–tandem mass spectrometry method, and PK parameters were summarized using noncompartmental analysis
- Geometric mean ratios of maximum observed plasma concentration (C_{max}) and area under the concentration-time curve (AUC) were calculated for each hepatic impairment group (mild, moderate, severe) relative to the control group with normal hepatic function
- The primary analysis was an analysis of variance with hepatic condition (normal, mild, moderate, severe) as a fixed effect and the log transformed PK parameter as the dependent variable
  - A sensitivity analysis using matched pairs mixed models for repeated measures accounted for participant age and body mass index

RESULTS

- A total of 36 participants were enrolled in the study
  - All participants completed the study and were included in the safety and PK populations

Demographic Characteristics

	Mild Hepatic Impairment (n=8)	Moderate Hepatic Impairment (n=8)	Severe Hepatic Impairment (n=6)	Normal Control (n=14)
Male, n (%)	6 (75.0)	5 (62.5)	5 (83.3)	10 (71.4)
Age, years				
Mean (SD)	60.8 (8.9)	55.0 (8.5)	54.5 (8.6)	57.8 (7.5)
Range	49-75	39-64	42-69	42-70
Body mass index, kg/m^2				
Mean (SD)	31.8 (3.9)	31.4 (5.2)	28.0 (3.7)	30.7 (4.4)
Range	24.7-37.9	24.0-37.6	24.9-35.1	24.5-36.0

RESULTS

- Following single oral administration of 20-mg paltusotine, the mean plasma concentration of paltusotine peaked rapidly (median time to C_{max}: 1.6-3.0 hours postdose); thereafter, plasma concentrations declined across groups in a similar manner
  - Paltusotine was measurable in systemic circulation through 144 hours postdose
- PK parameters were similar across all hepatic impairment groups when compared with healthy participants, as indicated by geometric mean ratio values

Summary of Paltusotine Pharmacokinetic Parameters

	Mild Hepatic Impairment (n=8)	Moderate Hepatic Impairment (n=8)	Severe Hepatic Impairment (n=6)	Normal Control (n=14)
C_{max}, ng/mL	133.3 (56.6)	100.2 (74.6)	110.3 (72.7)	101.4 (53.7)
t_{max}, h	1.6 (0.8-4.0)	2.0 (0.8-6.0)	3.0 (0.8-4.0)	2.0 (0.8-6.0)
AUC_{0-t}, ng·h/mL	1821.5 (888.3)	1575.9 (1043.9)	1682.7 (1185.0)	1776.0 (913.9)
AUC_{0-inf}, ng·h/mL	1884.5 (926.0)	1616.8 (1046.1)	1736.6 (1225.9)	1838.2 (946.7)
$t_{1/2}$, h	29.5 (9.4)	31.2 (7.9)	29.5 (8.4)	32.8 (6.9)
CL/F, L/h	15.5 (13.5)	24.9 (25.9)	15.9 (8.5)	14.1 (7.5)
Vz/F, L	565.2 (347.5)	1052.0 (1105.8)	666.0 (479.1)	660.5 (407.3)

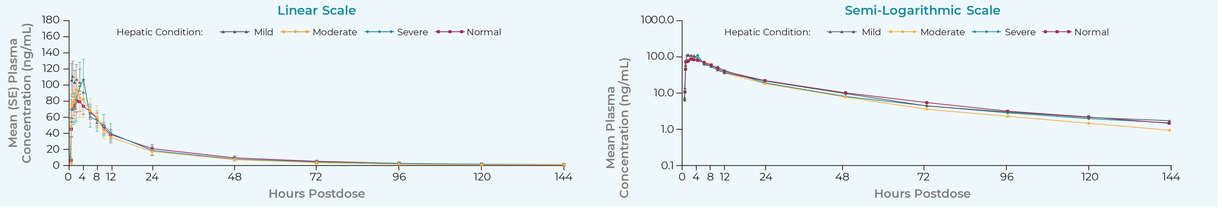
Values shown are mean (SD), except for t_{max}, which is median (range).
AUC_{0-inf} = AUC from time 0 extrapolated to infinity; AUC_{0-t} = AUC from time 0 to the last quantifiable concentration; CL/F = apparent total body clearance; $t_{1/2}$ = apparent terminal phase half-life; t_{max} = time to C_{max}; Vz/F = apparent volume of distribution during terminal phase.

Geometric Mean Ratios for Paltusotine Pharmacokinetic Parameters

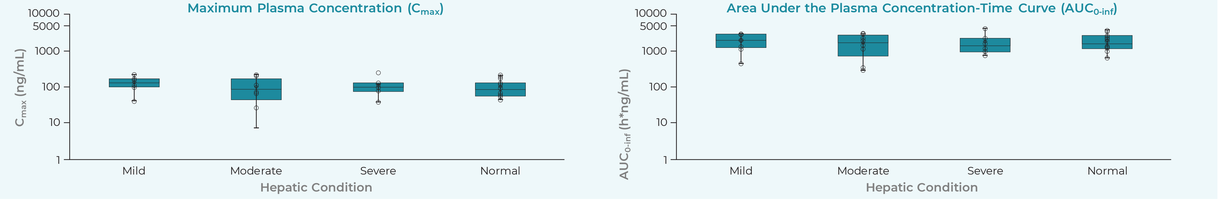
	Mild Hepatic Impairment (n=8)	Moderate Hepatic Impairment (n=8)	Severe Hepatic Impairment (n=6)
Primary Analysis*			
C_{max}, ng/mL	1.35 (0.79, 2.31)	0.76 (0.45, 1.31)	1.05 (0.58-1.90)
AUC_{0-t}, ng·h/mL	1.00 (0.60, 1.68)	0.74 (0.44, 1.24)	0.9 (0.51, 1.59)
AUC_{0-inf}, ng·h/mL	1.00 (0.60, 1.66)	0.75 (0.45, 1.24)	0.90 (0.51, 1.57)
Sensitivity Analysis†			
C_{max}, ng/mL	1.38 (0.87, 2.20)	0.74 (0.39, 1.41)	1.04 (0.59, 1.85)
AUC_{0-t}, ng·h/mL	0.95 (0.59, 1.52)	0.71 (0.40, 1.25)	0.93 (0.51, 1.70)
AUC_{0-inf}, ng·h/mL	0.94 (0.59, 1.50)	0.72 (0.41, 1.25)	0.94 (0.52, 1.70)

Values shown are geometric mean ratio (90% CI).
*Analysis of covariance with hepatic condition (normal, mild, moderate, severe) as a fixed effect and log transformed PK parameter as the dependent variable.
†Matched pairs mixed models for repeated measures model with hepatic condition (normal vs mild, moderate, or severe), age, and BMI as fixed effects and log transformed PK parameter as the dependent variable. Separate models were fit for each hepatic impairment group.
AUC_{0-inf} = AUC from time 0 extrapolated to infinity; AUC_{0-t} = AUC from time 0 to the last quantifiable concentration.

Mean Plasma Concentration of Paltusotine Over Time



Paltusotine Pharmacokinetic Parameters, by Degree of Hepatic Impairment



- The incidence of treatment-emergent adverse events (TEAEs) was similar across all 4 groups
  - No participants discontinued from the study due to a TEAE
  - The most common TEAEs were diarrhea (16.7% overall) and headache (5.6% overall)
  - One participant in the mild hepatic impairment group died of natural causes 26 days after administration of paltusotine; this serious adverse event was considered by the investigator as not related to study drug

Summary of Adverse Events

	Mild Hepatic Impairment (n=8)	Moderate Hepatic Impairment (n=8)	Severe Hepatic Impairment (n=6)	Normal Control (n=14)
Any TEAE	2 (25.0)	2 (25.0)	2 (33.3)	4 (28.6)
Severe TEAE	1 (12.5)	0	0	0
Drug-related TEAE	2 (25.0)	2 (25.0)	2 (33.3)	3 (21.4)
Serious TEAE	1 (12.5)	0	0	0
Serious drug-related TEAE	0	0	0	0
Most common TEAEs*				
Diarrhea	1 (12.5)	1 (12.5)	1 (16.7)	3 (21.4)
Headache	0	1 (12.5)	1 (16.7)	0

*≥5% of participants overall.
TEAE = treatment-emergent adverse event.

CONCLUSIONS

- After single oral administration of paltusotine 20-mg tablet, peak and total plasma exposures of paltusotine were similar across participants with varying degrees of hepatic impairment when compared with participants with normal hepatic function
- There were no changes in paltusotine plasma exposure that would be considered clinically meaningful or sufficient to warrant dose adjustment for mild, moderate, or severe hepatic impairment
- Single oral administration of paltusotine 20-mg tablet was generally safe and well tolerated in this study

REFERENCES
1. Zhao J, et al. *ACS Med Chem Lett.* 2023;14(1):66-74. **2.** Madan A, et al. *Pituitary.* 2022;25(2):328-339. **3.** Gadelha MR, et al. *J Clin Endocrinol Metab.* 2023;108(5):e148-e159.

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DISCLOSURES
All authors are employees of Crinetics Pharmaceuticals, Inc.