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Effect of Hepatic Impairment on Pharmacokinetics, Safety, and Tolerability of Oral Paltusotine, a Small-Molecule, Selective Somatostatin Receptor Subtype 2 Agonist

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BACKGROUND

Paltusotine is an investigational oral, once-daily, small molecule somatostatin receptor type 2 agonist in development for the treatment of acromegaly and carcinoid syndrome associated with neuroendocrine tumors.

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. A single 20-mg oral dose of paltusotine was administered after an overnight fast (≥10 hours). Analysis of paltusotine in plasma was performed using validated liquid chromatography–tandem mass spectrometry. Geometric mean ratios of pharmacokinetic (PK) parameters were calculated from an analysis of variance (primary analysis) with hepatic condition (normal, mild, moderate, severe) as a fixed effect and log transformed PK parameter as the dependent variable. A sensitivity analysis (matched pairs mixed models for repeated measures) accounted for participant age and BMI.

RESULTS

The study enrolled participants with mild (n=8), moderate (n=8), or severe (n=6) hepatic impairment and matched healthy controls (n=14). Most participants were male (72.2%); mean age was 57.3 years, and mean BMI was 30.7 kg/m2. Following single oral administration of 20-mg paltusotine, mean plasma concentration of paltusotine peaked rapidly; median time to maximum concentration was 2.0 hours postdose in healthy controls and 1.6 to 3.0 hours in hepatic impairment groups. Maximum plasma concentration and total plasma exposure of paltusotine were similar across all hepatic impairment groups when compared with healthy participants (Table). Results of the sensitivity analysis were consistent with those from the primary analysis. The most common (≥5% of participants) treatment-emergent adverse events (TEAEs) were diarrhea (16.7%) and headache (5.6%). The incidence of TEAEs was similar across all 4 groups. No participant discontinued the study due to a TEAE, and no serious drug-related TEAEs were reported.

Paltusotine Pharmacokinetics: Geometric Mean Ratios

	Mild Hepatic Impairment (n=8)	Moderate Hepatic Impairment (n=8)	Severe Hepatic Impairment (n=6)
C_{max}, ng/mL	1.35 (0.79-2.31)	0.76 (0.45-1.31)	1.05 (0.58-1.90)
AUC_{0-inf}, ng●h/mL	1.00 (0.60-1.66)	0.75 (0.45-1.24)	0.90 (0.51-1.57)

Values shown are geometric mean ratio (90% CI) for each impairment group versus healthy controls. C_{max}=maximum plasma concentration; AUC_{0-inf}=area under the concentration-time curve from time 0 extrapolated to infinity.

CONCLUSIONS

Peak and total plasma exposure, safety, and tolerability profiles of paltusotine were similar in participants with varying degrees of hepatic impairment 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.

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