Absolute Oral Bioavailability and Absorption, Metabolism, Excretion of [^{14}C]-Labeled Paltusotine (CRN00808), an Orally Bioavailable, Nonpeptide, Selective, Somatostatin Receptor 2 (sst2) Biased Agonist for the Treatment of Acromegaly

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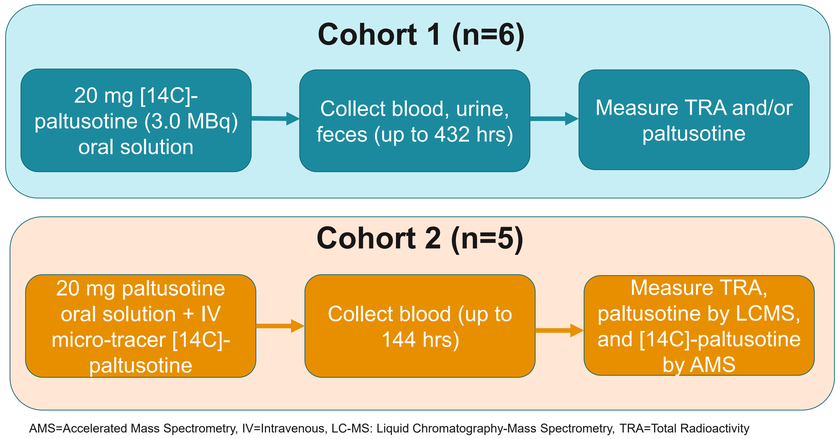
Summary

Injected depot formulations of somatostatin peptide analogs are routinely used to treat acromegaly and neuroendocrine tumors (NETs). Paltusotine (CRN00808), a small molecule nonpeptide selective somatostatin receptor 2 (sst2) agonist, is being evaluated for efficacy and safety in patients with acromegaly. The current Phase 1 study (NCT04246749) was conducted in two Parts: In Part A, the absorption, metabolism, excretion, and mass balance of a single oral dose of 20 mg [^{14}C]-paltusotine (3.0 MBq) oral solution was characterized in six healthy male subjects. Plasma, blood, urine, and feces were collected for up to 432 hours, and were analyzed for total radioactivity and paltusotine concentrations (plasma only). Metabolite profiling was conducted on the plasma, urine, and feces samples. In Part B, the absolute bioavailability of paltusotine was determined by administering a single oral dose of 20 mg paltusotine compared with a single micro-tracer intravenous (IV) bolus injection of 50 µg [^{14}C]-paltusotine (0.0185 MBq) in five healthy male subjects. The IV dose was administered approximately 90 minutes after the oral dose. Plasma samples were collected for up to 144 hours and were analyzed for paltusotine and [^{14}C]-paltusotine concentrations. Part A of the study show that >90% of radioactivity was recovered within 7 days of dosing. The primary route of excretion was the feces (89.9% of dose) with minimal excretion in the urine (3.9% of dose). Absorption of total [^{14}C]-paltusotine-derived radioactivity in plasma was rapid (median t_{max}=1 hour), and the geometric mean of C_{max}, $AUC_{0\text{-}inf}$, and $t_{1/2}$ were determined to be 189 ng-equivalents/mL, 3180 ng-equivalents.hr/mL, and 31 hours, respectively. The pharmacokinetic parameters of unchanged paltusotine in plasma were similar, suggesting that majority of the circulating drug-derived radioactivity is accounted for by unchanged paltusotine and there are no abundant circulating metabolites. Data from Part B of the study show that the mean oral bioavailability of paltusotine was 70% and the mean clearance and volume of distribution after IV administration were 5.3 L/h and 240 L, respectively. Treatment emergent adverse events associated with paltusotine were generally mild and transient, and consistent with those reported with other somatostatin agonists. In conclusion, results from this clinical trial in healthy volunteers confirm that paltusotine has excellent drug-like properties for chronic once-daily oral treatment of patients with acromegaly and NETs.

ClinicalTrials.gov Identifier: NCT04246749

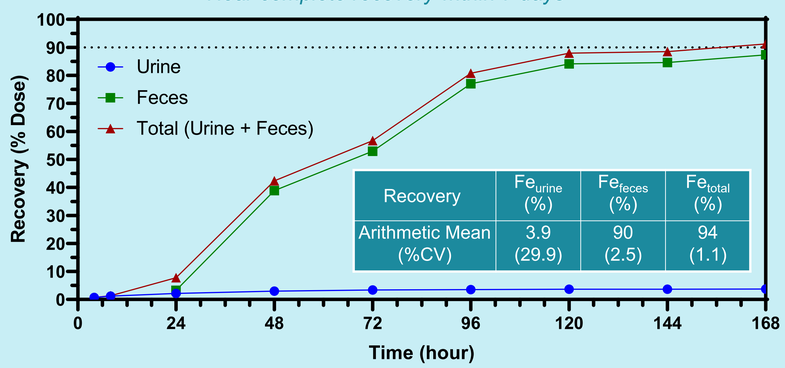
Study Design and Methods



AMS=Accelerated Mass Spectrometry, IV=Intravenous, LC-MS: Liquid Chromatography-Mass Spectrometry, TRA=Total Radioactivity

Recovery of Paltusotine in Excreta

Near complete recovery within 7 days



Recovery	Fe_{urine} (%)	Fe_{feces} (%)	Fe_{total} (%)
Arithmetic Mean (%CV)	3.9 (29.9)	90 (2.5)	94 (1.1)

Figure 1: Mean Cumulative Total Radioactivity Recovery in Urine, Feces, and Total Recovery (n=6)

Fe=Fraction dose excreted. Data shown in the graph are geometric means.

Plasma Total Radioactivity (TRA) and Paltusotine

Unchanged paltusotine is the primary circulating species

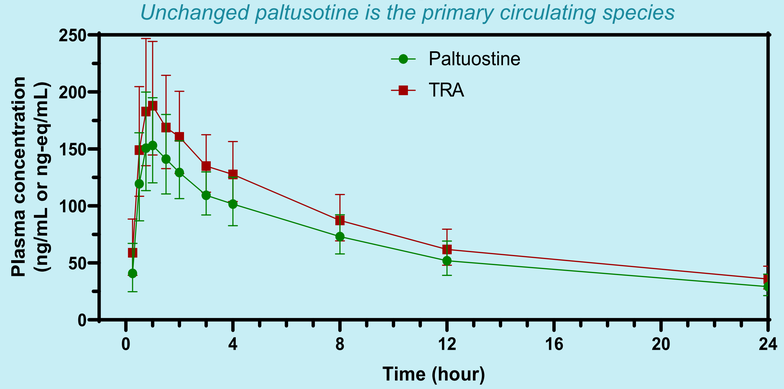


Figure 2: Mean Concentration-Time Profiles of Total Radioactivity and Paltusotine in Plasma (n=6)

TRA=Total Radioactivity. Data shown are geometric means with 95% confidence intervals

Absolute Oral Bioavailability of Paltusotine

Oral bioavailability of paltusotine is high (70%)

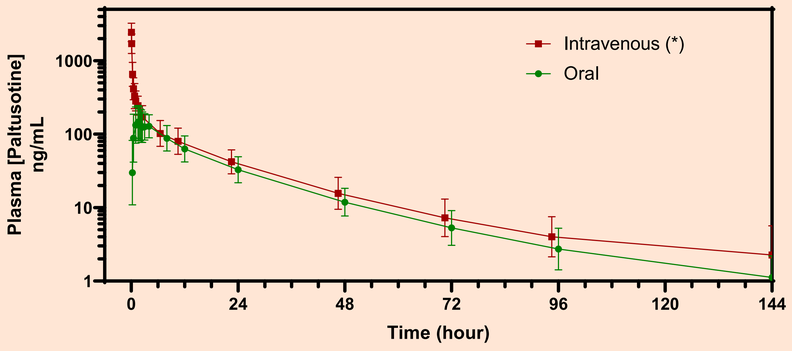


Figure 3: Concentration-Time Profiles of Paltusotine and Dose Normalized [^{14}C]-Paltusotine in Plasma (n=5)

* Dose normalized concentration. Data shown are geometric means with 95% confidence intervals
Time 0 is the nominal time 0 relative to oral CRN00808 and IV [^{14}C]-paltusotine dosing, respectively

IV/Oral PK parameters

Paltusotine is suited for once-a-day dosing

Statistic	C_{max} (ng[eq]/mL)	t_{max}[a] (h)	$AUC_{0\text{-}last}$ (ng[eq].h/mL)	$AUC_{0\text{-}inf}$ (ng[eq].h/mL)	$t_{1/2}$ (h)	CL[b] (L/h)	V_z[b] (L)	%F[c]
Plasma paltusotine after oral administration								
Arithmetic Mean (%CV)	170 (37.4)	1.5	2740 (30.6)	2790 (29.7)	29 (24.2)	NA	NA	70 (17.0)
Min-Max	138 - 283	1.0 - 4.0	1930 - 4080	1970 - 4100	20 - 38	NA	NA	59 - 82
Plasma [^{14}C] paltusotine after IV administration								
Arithmetic Mean (%CV)	2480 (23.4)	0.03	3930 (29.3)	4030 (29.0)	31 (31.9)	5.3 (25.7)	240 (43.8)	NA
Min-Max	1880 - 3300	0.030 - 0.030	2970 - 5530	3050 - 5690	20 - 45	3.5 - 6.6	120 - 390	NA

Table 1: Summary Statistics of Pharmacokinetic Parameters for Paltusotine and Dose Normalized [^{14}C]-Paltusotine in Plasma (n=5)

CV=coefficient of variation; IV=intravenous; Max=maximum; Min=minimum, PK=pharmacokinetics, NA=Not applicable
[a] For t_{max} the median is presented instead of geometric mean
[b] CL and V_z for [^{14}C]-paltusotine in plasma after IV administration only.
[c] Absolute bioavailability of oral paltusotine was calculated as plasma paltusotine oral $AUC_{0\text{-}inf}$ against dose normalized [^{14}C]-paltusotine IV $AUC_{0\text{-}inf}$, expressed as: $AUC_{0\text{-}inf,oral}$/dose normalized $AUC_{0\text{-}inf,IV}$

Conclusions

Pharmacokinetics

- The parent drug paltusotine appears to be the primary circulating species and drug-derived metabolite(s) account for a relatively small portion (<25%) of the total plasma radioactivity.
- After administration as an oral solution an arithmetic mean of 94% of the administered dose of 20 mg [^{14}C]-paltuostine (3.0 MBq radioactivity) was recovered in urine and feces. The total radioactivity was mainly excreted in feces (90%) and to a lesser extent in urine (3.9%).
- The absolute bioavailability of 20 mg paltusotine after a single oral dose was 70%.

Safety

- Treatment emergent adverse events were generally mild and transient, and consistent with those reported with other somatostatin agonists.
- Paltusotine was well tolerated by healthy volunteers in this study.

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