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 and NETs. 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 [14C]-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 [14C]-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 [14C]-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 (93.9% of dose). Absorption of total [14C]-paltusotine-derived radioactivity in plasma was rapid (median tmax=1 hour), and the geometric mean of Cmax, AUC0-∞, and t1/2 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 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.

### Summary

The absolute oral bioavailability of paltusotine is high (70%). Paltusotine was well tolerated by healthy volunteers in this study.

### Clinical Trials

ClinicalTrials.gov Identifier: NCT04246749

### Study Design and Methods

#### Cohort 1 (n=6)
- 20 mg [14C]-paltusotine (3.0 MBq) oral solution
  - Collect blood, urine, feces (up to 432 hrs)
  - Measure TRA and/or paltusotine

#### Cohort 2 (n=5)
- 20 mg paltusotine oral solution + IV micro-tracer [14C]-paltusotine
  - Collect blood (up to 144 hrs)
  - Measure TRA paltusotine by LCMS, and [14C]-paltusotine by AMS

### IV/Oral PK parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IV (ng/mL or ng-eq/mL)</th>
<th>Oral (ng/mL or ng-eq/mL)</th>
<th>Arithmetic Mean (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tmax (h)</td>
<td>1.5</td>
<td>1.0</td>
<td>1.5 (29.9)</td>
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<td>Cmax (ng/mL)</td>
<td>2740</td>
<td>2790</td>
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<td>t1/2 (h)</td>
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<td>31 (31.5)</td>
<td>31 (31.5)</td>
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<td>CLb (L/h)</td>
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<td>29.7</td>
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<tr>
<td>Vz (L)</td>
<td>5.3 (26.7)</td>
<td>70 (17.0)</td>
<td>70 (17.0)</td>
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<tr>
<td>Min-Max</td>
<td>1880 - 3300</td>
<td>1930 - 4080</td>
<td>1930 - 4080</td>
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</tbody>
</table>

### 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 [14C]-paltusotine (3.0 MBq radioactivity) was recovered in urine and feces. The total radioactivity was mainly excrated in feces (90%) and to a lesser extent in urine (3%).
- 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.