Pharmacokinetics and Safety of an Improved Oral Formulation of Paltusotine, a Selective, Nonpeptide Somatostatin Receptor 2 (SST2) Agonist for the Treatment of Acromegaly

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Introduction

- Depot injection formulations of peptide somatostatin receptor ligands (SRLs) are routinely used to treat acromegaly and neuroendocrine tumors (NETs)
- Paltusotine (CRN00808), an orally administered small molecule nonpeptide selective somatostatin receptor 2 (SST2) agonist has been shown to maintain GH and IGF-1 levels in acromegaly patients previously on depot SRLs (ACROBAT Edge NCT03789656; Endo 2021 Abstract #7452)
- In healthy volunteers, the capsule formulation used did not exhibit dose proportional pharmacokinetics (PK) at doses >40 mg, required a 2-hour post-dose fast in overnight fasted subjects, and had the potential for reduced bioavailability when taken with proton pump inhibitors (PPI)
- In this poster, we provide data from a study in healthy volunteers of a spray-dried dispersion (SDD) tablet formulation of paltusotine developed with improved solubility in the physiological pH range

Study Design

Male and female healthy volunteers (n=48) who met inclusion/exclusion criteria were enrolled in a single-center Phase 1 study (ACTRN12619001562167; Study CRN00808-07). See Table 1.

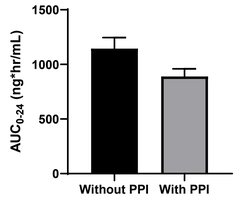
Cohort Objectives	Formulation	Period	Condition	Dose
Dose proportionality, effect of PPI, and food effect (Figures 1 and 2)	SDD Tablets	1	With PPI	20 mg
		2	Without PPI	20 mg
		3	Food effect	20 mg
		4	High dose	60 mg
Formulation comparison and effect of food timing (Figure 3)	HMG Caps	1	2 hr post-dose fast	20 mg
	SDD Tablets	2	2 hr post-dose fast	20 mg
		3	1 hr post-dose fast	20 mg
		4	0.5 hr post-dose fast	20 mg
Dose proportionality and effect of fasting (Figure 4)	SDD Tablets	1	1 hr post-dose fast	40 mg
		2	1 hr post-dose fast	80 mg
		3	4 hr post-dose fast	80 mg

HMG Caps=hot melt granulation capsule formulation, PPI=proton-pump inhibitor, SDD=spray dried dispersion tablet formulation
PPI: Lanzoprazole 15 mg was administered two times a day for three days prior to administration of paltusotine
Food effect was evaluated with coadministration of SDD tablets with high fat high calorie meal. For other periods in the same cohort, food was administered 2 hours post dose.
All subjects in all periods were fasted overnight. Sample size was 8-12 subjects in each period. 10 mg SDD tablets were used in this study.

Food Effect

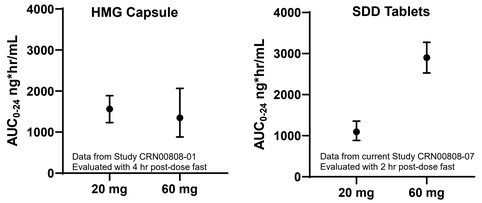
When SDD tablets were co-administered with a high-fat, high-calorie meal, AUC_{0-24} was decreased 83% compared to a fasting state. This is consistent with an 83% decrease in AUC when the HMG capsule formulation was co-administered with a high-fat, high calorie meal.

Figure 1. Effect of PPI on AUC_{0-24} of SDD Tablets (20 mg)



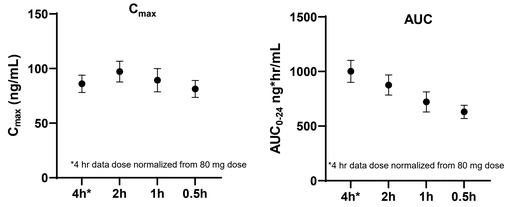
PPI decreased AUC of SDD tablets (20 mg) by only 25%

Figure 2. Comparison of dose proportionality of HMG capsules and SDD Tablets



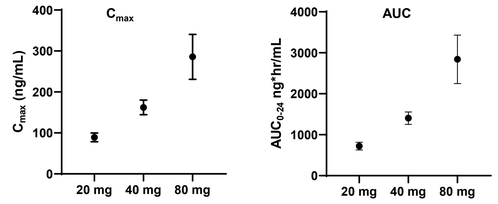
SDD tablets exhibit dose proportional increase in AUC compared with HMG capsules

Figure 3: Effect of post-dose fasting time on pharmacokinetics of SDD tablets (20 mg)



SDD tablets show small decrease in C_{max} and AUC as the post-dose fast time is reduced to 0.5 hr. A 0.5-1.0 hr post-dose fast balances patient convenience with highest achievable bioavailability at 4 hr post-dose fast

Figure 4. Dose proportionality of SDD tablets with 1 hr post-dose fast



SDD tablets exhibit dose proportional pharmacokinetics in the dose range 20-80 mg when administered with a 1 hr post-dose fast

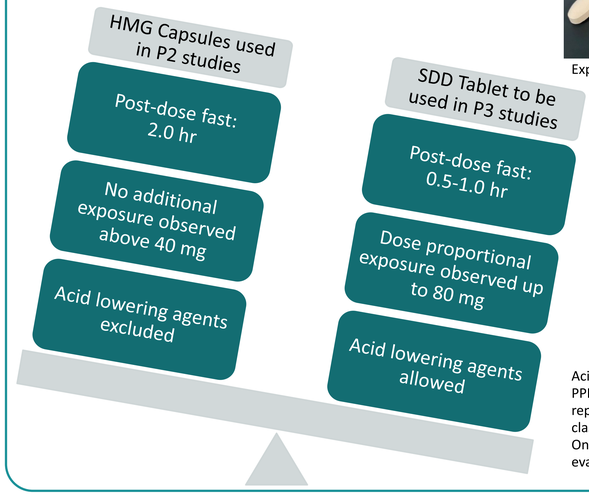
All data shown are Arithmetic Mean ± Standard Error of Mean.
For Study CRN00808-07 sample size was 8-12 subjects (All figures).
For Study CRN00808-01, data are from 5-6 subjects (HMG capsule data in Figure 2 only)

Safety

- The SDD tablet formulation of paltusotine was well tolerated
- Most common adverse events were diarrhea, abdominal pain, and headache, consistent with those previously reported and are similar to those observed with parenteral somatostatin receptor ligands
- There were no serious adverse events

SDD Tablets Exhibit Properties Superior to HMG Capsules

Expected ambient shipping and storage



Acid lowering agents include PPI, H2 blockers, antacids. PPIs represent the more effective class of acid lowering agents. Only the effect of PPI was evaluated in this study.

Conclusion

- An improved SDD tablet formulation of paltusotine has been identified and is planned to be utilized with a 1.0 hr post-dose fast in future trials including the P3 trials in acromegaly
- The SDD tablet formulation is expected to be more convenient for patients because it can be taken with acid lowering drugs and reduces the post-dose fasting time to 0.5-1.0 hr