T-2

Dose Selection for Paltusotine, a Once Daily Oral Nonpeptide, Somatostatin Receptor 2 Ligand, for the Treatment of Patients with Carcinoid Syndrome (CS)

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BACKGROUND: Long-acting somatostatin receptor ligands (LA-SRLs) are first line therapy for neuroendocrine tumor (NET) syndromes including acromegaly and the carcinoid syndrome (CS). In acromegaly, usually caused by a benign growth hormone-secreting pituitary tumor, two phase 2 studies (NCT 03789656 and 03792555) suggested that patients injected with SRLs can switch to once daily oral paltusotine (CRN00808), a nonpeptide, small molecule, somatostatin type 2 (SST2) receptor ligand (SRL) with 70% bioavailability, while maintaining stable serum IGF-1 levels. However, CS patients may require higher doses of an orally administered drug due to malabsorption and/or maldigestion commonly associated with the syndrome or its treatment and the pharmacokinetics (clearance and volume of distribution) of paltusotine may differ between CS and acromegaly because of differences in metabolic capacity of the liver and body composition.

METHODS: To design a PK/PD study evaluating the use of once daily oral paltusotine to control symptoms and inhibit functional tumor markers in patients with CS, we analyzed data from the capsule formulation used in the acromegaly patient studies to determine dose- and exposure-response and from a new tablet formulation evaluated in healthy volunteers.

RESULTS: The dose- and exposure-response data from NCT 03789656 and 03792555 will be presented. These data suggest that a dose range of 40 to 60 mg once daily results in consistent IGF-1 suppression in patients with acromegaly.

CONCLUSION: We propose a similar starting dose for paltusotine in CS as in acromegaly. This dosing range (40-80 mg once daily) is further supported by clinical experience with LA-SRL therapies in gastro-entero-pancreatic NETs for which the approved doses are the same as acromegaly. Therefore, we will evaluate in an exploratory trial a paltusotine dose range from 40 to 80 mg/day with the potential, if required, for up titration to higher doses.

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