A Phase 2, Randomized, Parallel Group Study to Evaluate the Safety, Pharmacokinetics, and Dose Response of Paltusotine Treatment in Subjects with Carcinoid Syndrome

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BACKGROUND

- Neuroendocrine tumors (NETs) are classified as functional or non-functional based on the presence of characteristic symptoms, related to tumoral secretion of biologically active peptides or amines
- Carcinoid syndrome (CS) is the most common functional NET syndrome, seen at diagnosis in 10% to 20% of patients[1]
- It is characterized in over 80% of cases by secretory diarrhea (mainly due to serotonin hypersecretion) or cutaneous flushing[2]
- Somatostatin is a neuropeptide that inhibits the secretion of many hormones, including pituitary growth hormone and serotonin from functional NETs
- While long-acting somatostatin receptor ligands (SRLs) are mainstay treatments for CS, relief of the symptoms at labeled doses is inadequate for many patients
- Paltusotine is a novel oral, nonpeptide, selective somatostatin receptor type 2 (SST2) agonist under investigation for treatment of acromegaly and carcinoid syndrome
- It appears equally effective with long acting injectable SRLs in maintaining plasma insulin-like growth factor 1 (IGF-1) levels in patients with acromegaly
- Paltusotine was well tolerated in Phase 2 acromegaly studies, with the most common adverse events (AEs) being headache, arthralgia, diarrhea, and abdominal pain

OBJECTIVES

- To evaluate the safety and tolerability of paltusotine at 40, 80, and 120 mg QD doses in the treatment of patients with CS
- To assess the pharmacokinetics of paltusotine at 40, 80, and 120 mg
- Exploratory efficacy for randomized treatment phase
  - To derive responder rates for the different dose arms
  - To evaluate the effect of paltusotine treatment on frequency of bowel movements (BMs) per day and flushing episodes per day
  - To evaluate the effect of paltusotine treatment on biochemical markers of carcinoid syndrome (chromogranin A, serotonin, and 5-HIAA)
- Open-label extension (OLE) phase
  - To evaluate the safety and tolerability of paltusotine

RATIONALE

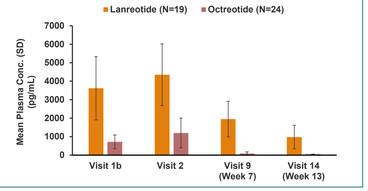
- CS usually occurs in intestinal NETs with liver metastases, which makes surgical cure very difficult in most patients
- Excess serotonin and other hormonally active substances (including histamine, tachykinins, kallikrein, and prostaglandins) produced by some NETs are responsible for the symptoms collectively referred to as carcinoid syndrome[2]
- Long-acting SRL therapies may be associated with significant dose-to-dose exposure variability related to injection techniques. For example, nurses at MD Anderson Cancer Center successfully delivered only 52% of 328 octreotide long-acting release (LAR) depot injections to the intramuscular space when evaluated by computed tomography[3]
- Negative experiences with chronic injections of long-acting SRL therapies, particularly octreotide LAR, also have been identified in patients with carcinoid syndrome, including injection site pain or soreness[4]
- A daily oral treatment such as paltusotine may achieve higher drug concentrations in the liver, which is the most common source of the vasoactive mediators causing carcinoid syndrome symptoms
- Paltusotine, an orally administered nonpeptide SST2 agonist, under investigation for the treatment of CS, has the potential to improve treatment outcomes, achieving symptom control while eliminating painful injections
- Pharmacokinetics of long-acting somatostatin agonists seen in Phase 2 acromegaly trial (details in insert) informed the clinical trial design

METHODS

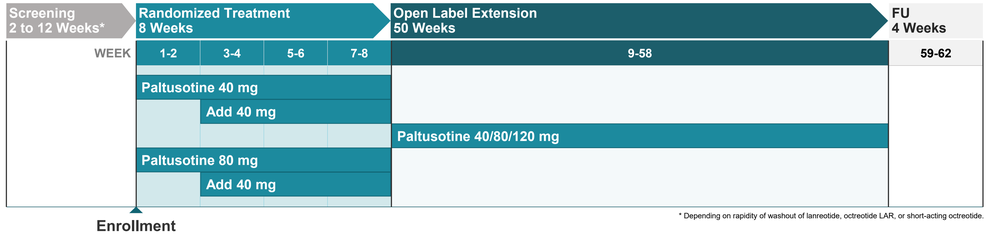
- This randomized, open-label, parallel-group, multi-center study will examine the safety, tolerability, pharmacokinetics, and exploratory efficacy of paltusotine in subjects with CS[5]
- Subjects with documented well-differentiated, grade I or II, NETs with CS
- Two groups of subjects will be enrolled in this study
  - Subjects naïve to SRLs and actively symptomatic (average of ≥4 BMs per day or >2 flushing episodes per day in at least 2 days over a period of 2 weeks)
  - Subjects currently treated with lanreotide, octreotide LAR, or short-acting octreotide (subcutaneous or oral) who are currently symptomatically controlled and willing to wash out of their medication. The subject must demonstrate symptomatic worsening after washout
- The study includes a screening period of 2 weeks in subjects naïve to SRLs and up to 12 weeks in subjects washing out of SRLs
- An electronic diary will be used to capture symptom frequency
- Subjects washing out of SRLs will be eligible for randomization when symptomatic worsening occurs over any 7-day period
- After completion of screening, subjects will be randomly assigned to the 40 mg versus 80 mg daily open-label dose groups for 8 weeks. The dose may be increased up to 120 mg if tolerated and required for efficacy
- In addition to collection of safety data and plasma paltusotine levels (to generate pharmacokinetic profiles in this subject population), a full suite of biomarkers and efficacy assessments will be explored for paltusotine in NETs
- Following completion of the randomized treatment phase, subjects may be eligible to enter the OLE phase of the study in which they will receive paltusotine for an additional 50 weeks

Plasma Octreotide and Lanreotide Concentrations (from the Phase 2 Acromegaly Study)

Octreotide or lanreotide levels were measured during the screening period at Visit 1b immediately prior to the last depot injection and Visit 2 (1-2 weeks after the last depot injection). During the paltusotine dosing period, they were measured at W7 (12 weeks after last depot injection) and at W13 (17 weeks after last depot injection). In the overall study population, 24 subjects switched from octreotide LAR and 19 switched from lanreotide depot. Significant differences (decreases) in median residual plasma concentrations of octreotide and lanreotide levels from visit 2 to visit 14 were observed. In the case of octreotide, median residual concentrations fell to the lower limit of quantitation of the octreotide assay by W7 (12 weeks after last depot injection). In the case of lanreotide, residual concentrations had fallen by a median of 50.1% by W7 and by 77.3% at W13. IGF-1 levels rose robustly in the presence of any residual octreotide/lanreotide concentrations when paltusotine was withdrawn at Week 13 (17 weeks after last injection).



STUDY DESIGN



KEY INCLUSION CRITERIA

- Male or female subjects ≥18 years of age, at the time of screening
- Documented carcinoid syndrome requiring medical therapy including at least one historical instance of an elevated 5-HIAA level
  - Plasma 5-HIAA ≥2× ULN during screening for naïve subjects not washing out of SRLs
- Eligible subjects are either naïve to SRLs or are currently being treated and are symptomatically controlled
- Evaluable documentation of locally advanced or metastatic histopathologically confirmed well-differentiated NET
- Tumors must be grade 1 or grade 2 (Ki-67 index ≤20%)
- No significant disease progression over prior 6 months (by CT or MR imaging for subjects on SRL, or by symptoms or biomarkers in SRL naive subjects)
- Historical documentation of positive SSTR tumor status by PET or somatostatin receptor scintigraphy (if subject does not have historical documentation, this can be done during screening)

KEY EXCLUSION CRITERIA

- Diarrhea attributed to any condition(s) other than carcinoid syndrome (including but not limited to fat malabsorption, bile acid malabsorption, short bowel syndrome, pancreatic exocrine insufficiency)
- Requires second line treatments (e.g., telotristat) for control of carcinoid syndrome symptoms in the opinion of the Investigator

Safety Monitoring Committee

- A Safety Monitoring Committee (SMC), composed of independent subject matter experts, has been established to assess the risk versus benefit of the interventions during the trial

Screening Schematics for Subjects Using Pretrial Lanreotide Depot or Octreotide LAR

Screening Visit 1 (S1) scheduled so that the interval between the last pretrial injection of lanreotide or octreotide LAR and the expected visit Screening Visit 2 (S2) is not longer that the subject's usual interval between injections.
Completion of the daily electronic symptom diary should begin immediately after Informed consent is given at S1.

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S2 scheduled approximately 2 weeks after S1.
Assessment of symptom control from lanreotide or octreotide LAR .

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Symptomatically controlled subjects will proceed in screening.

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With symptomatic worsening, subjects proceed to Day 1.
Day 1 randomization may occur up to 10 weeks after S2.

ENDPOINTS

Safety

- Incidence of treatment-emergent AEs (TEAEs), including serious TEAEs and TEAEs leading to discontinuation
- Clinical laboratory tests, physical exam findings, vital signs, electrocardiogram parameters

Pharmacokinetics

- Steady state trough levels at each dose

Exploratory Efficacy

- Proportion of clinical responders by dose
  - In subjects who meet diarrhea entry criteria only:
    - Have less than four mean BMs daily
    - Have a >20% reduction in the mean daily number of BMs compared with baseline
  - In subjects who meet flushing entry criteria only:
    - Have a >30% reduction compared with baseline in the mean daily number of flushing episodes
  - In subject who meet both diarrhea and flushing entry criteria:
    - Have less than four mean BMs daily
    - Have a >20% reduction in the mean daily number of BMs compared with baseline
    - Have any reduction from baseline in the mean daily number of flushing episodes
- Change in mean daily BMs
- Change in mean daily number of flushing episodes
- Change from baseline (biomarkers):
  - Plasma 5-HIAA
  - Plasma pancreastatin
  - Serum chromogranin A
  - Serum serotonin
- Change from baseline health-related quality of life (HRQOL):
  - EORTC QLQ-C30
  - EORTC QLQ-GI.NET21 scores
  - EQ-5D-5L
  - FACT-CS

Summary

This is a randomized, open-label, multi-center study designed to assess the safety, tolerability, pharmacokinetics, and exploratory efficacy of oral paltusotine in carcinoid syndrome. The study is currently enrolling adults with carcinoid syndrome who are treatment-naive, actively symptomatic or controlled on lanreotide or octreotide (NCT05361668).

References:

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Acknowledgements:

- Funding for this study is provided by Crinetics Pharmaceuticals, Inc. Graphic design support was provided by Lee Potts of SlideSource; funding for this support was provided by Crinetics Pharmaceuticals, Inc.

Poster T-3 presented at the North American Neuroendocrine Tumor Society NET Medical Symposium – October 27-29, 2022 – Washington, DC