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

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Background:

- Paltusotine is a novel oral, once-daily, small-molecule, nonpeptide, selective somatostatin receptor type 2 agonist in development for treatment of acromegaly (phase 3) and carcinoid syndrome (CS)[1,2]
- In a phase 2 study, paltusotine maintained plasma IGF-I levels in patients with acromegaly switching from long- acting SRLs and was well tolerated[3]

Objective:

- To evaluate the safety, tolerability, pharmacokinetics, and exploratory efficacy of paltusotine in patients with CS

Methods:

- Randomized, open-label, parallel-group, multicenter study with an optional open-label extension of 50 weeks (NCT05361668)
- Electronic symptom diary to capture symptom frequency and severity in both SRL treatment-naive patients and those controlled on SRL injections
- Assessment of symptom worsening after SRL washout during screening period in patients using pretrial SRL injections
  - Symptomatic worsening defined by increase in frequency of BMs and/or flushing
  - 7-day rolling average to determine symptomatic worsening
- Upon meeting eligibility symptom criteria, patients are randomized to paltusotine (40 mg or 80 mg) as soon as possible

REFERENCES

1. Zhao J, et al. *ACS Med Chem Lett*. 2023;14(1):66-74. **2.** Madan A, et al. *Pituitary*. 2022;25(2):328-339. **3.** Gadelha MR, et al. *J Clin Endocrinol Metab*. 2022. dgac643.

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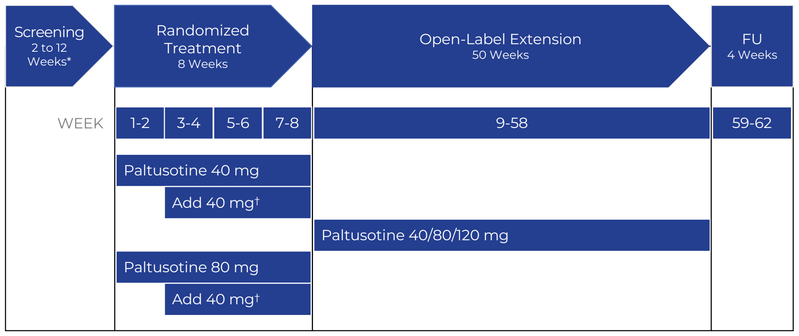
Study Design



*Depending on rapidity of washout of lanreotide, octreotide LAR, or short-acting octreotide.
†During the first 4 weeks, dose uptitration by 40 mg/d is an option, based on symptomatology.

Key Inclusion Criteria

- Male or female ≥18 years of age
- Locally advanced or metastatic, histopathology-confirmed, well-differentiated NET; grade 1 or grade 2
- CS requiring medical therapy and a history of ≥1 elevated 5-HIAA level
- Two patient groups:
  - Naïve to SRLs, with plasma 5-HIAA ≥2x ULN and actively symptomatic (average of ≥4 BMs per day or >2 flushing episodes per day in ≥2 days over a period of 2 weeks)*
  - On octreotide or lanreotide with symptomatic control (BMs, flushing frequency), with demonstrated symptom worsening after SRL washout
- No significant disease progression over the prior 6 months

Key Exclusion Criteria

- Diarrhea attributed to any condition(s) other than CS
- Requires second-line treatments (eg, telotristat) for control of CS symptoms
- Prior therapy with hepatic embolization, radiotherapy, PRRT, or tumor debulking (past 12 weeks)

*Based on daily electronic symptom diary, initiated after informed consent is obtained.
PRRT = peptide receptor radionuclide therapy.

Summary

This open-label study is currently enrolling adults with CS who are either SRL treatment-naïve and symptomatic or controlled on long-acting SRL (lanreotide or octreotide)

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Safety Endpoints

- Incidence of TEAEs, including serious TEAEs and TEAEs leading to discontinuation
- Clinical laboratory tests, physical exam findings, vital signs, and ECG parameters

Pharmacokinetic Endpoints

- Steady-state trough levels at each dose

Exploratory Efficacy Endpoints

Change from baseline in:

- **BM frequency:** mean daily number of BMs
- **Flushing frequency:** mean daily number of flushing episodes
- **Stool consistency:** highest (worst) stool score in the last 24 hours (Bristol Stool Scale)
- **Urgency:** mean daily urgency episodes
- **Incontinence:** mean daily fecal incontinence episodes
- **Abdominal pain:** worst abdominal pain in the last 24 hours (NRS, 0-10)
- **Biomarkers:** plasma 5-HIAA, pancreastatin; serum chromogranin A, serotonin
- **HRQoL:** EORTC QLQ-C30, EORTC QLQ-GI.NET21 score, EQ-5D-5L, FACT-CSI
- **Rescue medication use with short-acting octreotide:** proportion of days on short-acting octreotide, mean daily dose of octreotide

Proportion of clinical responders by dose:

- Based on symptom frequency during the last week of the randomized treatment phase

Patient perception of CS symptoms:

- **Change from baseline in PGI-S:** 4 items (diarrhea, abdominal pain, flushing, overall CS) rated as none, mild, moderate, or severe
- **PGI-C:** 4 items (as above) rated on a 7-point scale, from “much better” to “much worse”

EORTC = European Organization for Research and Treatment of Cancer; EORTC QLQ-GI.NET21 = EORTC quality of life questionnaire GI.NET 21; EORTC QLQ-C30 = EORTC quality of life questionnaire Core 30; EQ-5D-5L = EuroQoL 5 Dimensions 5 Level; FACT-CSI = Functional Assessment of Cancer Therapy – Carcinoid Syndrome Symptom Index; HRQoL = health-related quality of life; NRS = numeric rating scale; PGI-C = patient global impression of change; PGI-S = patient global impression of status; TEAE = treatment-emergent adverse events.