CAREFNDR: Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Paltusotine in Adults With Carcinoid Syndrome Due to Well-Differentiated Neuroendocrine Tumors

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Background

- Paltusotine (PALSONIFY™) is an oral, once-daily, non-peptide, selective somatostatin 2 (SST2) receptor agonist approved by the US FDA for the treatment of adults with acromegaly who had an inadequate response to surgery and/or for whom surgery is not an option[1,2]
- Paltusotine is currently being investigated for the treatment of carcinoid syndrome (CS); the safety and efficacy for use in this new indication have not been fully evaluated by Regulatory Authorities
- In a phase 2, open-label, dose-ranging study (NCT05361668), paltusotine reduced the frequency and severity of CS symptoms and was well tolerated

Objective

- To evaluate the efficacy and safety of paltusotine for the treatment of patients with CS in a phase 3, randomized, double-blind, placebo-controlled trial

Key Inclusion Criteria

- Male or female ≥18 years of age
- Well-differentiated Grade 1 or Grade 2 neuroendocrine tumor (NET)
  - Positive somatostatin receptor tumor status (previously documented or established during screening)
- Carcinoid syndrome: flushing with or without frequent bowel movements (BMs)
- Somatostatin receptor ligand (SRL) naïve or untreated for ≥16 weeks *or* currently treated with SRL and agree to washout
- If SRL naïve or untreated for ≥16 weeks
  - >1 flushing episode/day (14-day average)
  - 5-HIAA or serotonin ≥2× the upper limit of normal
- If SRL washout
  - Symptom control on SRL
  - Increase in flushing frequency to >1 flushing episode/day (14-day average)
  - History of elevated 5-HIAA or serotonin (in urine or blood sample)

Key Exclusion Criteria

- Diarrhea attributed to any condition(s) other than CS
- Need second-line treatment (eg, telotristat) for control of CS symptoms
- Treatment with specific NET therapy (eg, everolimus, sunitinib) <4 weeks before screening or hepatic embolization, radiotherapy, peptide receptor radionuclide therapy, and/or tumor debulking <12 weeks before screening
- Documented prior nonresponse to SRL

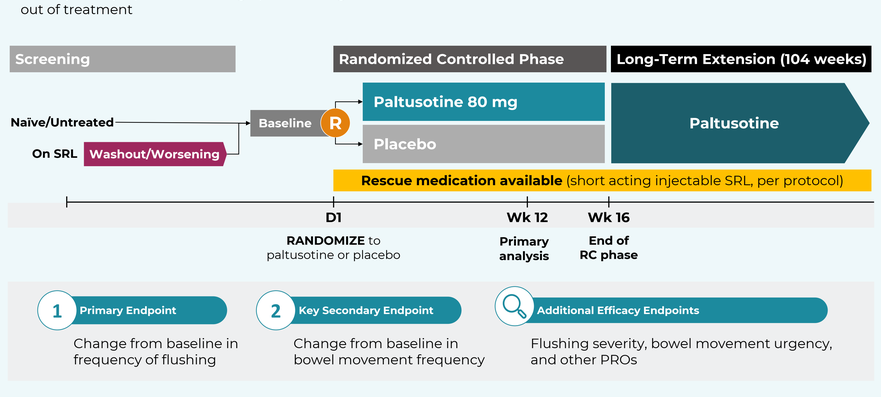
Methods

- Phase 3, multicenter, randomized, parallel-group double-blind, placebo-controlled trial (NCT07087054)
- Approximately 141 adults with CS to be randomized in a 2:1 ratio to once-daily paltusotine 80 mg or matching placebo
- Electronic CS symptom diary (CSSD) to be completed daily
- Antidiarrheal medications (eg, loperamide, diphenoxylate atropine) and rescue medications (eg, short-acting octreotide) are permitted
- Open-label extension to include assessment of anti-tumor effects (eg, progression-free survival)

Study Design

Key Eligibility Criteria:

- Grade 1 or 2 NET, positive SST receptor expression
- Treatment naïve or currently untreated and actively symptomatic –*OR*– controlled on SRL therapy and symptom worsening upon washing out of treatment



NET = neuroendocrine tumor; PRO = patient-reported outcome; RC = randomized controlled; SRL=somatostatin receptor ligand; SST=somatostatin.

Efficacy Endpoints

Primary Endpoint

- Flushing episodes per day: change from baseline to Week 12 (14-day average)

Key Secondary Endpoint

- BMs per day: change from baseline to Week 12 (14-day average)

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.

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DISCLOSURES

A. Chauhan reports serving as a principal investigator for Crinetics; receiving research support from Bristol Myers Squibb, Clovis Oncology, EMD Serono, Lexicon Pharmaceuticals, Nano-Pharmaceutics, Novartis, Seneca Therapeutics, and TerSera Therapeutics; and being an advisor for Boehringer Ingelheim, Crinetics, Exelixis, Ipsen Biopharmaceuticals, Lexicon Pharmaceuticals, Novartis/Advanced Accelerator Applications, Seneca Therapeutics, and TerSera Therapeutics. M. Caplin reports serving as a principal investigator for Crinetics. R. Garcia-Carbonero reports serving as a principal investigator for Crinetics. D. M. Halperin reports serving as a principal investigator for Crinetics. D. Hörsch reports serving as a principal investigator for Crinetics. A. Mohamed reports serving as a principal investigator and advisor for Crinetics and being a speaker for Ipsen Biopharmaceuticals. J. M. O'Connor reports serving as a principal investigator for Crinetics; receiving grant/research funding from Amgen, Bristol Myers Squibb, Merck Serono, MSD, Pfizer, and Sanofi; and receiving honoraria or being an advisor for Bristol Myers Squibb, MSD, Pfizer, and Sanofi. M. J. Demeure reports serving as a principal investigator for Crinetics. M. A. Maluccio reports serving as a principal investigator for Crinetics. D. Markova, T. P. Quock, Z. Sharafali, Z. Xiao, and B. Zhang are employees of Crinetics Pharmaceuticals.

Summary

- Results from the phase 2 study of paltusotine in patients with CS have supported the design of this phase 3 study
- The CAREFNDR phase 3 trial is underway and will enroll patients in approximately 100 sites (15 countries) to evaluate the efficacy and safety of paltusotine in the treatment of CS
- More information about this study is available at www.carefndr.com

Efficacy Endpoints (continued)

Other Secondary Endpoints

- BMs per day: change from baseline to Week 12 (14-day average) in patients with >3 BMs per day at baseline
- Flushing severity: change from baseline to Week 12 (14-day average)
- BM urgency episodes per day: change from baseline to Week 12 (14-day average) in patients with >1 BM urgency episode per day at baseline
- Percentage of treatment days with short-acting octreotide use
- Total number of treatment days with ≤3 BMs in participants with >3 BMs per day at baseline
- Percentage of treatment days with antidiarrheal medication use
- Total number of treatment days with zero flushing episodes; proportion of patients with zero flushing episodes (14-day average)

Exploratory Biomarkers

- Plasma 5-HIAA and serum serotonin

Safety Endpoints

- Incidence of adverse events (AEs), including serious AEs and AEs leading to treatment discontinuation
- Clinical laboratory tests, vital signs, electrocardiogram

Pharmacokinetic Endpoint

- Plasma paltusotine concentration

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