Once-Daily Oral Paltusotine in the Treatment of Patients With Carcinoid Syndrome: Safety and Exploratory Efficacy Results From a Phase 2, Randomized, Parallel-Group Study

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Background

- Paltusotine is a once-daily, selective, non-peptide, somatostatin receptor type 2 agonist in development as an oral treatment for acromegaly and carcinoid syndrome (CS)[1]

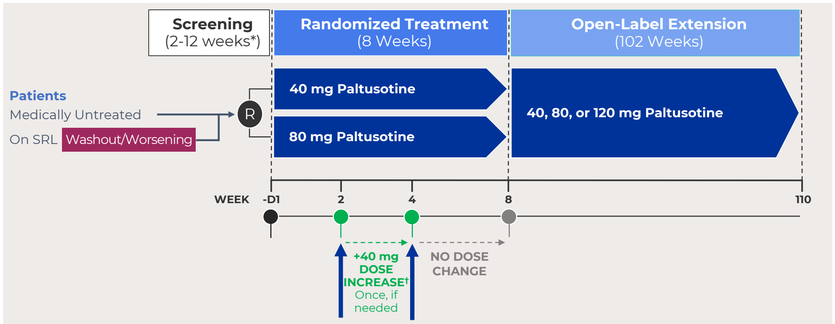
Objective

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

Methods

- Entry criteria: locally advanced or metastatic, well-differentiated, grade I or II neuroendocrine tumors (NETs) with CS either:
  - Somatostatin receptor ligand (SRL) treatment naïve or currently untreated and actively symptomatic (average of ≥4 BMs per day or >2 flushing episodes per day in ≥2 days over a 2-week period) *or*
  - Symptom control on SRL with demonstrated symptom worsening after SRL washout
- Exploratory efficacy assessed using daily diary

Study Design

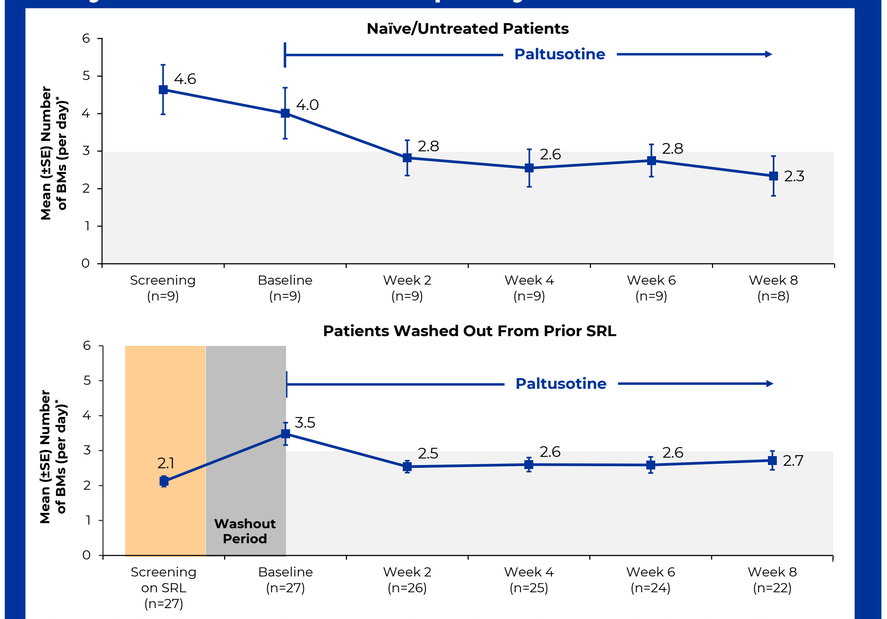


*Depending on rapidity of symptom worsening in washout patients.
†During the first 4 weeks, dose uptitration by 40 mg/d was an option in both treatment arms, based on symptomatology. Dose reduction (minimum, 40 mg/d) allowed at any time based on tolerability.

Patient Characteristics

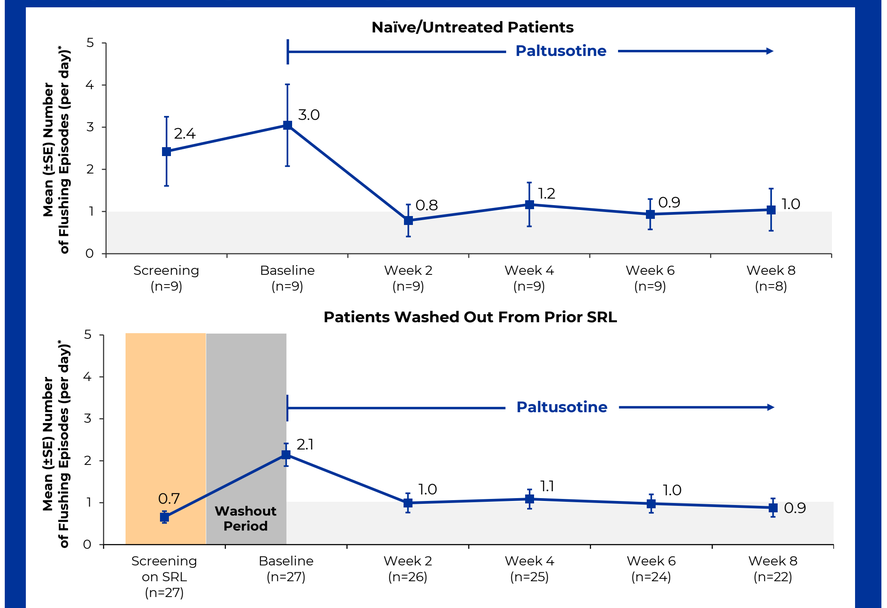
- 36 patients (n=9 treatment naïve or currently untreated, n=27 SRL washout)
  - Mean age 60.8 years (range, 35-83); 52.8% female; 47.2% with Grade 2 NET
  - Entry criteria met: BM only by 14 patients, flushing only by 11, and both by 11
  - Randomized dose: paltusotine 40 mg (n=18) or 80 mg (n=18); 9 patients had dose increase per protocol (n=6, 40 mg to 80 mg; n=3, 80 mg to 120 mg)

Daily Bowel Movement Frequency



In the overall patient population, mean ± SE daily BM frequency was 3.6±0.3 at baseline, 2.6±0.2 at Week 2, 2.6±0.2 at Week 4, 2.6±0.2 at Week 6, and 2.6±0.2 at Week 8.
*Frequency based on 14-day average during screening and 7-day average at baseline and all other timepoints.

Daily Flushing Frequency



In the overall patient population, mean ± SE daily flushing frequency was 2.4±0.3 at baseline, 0.9±0.2 at Week 2, 1.1±0.2 at Week 4, 1.0±0.2 at Week 6, and 0.9±0.2 at Week 8.
*Frequency based on 14-day average during screening and 7-day average at baseline and all other timepoints.

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Exploratory Efficacy

- In addition to reductions in BM frequency and flushing frequency (**see figures**)
  - Patients with excess BMs (>3 per day) at baseline: mean excess daily BM frequency decreased from 2.0 to 0.8 (-60%)
  - Patients with >1 flushing episode per day at baseline: mean daily flushing frequency decreased from 3.2 to 1.2 (-63%)
  - Mean serum serotonin decreased from 1553.0 ng/mL at baseline to 643.9 ng/mL at Week 8; mean plasma 5-HIAA decreased from 245.1 ng/mL to 159.7 ng/mL

Pharmacokinetics and Safety

- Pharmacokinetic findings indicative of dose proportionality
- No reduction in paltusotine exposure in this study relative to studies in healthy volunteers or patients with acromegaly
- Most common AEs: diarrhea (41.7%), abdominal pain (25.0%), headache (22.2%), nausea (19.4%), and flushing (13.9%); these AEs were mostly transient
- No severe or serious AEs considered treatment related

Conclusion

- In this phase 2 study, treatment with once-daily, oral paltusotine reduced the frequency and severity of CS symptoms and was well tolerated, justifying further clinical development
- Results from this phase 2 study supported the initiation of a phase 3 study, which is expected to begin enrollment soon in ~100 sites (15 countries); more information is available at www.carefndr.com

REFERENCE
1. Zhao J, et al. *ACS Med Chem Lett*. 2023;14(1):66-74.

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