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

C-5

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BACKGROUND

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

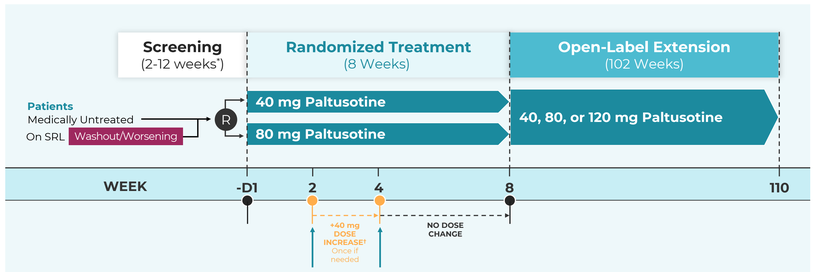
OBJECTIVE

- 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 electronic diary
- Meaningful within-patient change (MWPC) thresholds were derived using FDA-recommended methods:
  - Daily BM frequency -0.90 to -1.10 (single threshold: -0.90)
  - Daily flushing frequency -1.70 to -1.85 (single threshold: -1.80)

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.

RESULTS: 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; 41.7% identifying as Hispanic or Latino
  - 17 patients (47.2%) had Grade 2 NET
  - Entry criteria met: BM only by 14 patients (38.9%), flushing only by 11 (30.6%), and both by 11 (30.6%)
  - 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); 2 patients had dose decrease (80 mg to 40 mg)

REFERENCE

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

ACKNOWLEDGMENTS

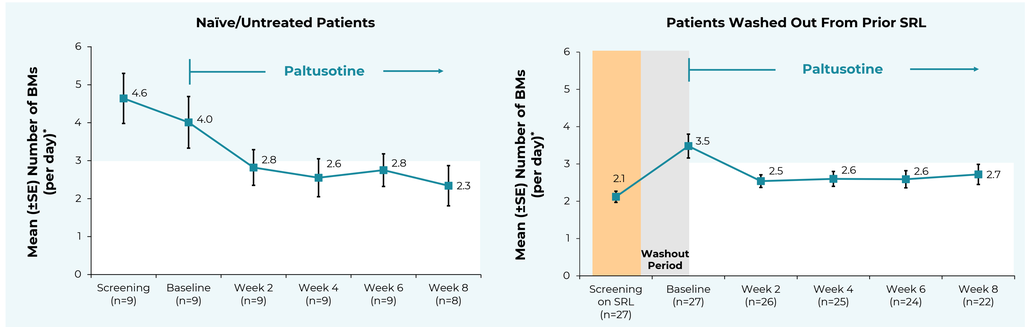
The authors thank the site investigators, study coordinators/nurses, clinical staff, and patients who participated in the study. This study was funded by Crinetics Pharmaceuticals, Inc. The authors thank Michael Keeley, PhD, Crinetics Pharmaceuticals, for his contributions. Technical editorial and medical writing assistance were provided under the direction of the authors by Janetricks Okeyo, PhD, Crinetics Pharmaceuticals, and Synchrony Medical Communications, LLC, West Chester, PA, USA; funding for this support was provided by Crinetics Pharmaceuticals, Inc.

DISCLOSURES

A. Chauhan reports receiving research support from Bristol Myers Squibb, Clovis Oncology, EMD Serono, Lexicon Pharmaceuticals, Nano-Pharmaceutics, and TerSera Therapeutics; and being an advisor for Ipsen Biopharmaceuticals, Lexicon Pharmaceuticals, Novartis/Advanced Accelerator Applications, Seneca Therapeutics, and TerSera Therapeutics. A. Mohamed reports being a speaker for Ipsen Biopharmaceuticals and an advisor for Crinetics Pharmaceuticals. J. Dillon reports being an advisor for Lantheus. S. Shaheen reports no conflicts of interest. J. M. O'Connor reports 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. S. Singh reports receiving honoraria or serving on advisory board for Advanz, Camurus, Crinetics, Pharmaceuticals, Ipsen Biopharmaceuticals, and Novartis. K. Usiskin, C. Mui, D. Zhou, T. P. Quock, Z. Sharafali, and A. Krasner are employees of Crinetics Pharmaceuticals.

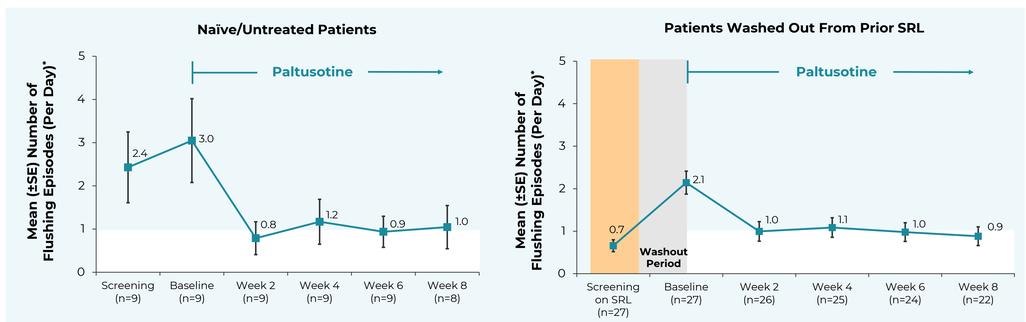
RESULTS: REDUCTIONS IN CARCINOID SYNDROME SYMPTOMS

Daily Bowel Movement Frequency



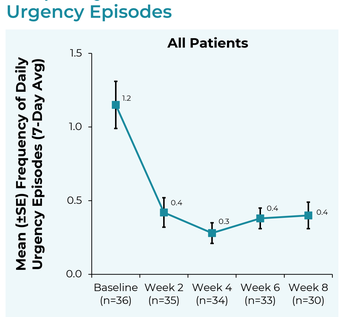
In the overall patient population, mean ± SE daily BM frequency was 3.6±0.3 at baseline, 2.6±0.2 at Week 2, 2.6±0.2 at Week 4, 2.6±0.2 at Week 6, and 2.6±0.2 at Week 8.
*Frequency based on 14-day average during screening and 7-day average at baseline and all other timepoints.

Daily Flushing Frequency

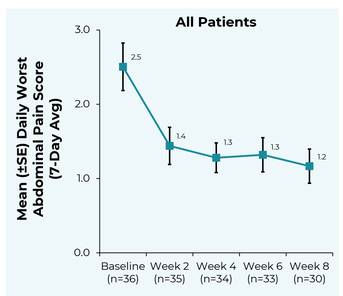


In the overall patient population, mean ± SE daily flushing frequency was 2.4±0.3 at baseline, 0.9±0.2 at Week 2, 1.1±0.2 at Week 4, 1.0±0.2 at Week 6, and 0.9±0.2 at Week 8.
*Frequency based on 14-day average during screening and 7-day average at baseline and all other timepoints.

Frequency of Bowel Movement Urgency Episodes

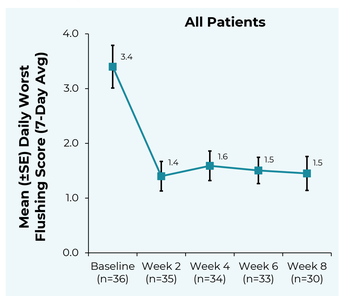


Abdominal Pain Severity



Abdominal pain was evaluated using numeric rating scale of 0 to 10.

Flushing Severity

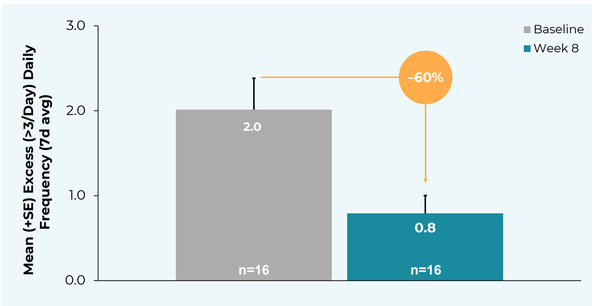


Flushing severity was evaluated using numeric rating scale of 0 to 10.

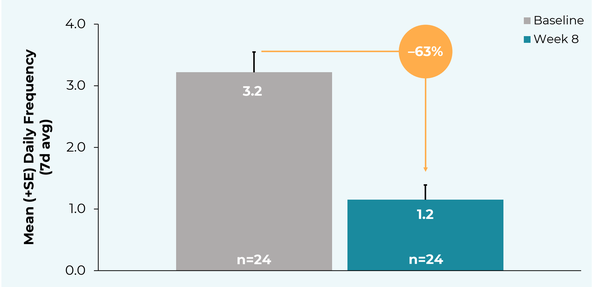
RESULTS: PHARMACOKINETICS AND SAFETY

- 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%)
- No severe or serious AEs considered treatment related
- 2 patients discontinued the study due to AEs (encephalopathy and bowel obstruction; not drug related)
- No new safety signals identified; open-label extension study is ongoing

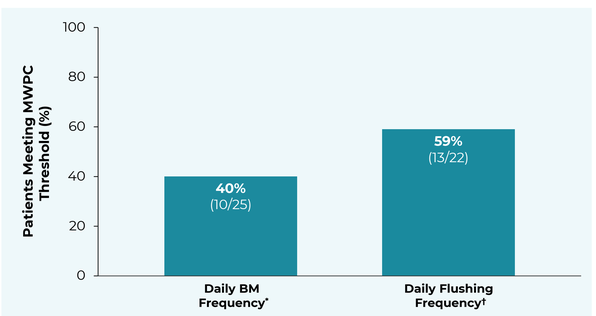
Excess Bowel Movement Frequency for Patients With >3/Day at Baseline



Flushing Frequency for Patients With >1/Day at Baseline



Meaningful Within-Patient Change in Daily Bowel Movement and Flushing Frequency



Thresholds derived from anchor-based analyses using PGI-S and PGI-C scores.
*MWPC threshold for daily BM frequency -0.90. †MWPC threshold for daily flushing frequency -1.80 (or no flushing at Week 8).

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

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