Crinetics Pharmaceuticals

# INITIAL RESULTS FROM ONGOING PALTUSOTINE CARCINOID SYNDROME OPEN LABEL PHASE 2 STUDY

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

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# Once Daily Oral Paltusotine Showed Strong Initial Results in Carcinoid Syndrome Patients

## SAFETY

- Paltusotine was well-tolerated with no severe or serious treatment related adverse events and consistent with prior studies

## PHARMACOKINETICS

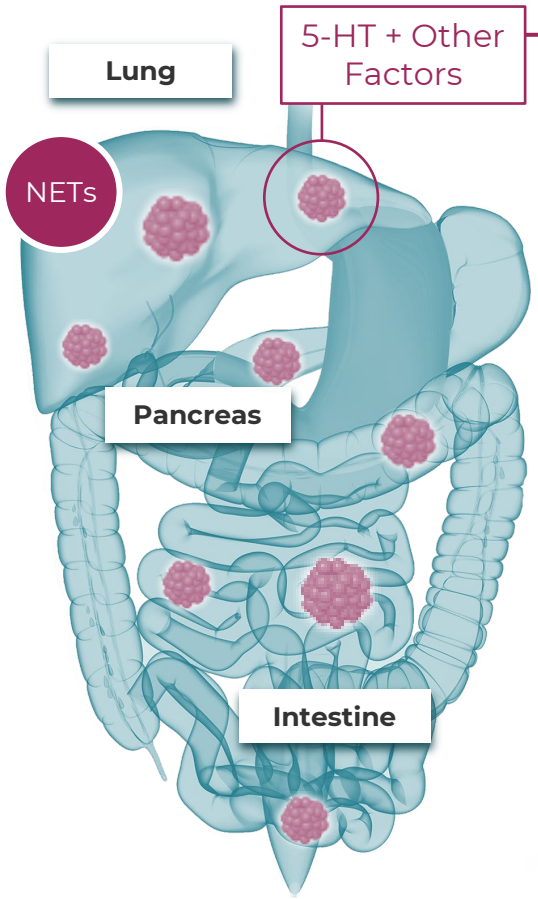
- Overall PK was generally consistent with expectations from healthy volunteers

## EFFICACY

- Significant reductions in frequency and severity of bowel movements and flushing with 40mg and 80mg

**Safety profile and efficacy observed to date with paltusotine supports progressing to Phase 3 study in carcinoid syndrome (pending complete data, expected 1H 2024)**

# Carcinoid Syndrome is a Serious Disease and Patients Need Better Treatment Options




## Carcinoid Syndrome

**~33,000** Patients Diagnosed with Carcinoid Syndrome (US)

**Excess bowel movements (>3/day) are highly disruptive**

***Goal:*** *reduce frequency and urgency (normal is ≤3/day)*

**Severe Flushing episodes can be debilitating and potentially dangerous**

***Goal:*** *reduce frequency and severity (normal is < 1/day)*

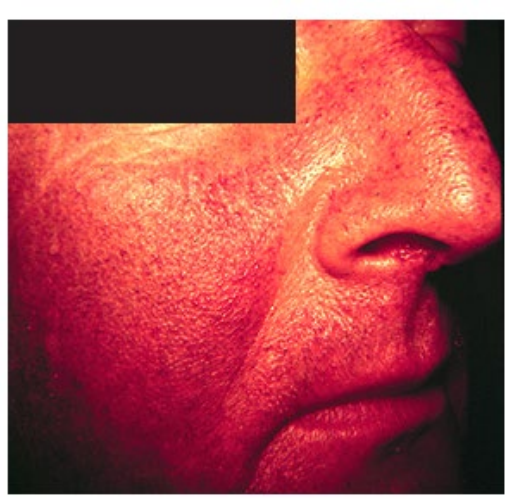
**Severe and life-threatening complications: carcinoid heart disease (found in up to 50% of patients) & carcinoid crisis**

***Goal:*** *prevent severe complications*

**Injected SRLs Impose a high burden of care and frequently don't last all month**

***Goal:*** *eliminate depot and rescue injections and provide consistent control throughout the month*

**Facial Flushing in a patient with carcinoid syndrome**



*Courtesy of Stephen E Goldfinger, MD* UpToDate®

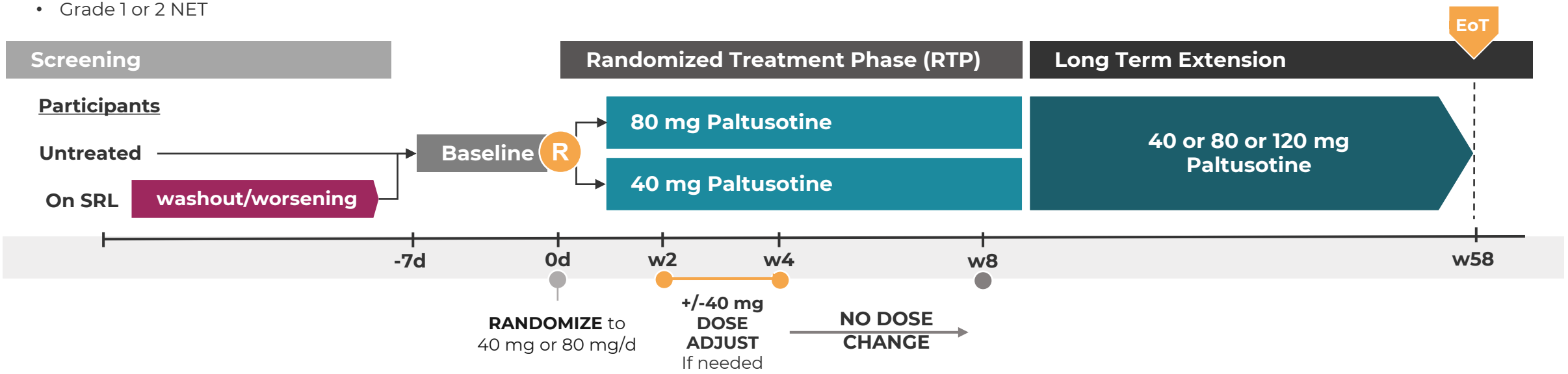
5-HT = Serotonin; NETs = Neuroendocrine tumors
SRL = somatostatin receptor ligand

# Phase 2 Study Design: Evaluating Safety, PK and Efficacy of Paltusotine in Carcinoid Syndrome Patients

**Protocol:** 8-week, open label parallel, randomized 2-dose study followed by Long Term Extension

**Key Eligibility Criteria:**

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




**1 Primary Endpoint**

Safety and tolerability of Paltusotine

**2 Secondary Endpoint**

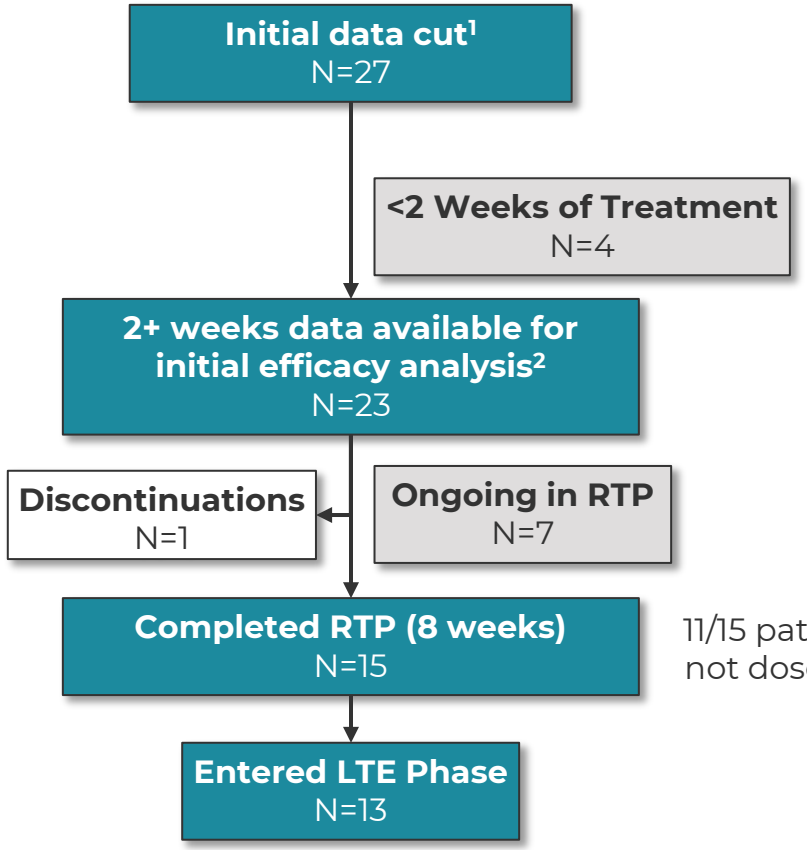
Pharmacokinetics of Paltusotine at 40, 80 and 120 mg doses

**Exploratory Endpoints**

Bowel movement and flushing frequency, octreotide rescue use, biomarkers, stool consistency, abdominal pain, PRO measures

SSTR = somatostatin receptor; SRL = somatostatin receptor ligand
EoT = end of treatment; PRO = patient reported outcome

# Disposition and Dosing for the Initial Data Cut (N=27)




11/15 patients were not dose adjusted

**Dose at Randomization (N=27 initial data cut)**

| | 40mg | 80mg | Total |
|---|---|---|---|
| Naïve/ Untreated | 5 | 4 | 9 |
| Switching | 8 | 10 | 18 |
| Total | 13 | 14 | 27 |

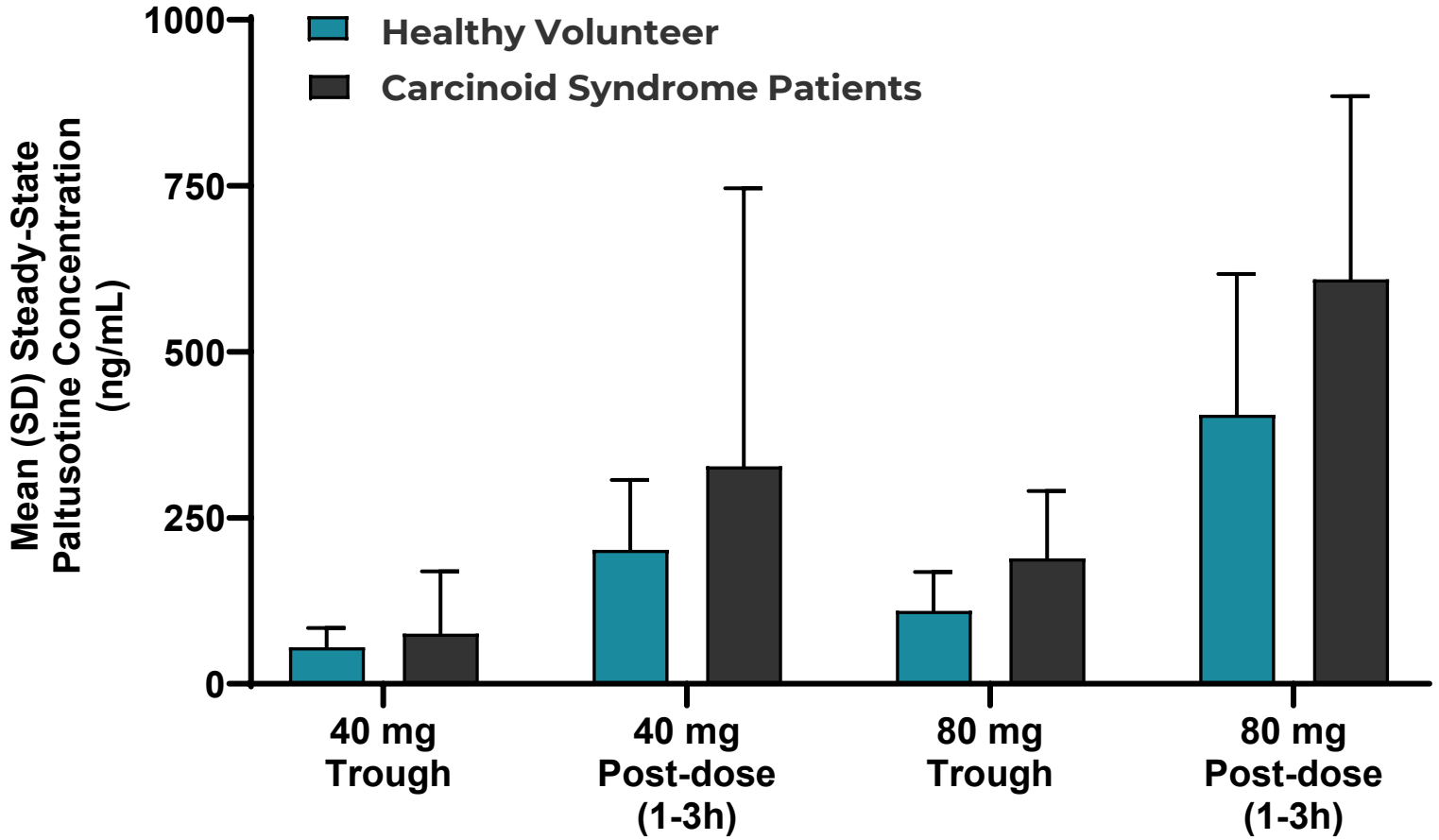
RTP = Randomized treatment phase (8 weeks); LTE = Long Term Extension

1. Safety analysis as of November 27, 2023 initial data cutoff
2. Efficacy analysis based on a minimum of 2 weeks of data available as of the November 27, 2023 data cutoff

# Baseline Demographics and Disease Characteristics

| | Naïve/Untreated Symptomatic N=9 | Switching from SRL N=18 | Overall N=27 |
|---|---|---|---|
| **Female, n(%)** | **6(67)** | **9(50)** | **15(56)** |
| **Male, n(%)** | **3(33)** | **9(50)** | **12(44)** |
| **Age at informed consent - Mean (SD), years** | **58.2 (19.5)** | **60.6(8.1)** | **59.8(12.7)** |
| **BMI - Mean (SD), kg/m²** | **30.0(14.0)** | **29.6(5.7)** | **29.8(9.1)** |
| **Geographic Region** | | | |
| North America, n(%) | 4(44) | 11(61) | 15(55) |
| Europe, n(%) | 1(11) | 0 | 1(3) |
| Latin America , n(%) | 4(44) | 7(38) | 11(40) |
| **Duration since Carcinoid Syndrome diagnosis – Median, months** | **8.2** | **64.4** | **60.2** |
| **NET Tumor Grade 1, n(%)** | **5(56)** | **8(44)** | **13(48)** |
| **NET Tumor Grade 2, n(%)** | **4(44)** | **10(56)** | **14(52)** |

# Paltusotine Exposure in Patients with Carcinoid Syndrome was Consistent with Expectations from Healthy Volunteers




Healthy volunteer data is from paltusotine population PK model sampling at steady-state trough and 2-hour post-dose.
Carcinoid Syndrome patients: N=7, N=4, N=9, and N=9 for 40 mg trough, 40 mg post-dose, 80 mg trough, and 80 mg post-dose, respectively.

# Paltusotine was Well-Tolerated with No Severe or Serious Treatment-Related Adverse Events

| Treatment-Emergent Adverse Events | Paltusotine N = 27 |
|---|---|
| **Any** | **18(66.7)** |
| Mild | 9(33.3) |
| Moderate | 7(25.9) |
| Severe | 2(7.4) |
| **Serious** | **3(11.1)** |
| **Death** | **1(3.7)*** |
| **Treatment-related** | **15(55.6)** |
| Mild | 9(33.3) |
| Moderate | 6(22.2) |
| Severe | 0 |
| **Serious** | **0** |
| **Death** | **0** |

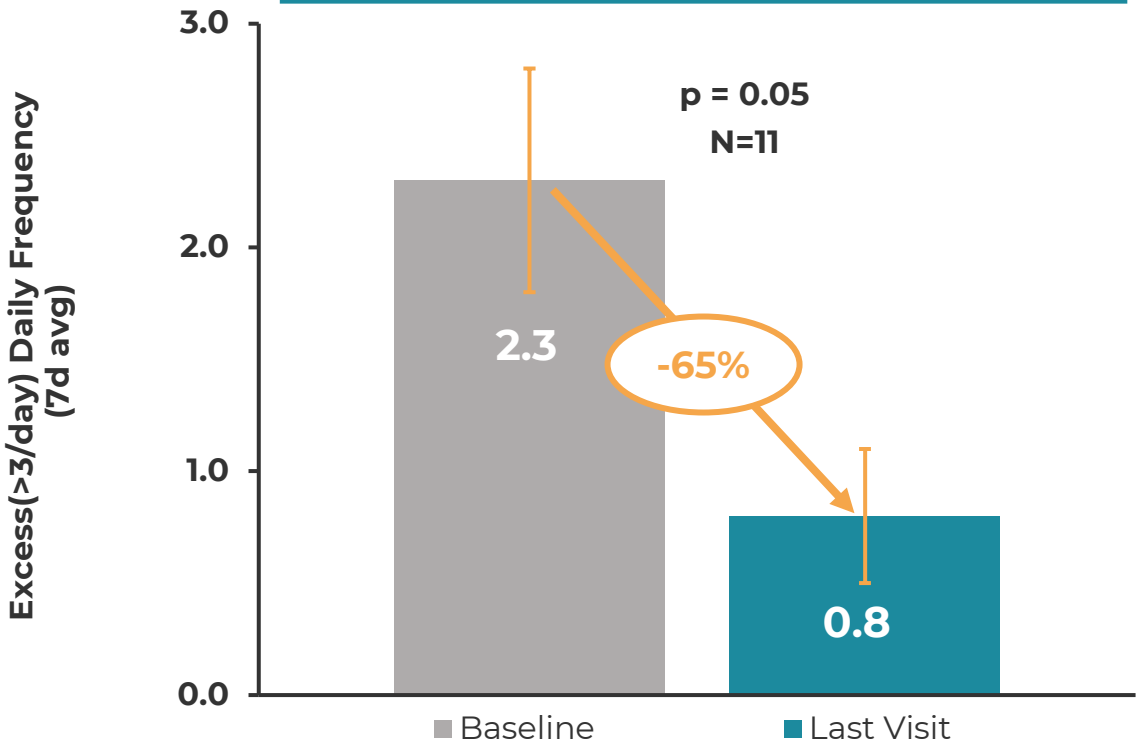
## Preliminary Safety Summary from Ongoing Carcinoid Syndrome Phase 2 Study

- Paltusotine was well-tolerated with no treatment related severe or serious treatment related adverse events
- The most frequently reported adverse events included diarrhea, headache and abdominal pain
- Adverse event findings were similar across paltusotine dosing of 40 and 80 mg
- No new safety signals have been observed during study monitoring of vital signs, ECGs, or safety laboratory values

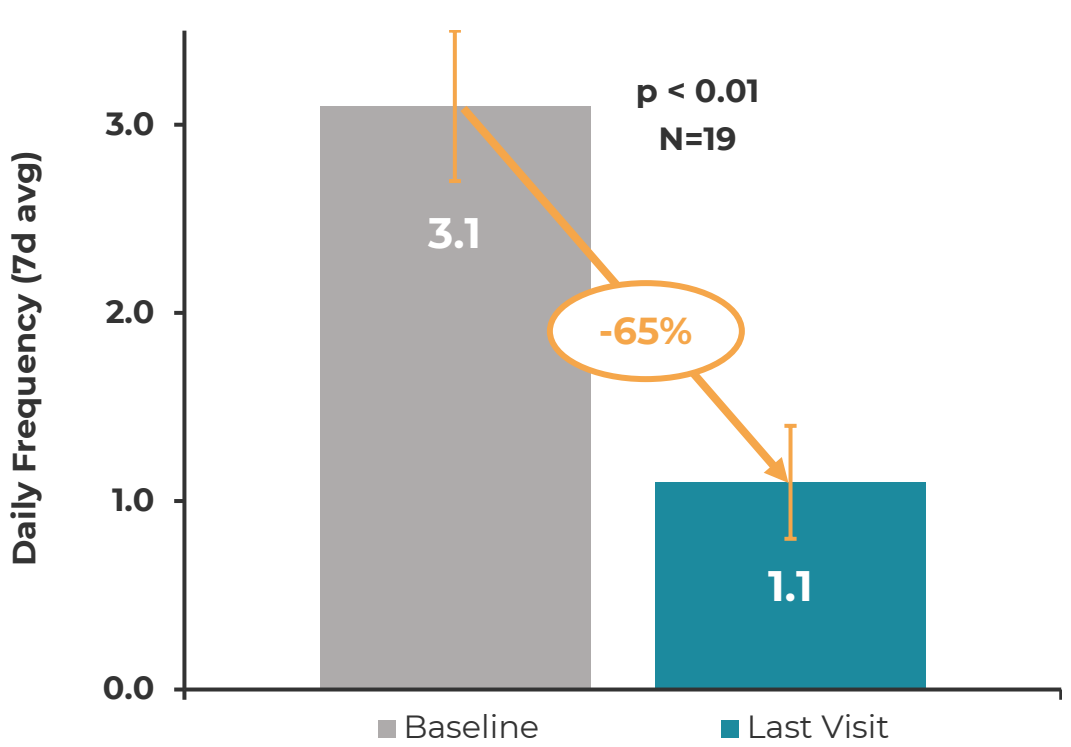
* The fatal outcome of one SAE (cardiac failure, most likely secondary to carcinoid heart disease) occurred 26 days after treatment discontinuation and was not treatment related.

# Paltusotine Reduced the Frequency of Both Key Carcinoid Syndrome Core Symptoms: Excess BM and Flushing

**Excess Bowel Movement* Frequency For Patients with >3/day at Baseline**



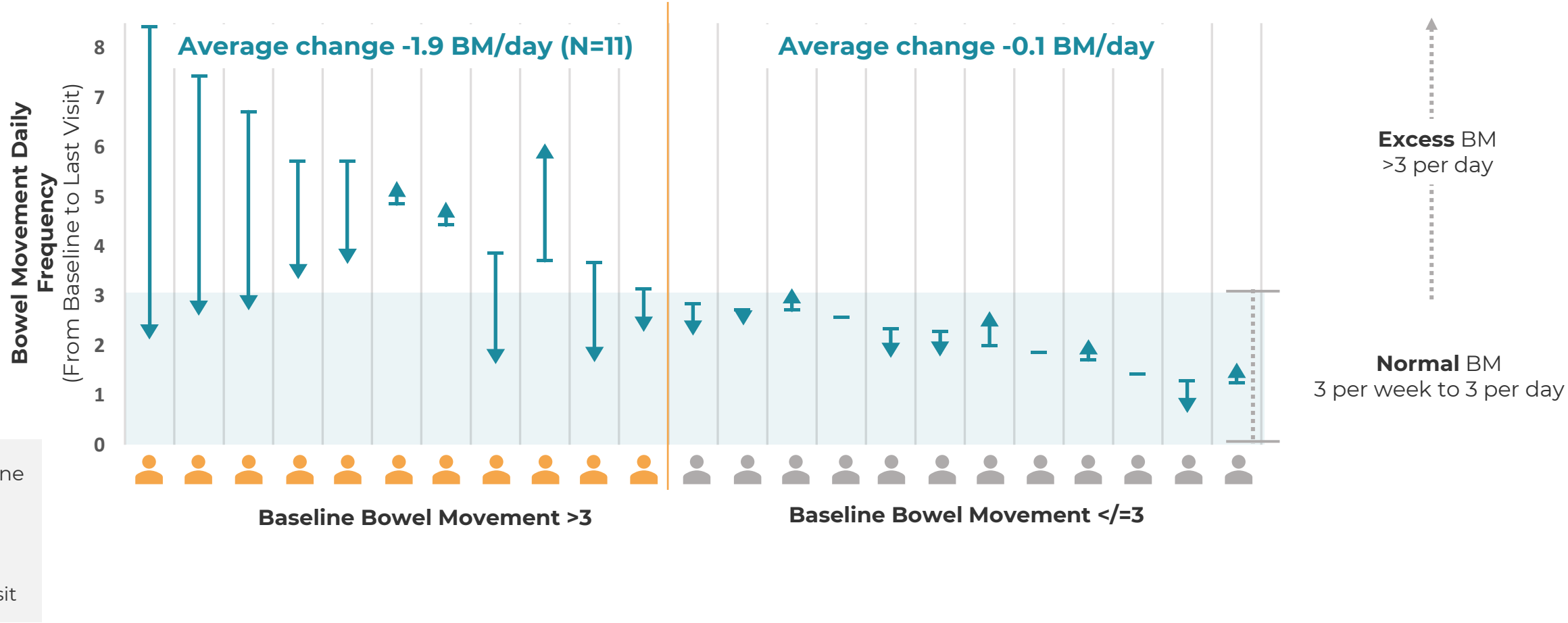

**Flushing Frequency for Patients with ≥1/day at Baseline**




*Excess bowel movements (BM) were defined as daily bowel movements above the upper limit of normal (3 per day)
Exploratory analysis of last visit prior to the preliminary data cut off includes 23 subjects: 15 subjects completed the week 8 visit, 4 subjects completed week 6 visit, 3 subjects completed week 4 visit and 1 subject completed week 2 visit.

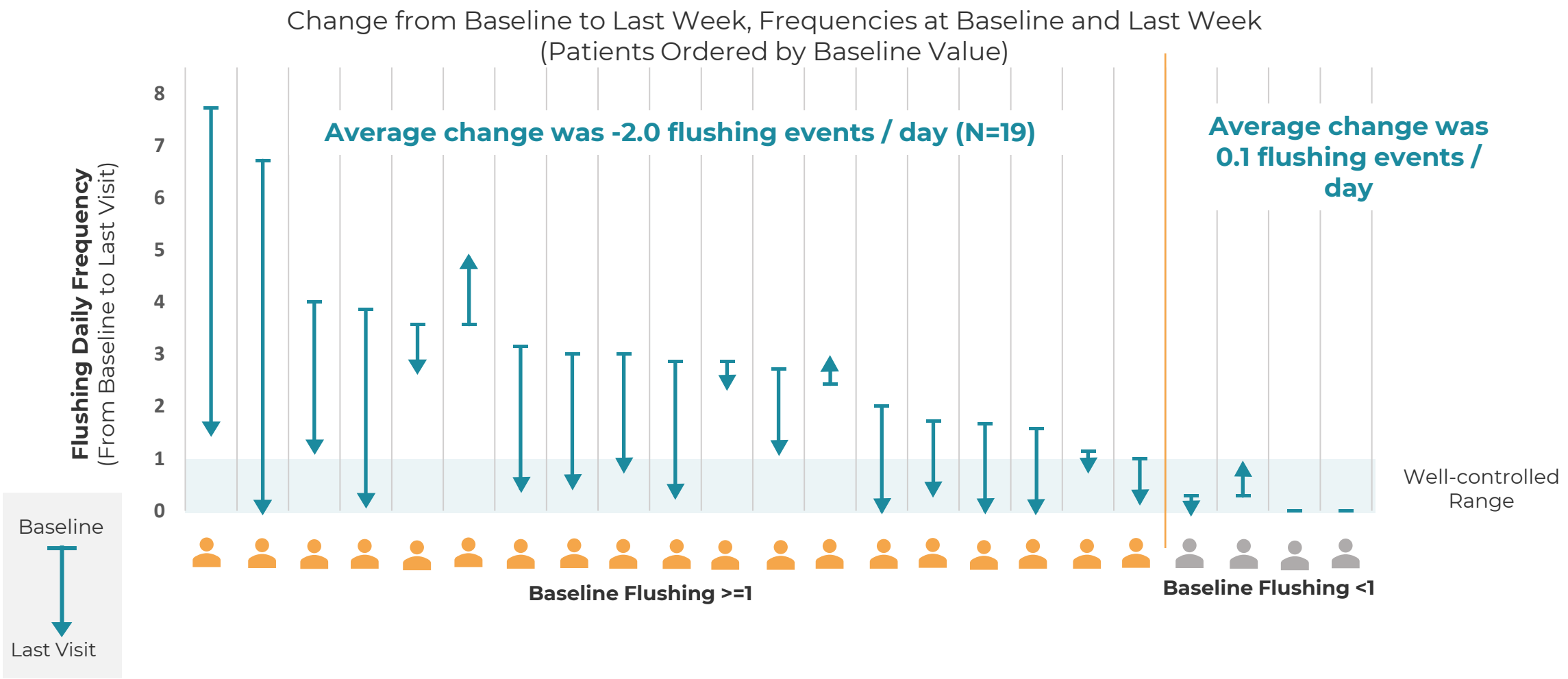
# Paltusotine had Clear Benefit on Subjects with Elevated Bowel Movement Frequency

Change from Baseline to Last Week of Treatment
(Patients Ordered by Baseline Value)




(1) End of each arrow represents the data from the last available week of treatment for each of the 23 subjects. 15 subjects completed the week 8 visit, 4 subjects completed week 6 visit, 3 subjects completed week 4 visit and 1 subject completed week 2 visit.

# Paltusotine Showed Improvements in Flushing Frequencies in Majority of Subjects

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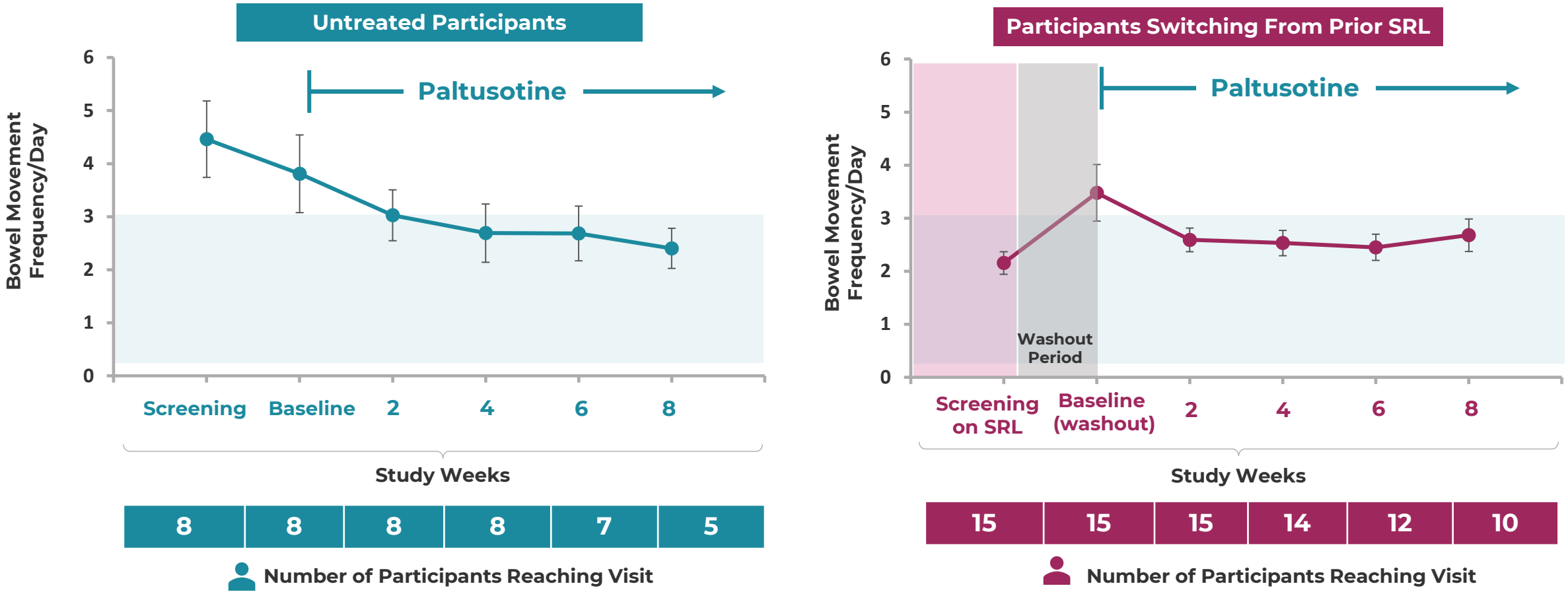
# Rapid Improvements in Bowel Movement Frequency were Observed within 2 Weeks of Treatment

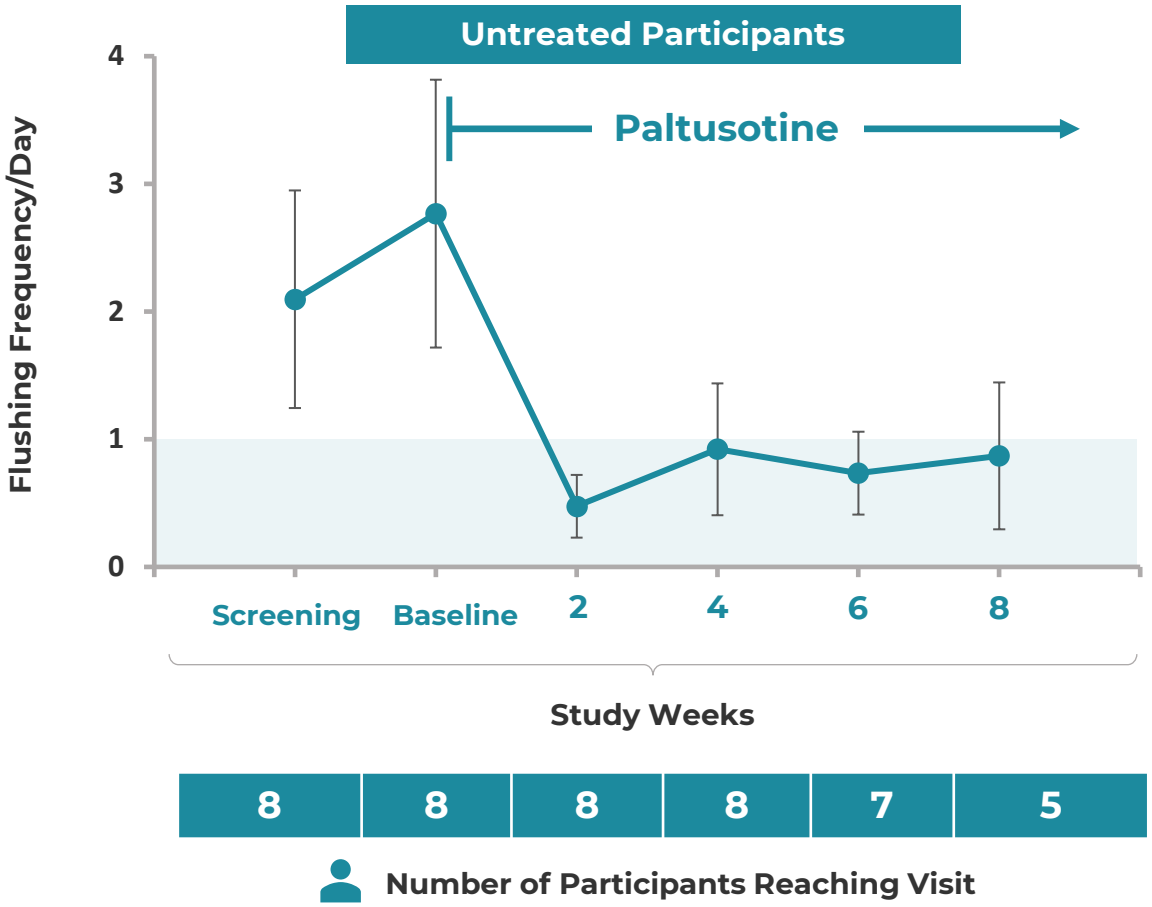
**Bowel Movement Frequency of All Participants (N=23) Whether Experiencing Excess BMs at Baseline or Not**

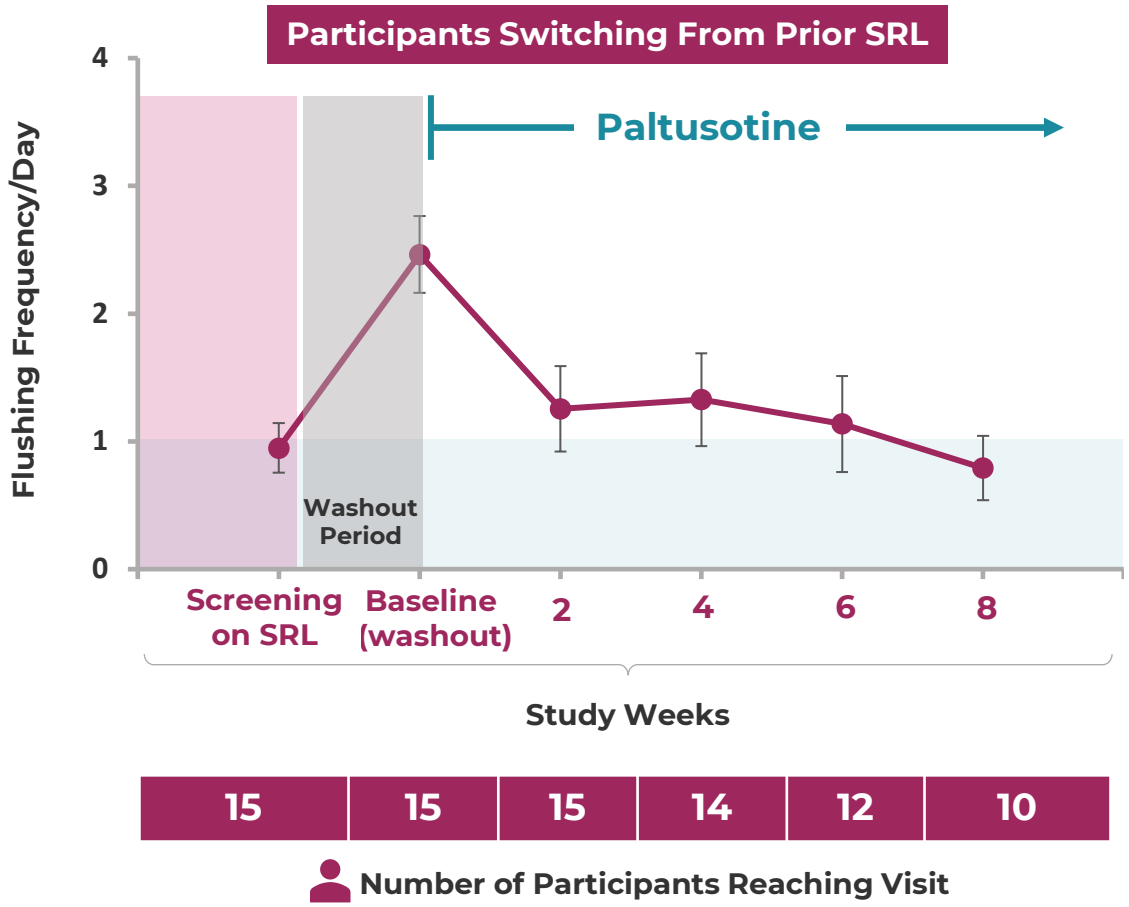



Frequency measure is based on the 14-day average during the screening period and 7-day average prior to baseline on all other timepoints
SRL = somatostatin receptor ligand

# Rapid Improvements in Flushing Frequency were Observed within 2 Weeks of Treatment

**Flushing Frequency of All Participants (N=23) Whether Experiencing Flushing at Baseline or Not**




Frequency measure is based on the 14-day average during the screening period and 7-day average prior to baseline on all other timepoints
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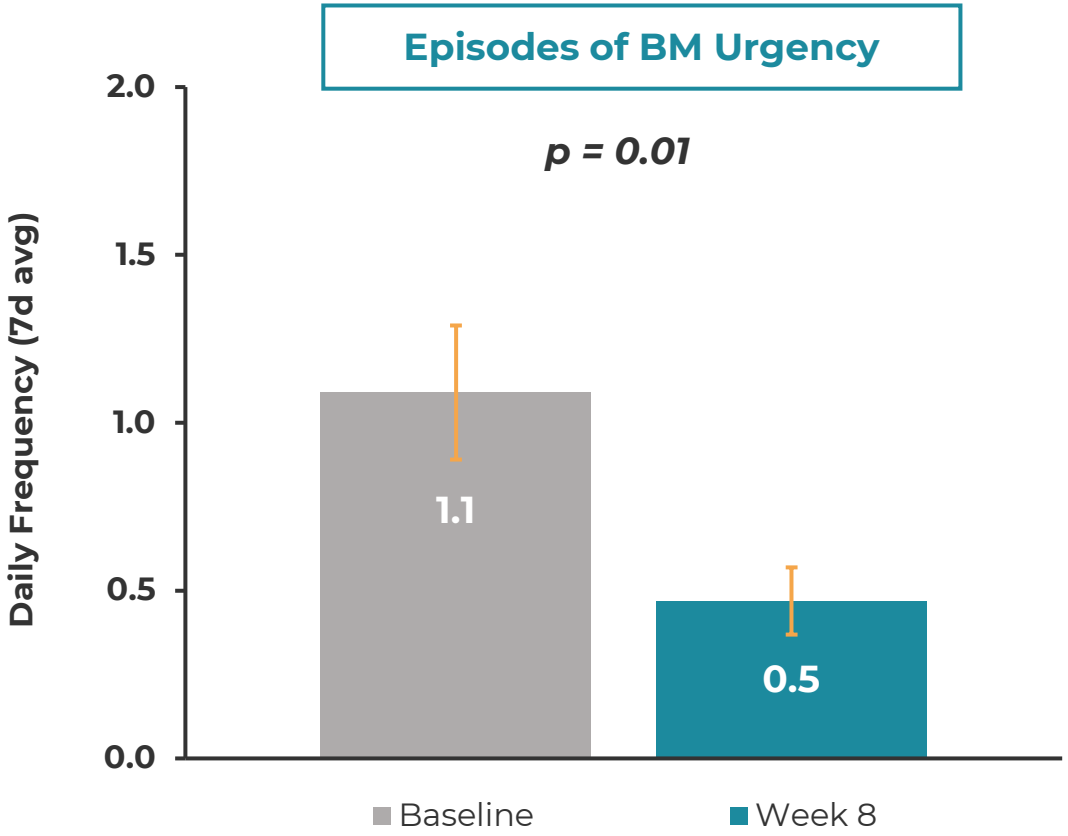
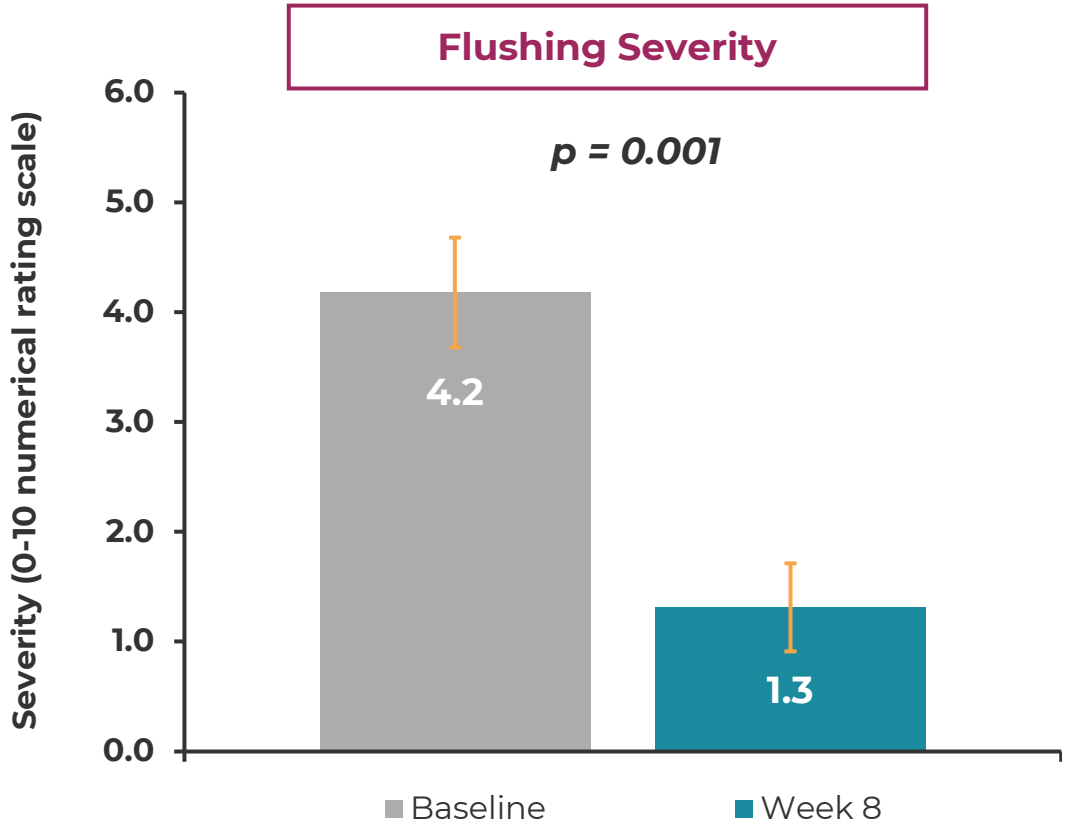
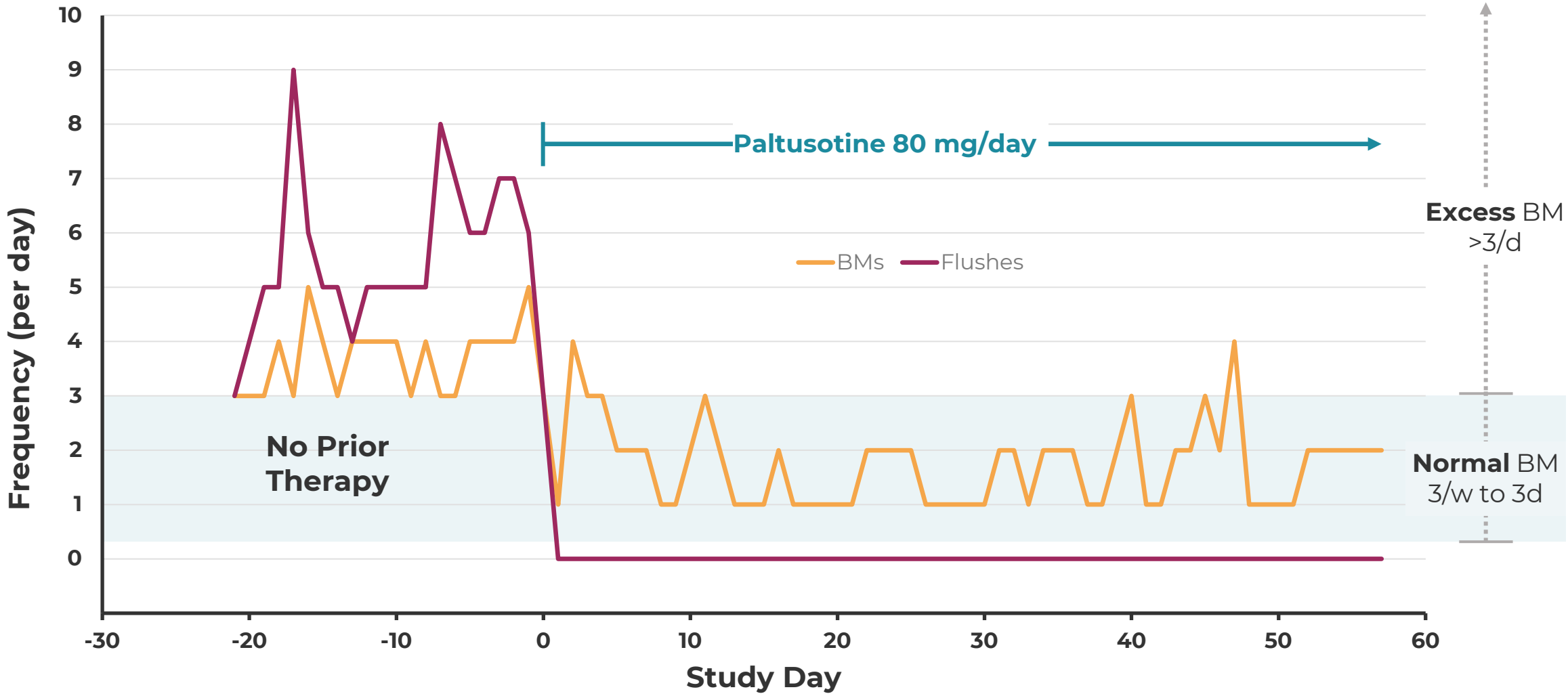
# Paltusotine Also Reduced the Severity of Key Carcinoid Syndrome Symptoms



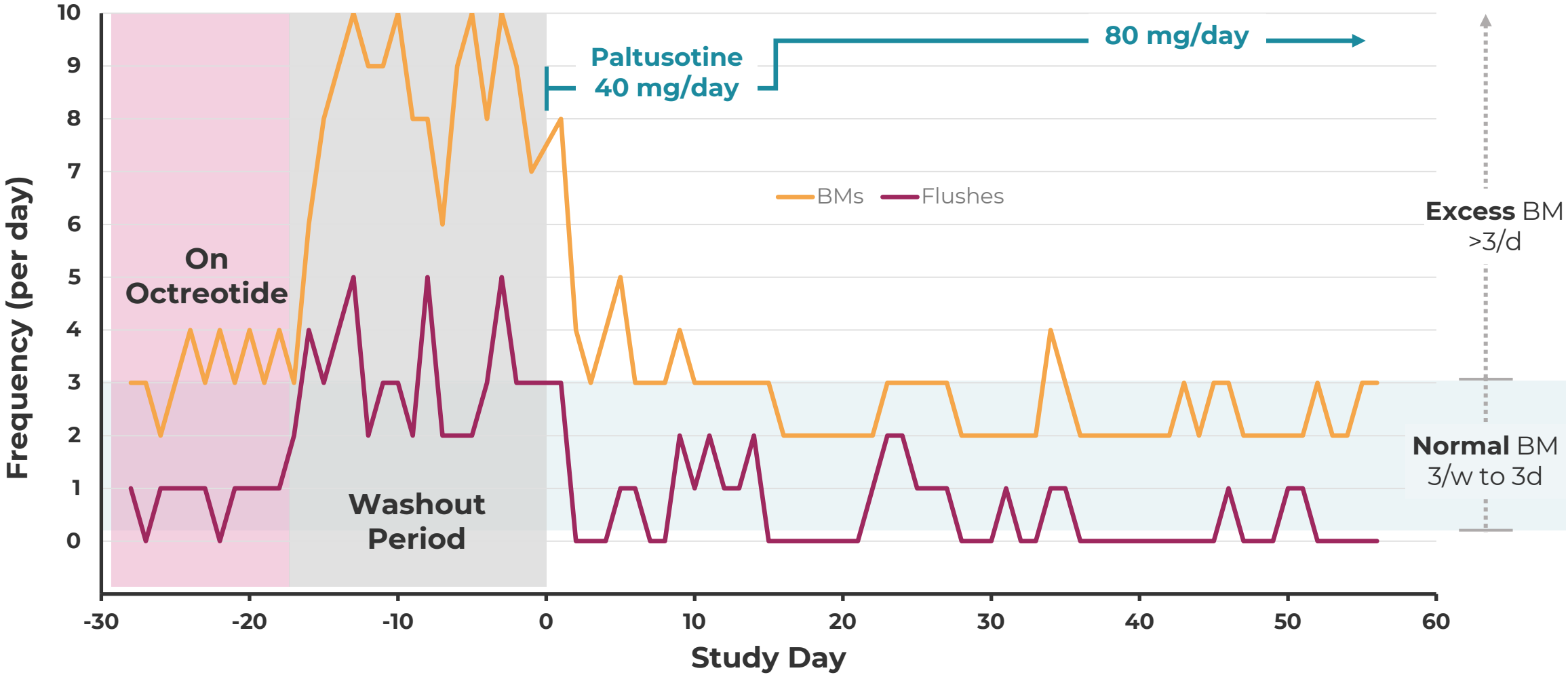

N=15 who completed the Randomized Treatment Period
BM = bowel movement

# Example Study Participant #1: Elimination of Flushing and Normalization of BMs




BM = bowel movement

# Example Study Participant #2: Meaningful Improvements in BM and Flushing Frequencies




BM = bowel movement

# Once Daily Oral Paltusotine Showed Strong Initial Results in Carcinoid Syndrome Patients

## Summary: Exceeded Initial Goals for the Study

- Significant reductions of frequency and severity of bowel movements and flushing with 40mg and 80mg
- Paltusotine was well-tolerated with no severe or serious treatment related adverse events
- Overall PK was generally consistent with expectations from healthy volunteers

## Next Steps: Initial Data Supports Preparation for Phase 3

- Analysis of biomarker and supplemental patient reported outcome data
- The study has completed enrollment (N=36), and the topline data from the complete study is expected in 1H 2024
- Expect to submit complete data set and engage with FDA first half of 2024

# Anticipated Paltusotine Milestones

**1Q24**
- Results from PATHFNDR-2 Phase 3 study in untreated acromegaly patients

**1H24**
- Topline results from carcinoid syndrome Phase 2 study (N=36)

**2H24**
- Acromegaly NDA submission
- Carcinoid syndrome Phase 3 start pending alignment with FDA


**Ongoing Open Label Extension Studies**
- N > 175 participants and increasing
- 26 patients from Phase 2 extension study have been treated with paltusotine for >3 years, 35 patients for >2 years

# Q&A

**Scott Struthers, Ph.D.**
Founder and Chief Executive Officer

**Dana Pizzuti, M.D.**
Chief Medical & Development Officer

**Alan Krasner, M.D.**
Chief Endocrinologist