Crinetics Pharmaceuticals

Results from 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

March 12, 2024

SAFE HARBOR STATEMENT

This presentation contains forward-looking statements. Crinetics Pharmaceuticals, Inc. ("Crinetics," the "company," "we," "us," or "our") cautions you that statements contained in this presentation regarding matters that are not historical facts are forward-looking statements. These statements are based on the company's current beliefs and expectations. Such forward-looking statements include, but are not limited to, statements regarding: the strategic objectives for paltusotine; the plans and timelines for the clinical development of paltusotine, including the therapeutic potential and clinical benefits or safety profile thereof; the expected timing of topline results data from the ongoing Phase 3 clinical study of paltusotine in acromegaly; the expected timing of the submission of a new drug application for paltusotine for the treatment of acromegaly and related open label extension studies; plans and timing for sharing the full results of the Phase 2 study of paltusotine in carcinoid syndrome with the FDA to align on a Phase 3 program and the plans and enrollment in related open label extension studies; the potential benefits of CRN04894 in patients with Congenital Adrenal Hyperplasia or Cushing's Disease and the expected plans and timing for data and topline data readouts from ongoing clinical studies; the potential benefits of PTH receptor antagonists for patients with hyperparathyroidism, the potential benefits of TSH antagonist for Graves' Disease or thyroid eye disease; the potential for any of our ongoing clinical studies to show safety or efficacy; the potential of our ongoing discovery efforts to target future indications for hyperparathyroidism, polycystic kidney disease, Graves diseases, thyroid eye disease, or diabetes/obesity, and the expected plans and timing for candidate selection and clinical development of such candidates; our plans to identify and create new drug candidates for additional diseases or the potential for any such new drug candidates to show safety or efficacy; the direction or trajectory of the Company's potential future growth, the receipt of any revenues from product sales and the ability of such revenues to support continued growth, and our expected plans and timing for commercialization of paltusotine and other product candidates pending regulatory approval. In some cases, you can identify forward-looking statements by terms such as "may," "believe," "anticipate," "could," "should," "estimate," "expect," "intend," "plan," "project," "will," "contemplate," "predict," "continue," "forecast," "aspire," "lead to," "designed to," "goal," "potential," "target" or the negative of or other similar terms.

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This presentation also contains information gathered from market research, estimates and other statistical data made by independent parties and by us relating to addressable patients, addressable market size and other data about our industry or the potential market opportunity for our product, including academic and community medical oncologist and other HCP opinions collected during market research. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to the opinions gathered in market research or to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

Once Daily Oral Paltusotine Showed Positive Results in Carcinoid Syndrome Patients

EFFICACY FINDINGS: Rapid and Sustained Reductions in Patient Symptoms

- ☑ **Flushing:** 63% reduction in frequency for patients with >1/day (p< 0.0001)
- ☑ **Flushing Severity:** 61% reduction in severity of episodes (p<0.0001)
- ☑ **Excess Bowel Movement:** 60% reduction in frequency for patients with >3/day (p=0.02)
- ☑ **Bowel Movement Urgency:** 64% reduction in urgent episodes (p<0.0001)

SAFETY

- ☑ Paltusotine was generally well-tolerated with no treatment-related severe or serious adverse events
- ☑ Paltusotine demonstrated no new safety signals

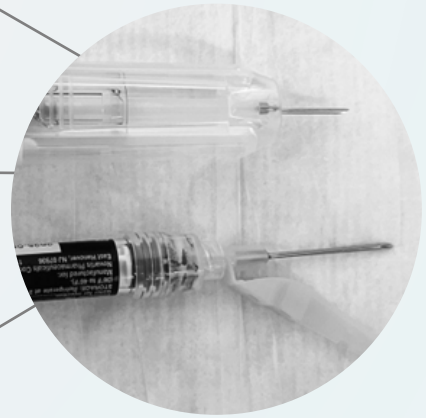
Efficacy and safety findings support progressing to a pivotal phase 3 trial
(pending discussions with the FDA)

Paltusotine is an investigational drug in clinical studies for the treatment of acromegaly and carcinoid syndrome.

Paltusotine: Designed to Allow People with Acromegaly and Carcinoid Syndrome to Focus on Living

CURRENT STANDARD OF CARE

- Inconsistent Symptom Control
- 77% report injection site reactions
- Painful, inconsistent and inconvenient dosing



VS

PALTUSOTINE TARGET PRODUCT PROFILE*

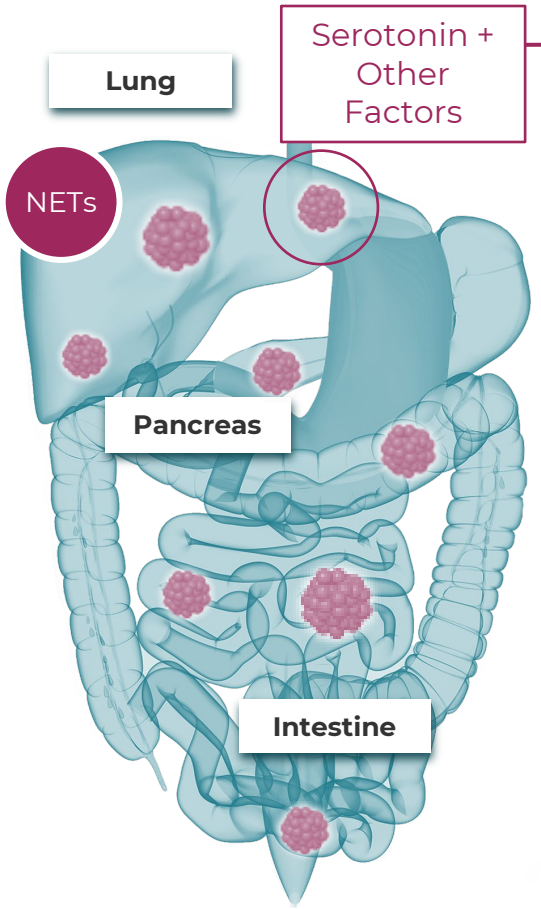
- Reliable, consistent, and durable control
- Well-tolerated
- Once-daily oral tablet
- No injections

Phase 3 design strategy

*Pending alignment with FDA on phase 3 study for Carcinoid Syndrome. Paltusotine is an investigational drug in clinical studies for the treatment of acromegaly and carcinoid syndrome.

References 1. Geer EB, Sisco J, Adelman DT, et al. Patient reported outcome data from acromegaly patients treated with injectable somatostatin receptor ligands (SRLs) in routine clinical practice. *BMC Endocr Disord*. 2020;20(1):117. doi:10.1186/s12902-020-00595-4; 2. Strasburger CJ, Karavitaki N, Störmann S, et al. Patient-reported outcomes of parenteral somatostatin analogue injections in 195 patients with acromegaly. *Eur J Endocrinol*. 2016;174(3):355-62. doi:10.1530/EJE-15-1042; 3. Fleseriu et al. Frontiers in Endocrinology; March 2021, Vol.12; 4. Boyd et al. Pancreas 2013;42: 878—882.

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



Carcinoid Syndrome

~33,000 Patients Diagnosed with Carcinoid Syndrome (U.S.)

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)*

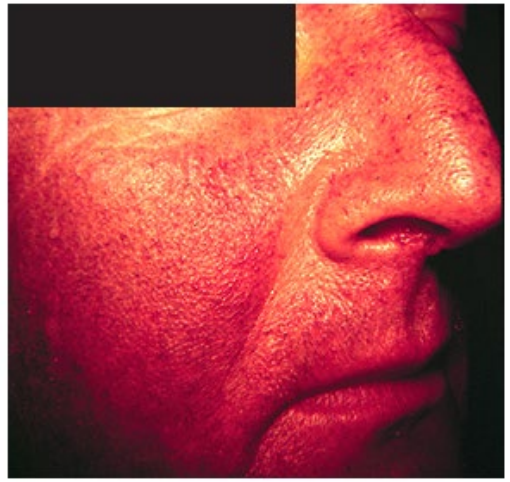
Severe and life-threatening complications: carcinoid heart disease (found in up to 50% of patients) & carcinoid crisis

Goal: *prevent severe complications*

Injected SRLs impose a high burden of care and frequently lose effectiveness before next injection

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®

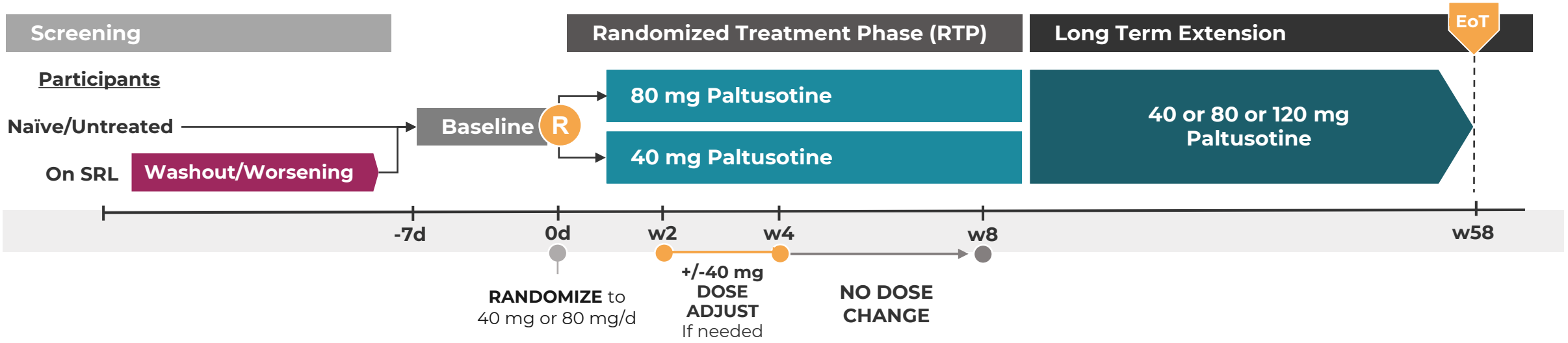
NETs = Neuroendocrine tumors; SRL = somatostatin receptor ligand.

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 a Long Term Extension phase

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

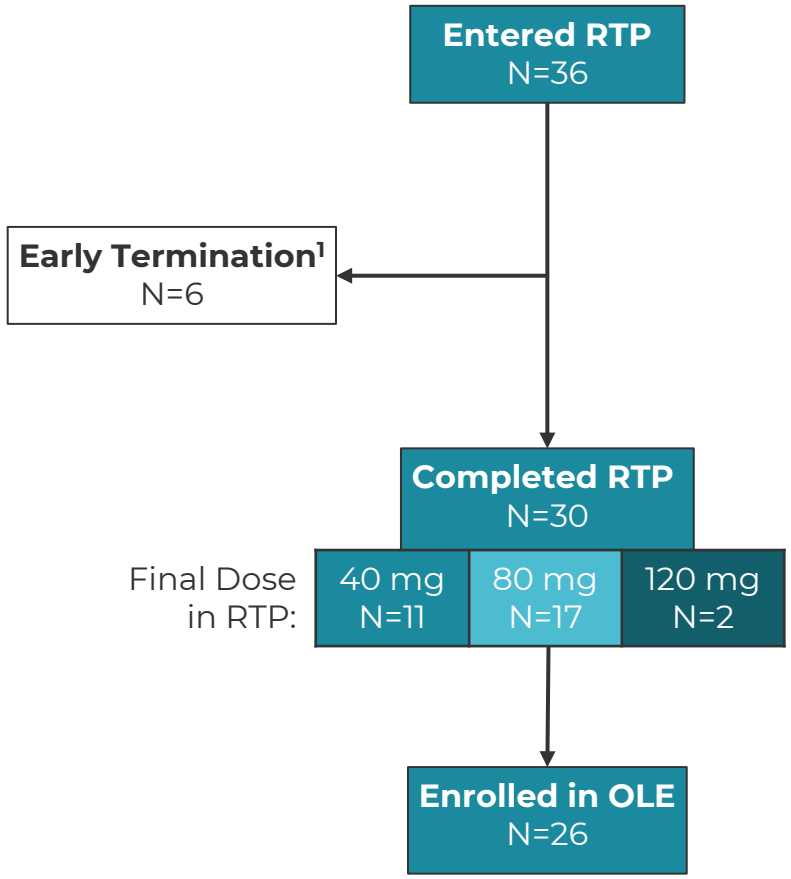
Pharmacokinetics of Paltusotine

Exploratory Efficacy Endpoints

Bowel movement and flushing frequency and severity markers, octreotide rescue use, biomarkers, PRO measures

EoT = end of treatment; NET = Neuroendocrine tumor; PK = Pharmacokinetics; PRO = patient reported outcome; SRL = somatostatin receptor ligand; SSTR = somatostatin receptor.

Subject Disposition and Dosing



	Total n (%)
Entered RTP	**36**
Naïve/Untreated	9
Switching	27
Discontinued	6 (17)
Withdrawal by subject	1 (3)
Adverse event	2 (6)
Investigator decision	2 (6)
Need for administration of a prohibited concomitant medication	1 (3)
Increased dose at Week 2 or 4	9
Completed RTP	**30 (83)**
Naïve/Untreated	8
Switching	22
Enrolled in OLE	**26 (87)**

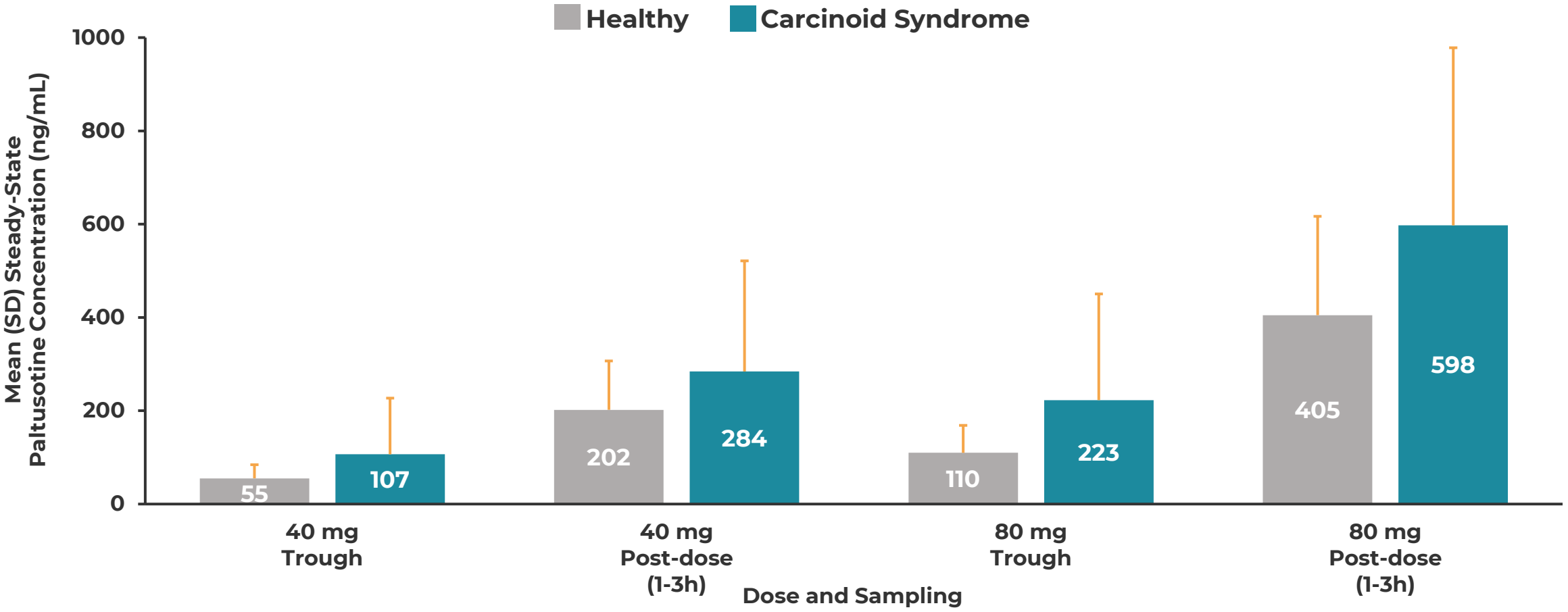
RTP = Randomized treatment phase (8 weeks); OLE=Open-label extension.
1. One subject who discontinued in the RTP dosed with paltusotine and had diary data through week 8 of the RTP.

Baseline Demographics and Disease Characteristics were Consistent Across Patient Groups

	Naïve/Untreated Symptomatic N=9	Switching from SRL N=27	Overall N=36
Female, n (%)	**6 (67)**	**13 (48)**	**19 (53)**
Male, n (%)	**3 (33)**	**14 (52)**	**17 (47)**
Age - Mean (SD), years	**58.2 (19.5)**	**61.6 (10.3)**	**60.8 (13.0)**
BMI - Mean (SD), kg/m²	**30.0 (14.0)**	**28.4 (5.3)**	**28.8 (8.1)**
Geographic Region			
North America, n (%)	4 (44)	15 (56)	19 (53)
Europe, n (%)	1 (11)	1 (4)	2 (6)
Latin America , n (%)	4 (44)	11 (41)	15 (42)
Duration Since Carcinoid Syndrome Diagnosis – Median, months	**8.2**	**72.1**	**69.4**
NET Tumor Grade 1, n (%)	**5 (56)**	**14 (52)**	**19 (53)**
NET Tumor Grade 2, n (%)	**4 (44)**	**13 (48)**	**17 (47)**

BMI=Body Mass Index; NET = Neuroendocrine tumor.

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



Healthy volunteers: simulated (n=1000) using paltusotine population PK model, sampling at steady-state trough and 2h post-dose. Carcinoid Syndrome patients: 40 mg trough (n=17), 40 mg post-dose (n=15), 80 mg trough (n=21), 80 mg post-dose (n=18), 120 mg trough (n=2), and 120 mg post-dose (n=2). 120 mg data omitted due to small sample size.

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

Treatment-Emergent Adverse Events, n (%)	Paltusotine N=36
Any	**26 (72.2)**
Mild/Moderate	22 (61.1)
Severe	4 (11.1)
Leading to discontinuation	2 (5.6)
Serious	4 (11.1)
Death	1 (2.8)*
Treatment-related	**16 (44.4)**
Mild/Moderate	16 (44.4)
Severe	0
Leading to discontinuation	0
Serious	0
Death	0

Preliminary Safety Summary from Ongoing Carcinoid Syndrome Phase 2 Study

- Paltusotine was generally well-tolerated with no treatment related severe or serious adverse events
- 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.
ECG = Electrocardiogram; SAE = Serious Adverse Event.

Most Frequent Treatment-Emergent Adverse Events Observed were Mild to Moderate

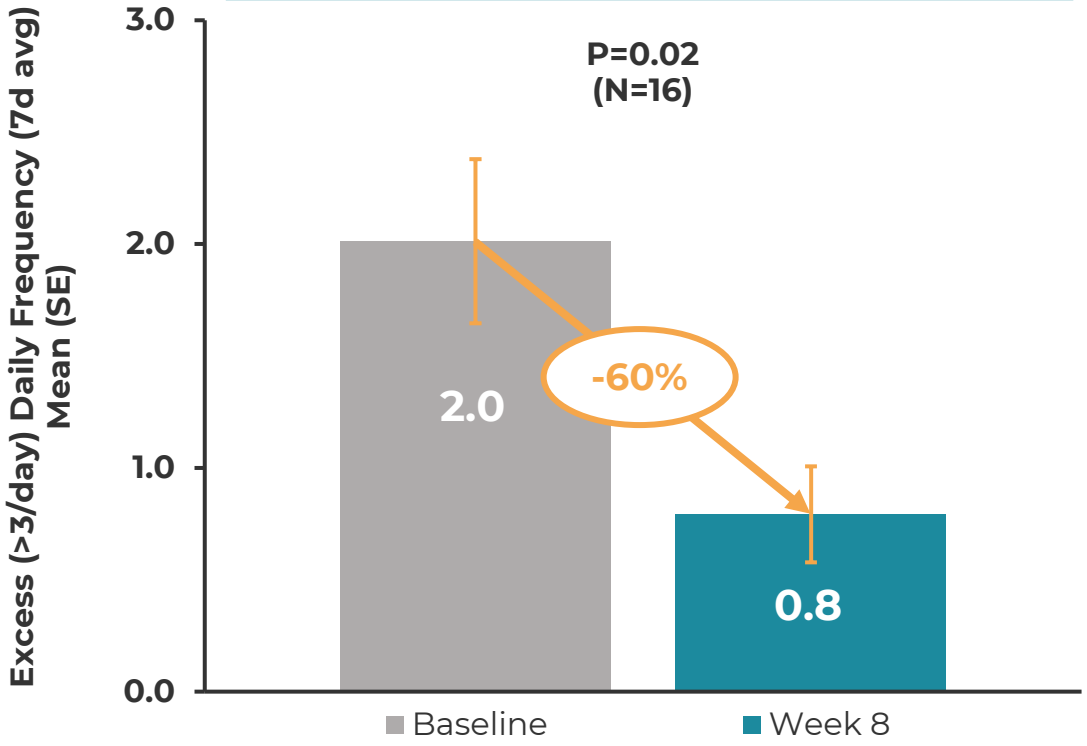
Treatment-Emergent Adverse Events, n (%)	Paltusotine N=36
Diarrhea	14 (38.9)
Abdominal Pain	7 (19.4)
Nausea	6 (16.7)
Headache	6 (16.7)
Flushing	5 (13.9)
Fatigue	4 (11.1)
Asthenia	3 (8.3)
ALT Elevation	2 (5.6)*
Vomiting	2 (5.6)
Hypertension	2 (5.6)
Myalgia	2 (5.6)
Pyrexia	2 (5.6)
Somnolence	2 (5.6)
Urinary tract infection	2 (5.6)

- Adverse event frequency was similar across both dose groups
- Most adverse events were mild to moderate in severity and transient
- Safety profile consistent with symptoms of carcinoid syndrome and SRL treatment effects

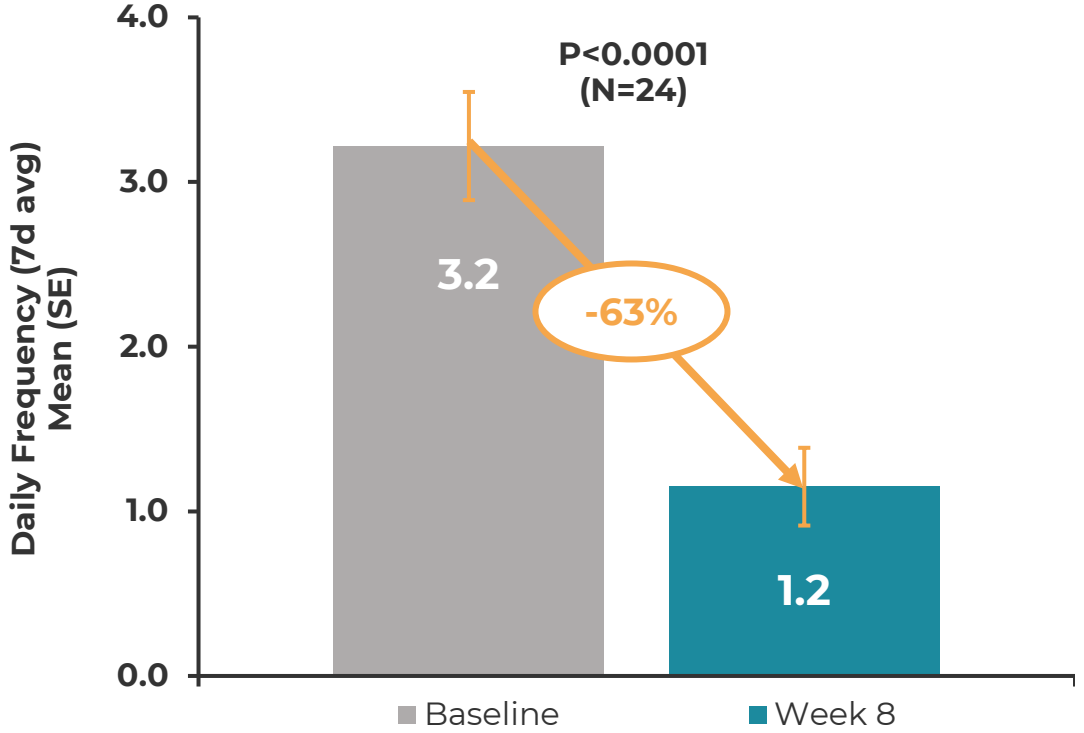
*The two cases of ALT elevation were < 3X ULN and not associated with elevated bilirubin or alkaline phosphatase.

Paltusotine Reduced Frequency of Key Carcinoid Syndrome Symptoms: Excess BM and Flushing

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



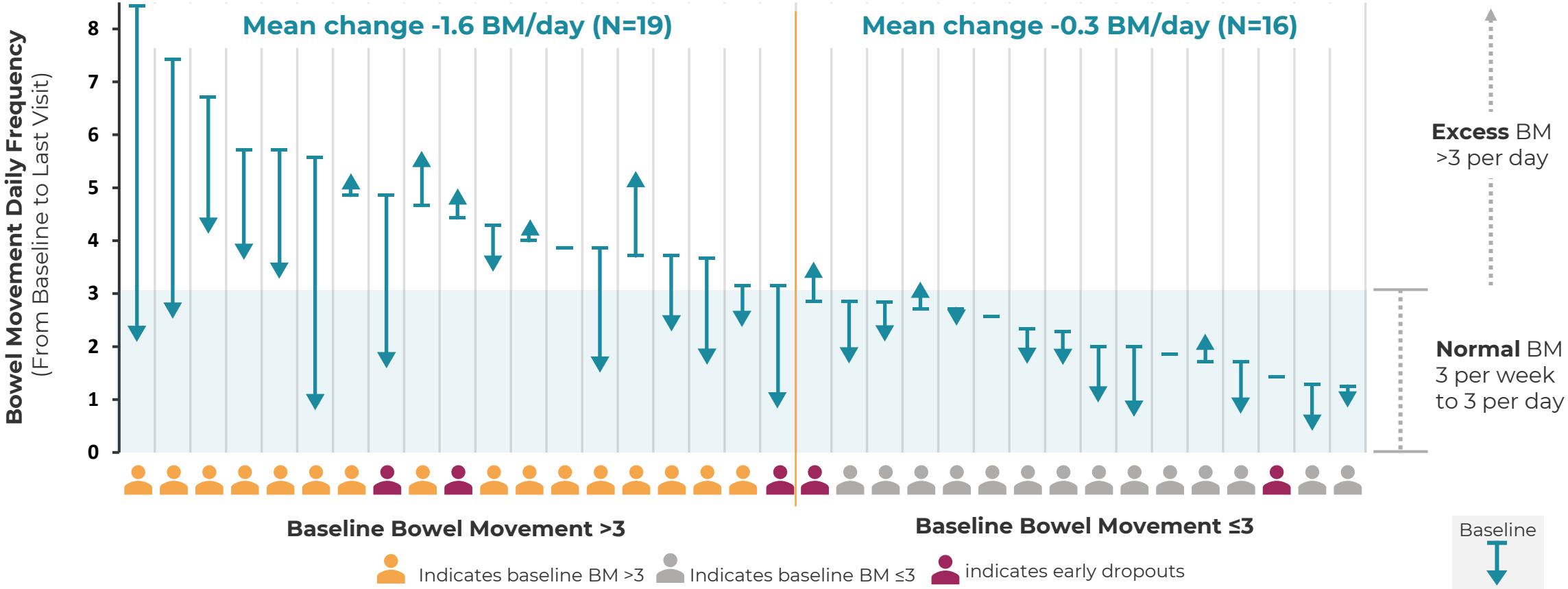
Flushing Frequency For Patients with >1/day at Baseline



*Excess bowel movements (BM) were defined as daily bowel movements above the upper limit of normal (3 per day).

Paltusotine Showed Improvements in Subjects with Elevated Bowel Movement Frequency

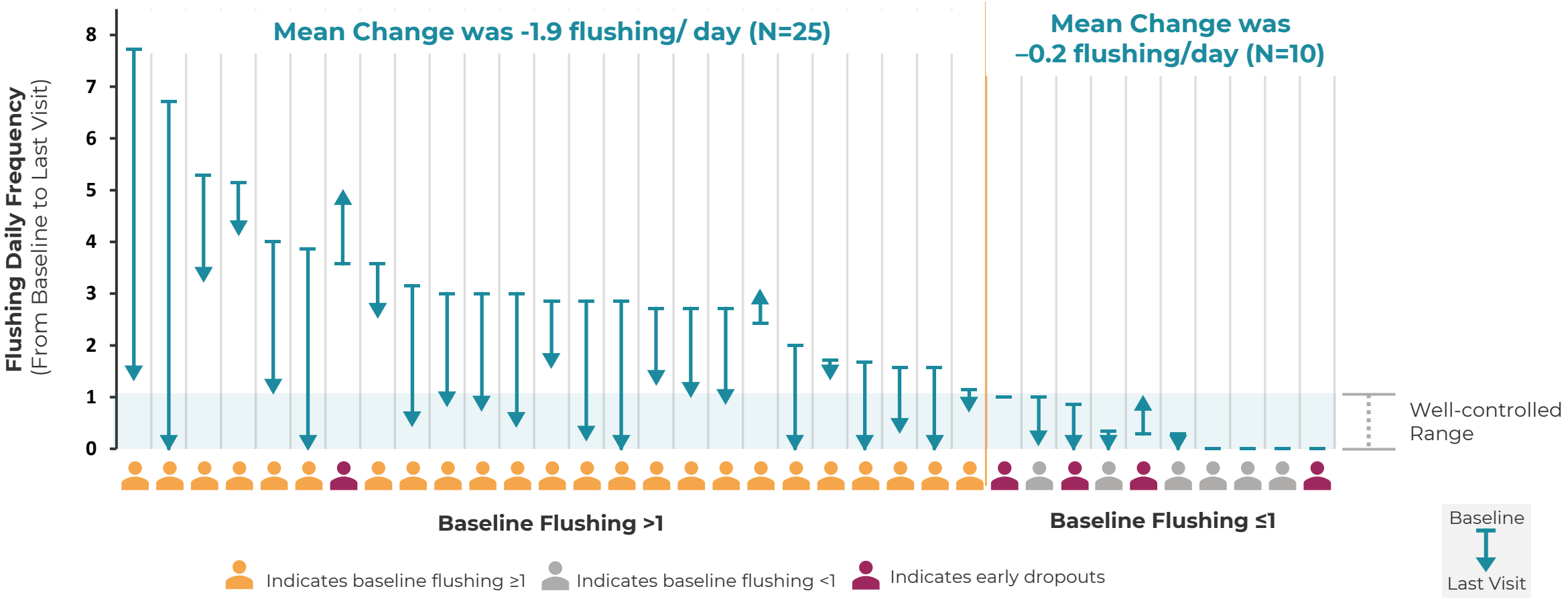
Change from Baseline to Last Week of Treatment
(Patients with at least 2 Weeks of RTP Data, Ordered by Baseline Value)



End of each arrow represents the data from the last available week of treatment for each of the 35 subjects, including that from early dropouts.
BM = Bowel Movement; RTP = Randomized Treatment Phase.

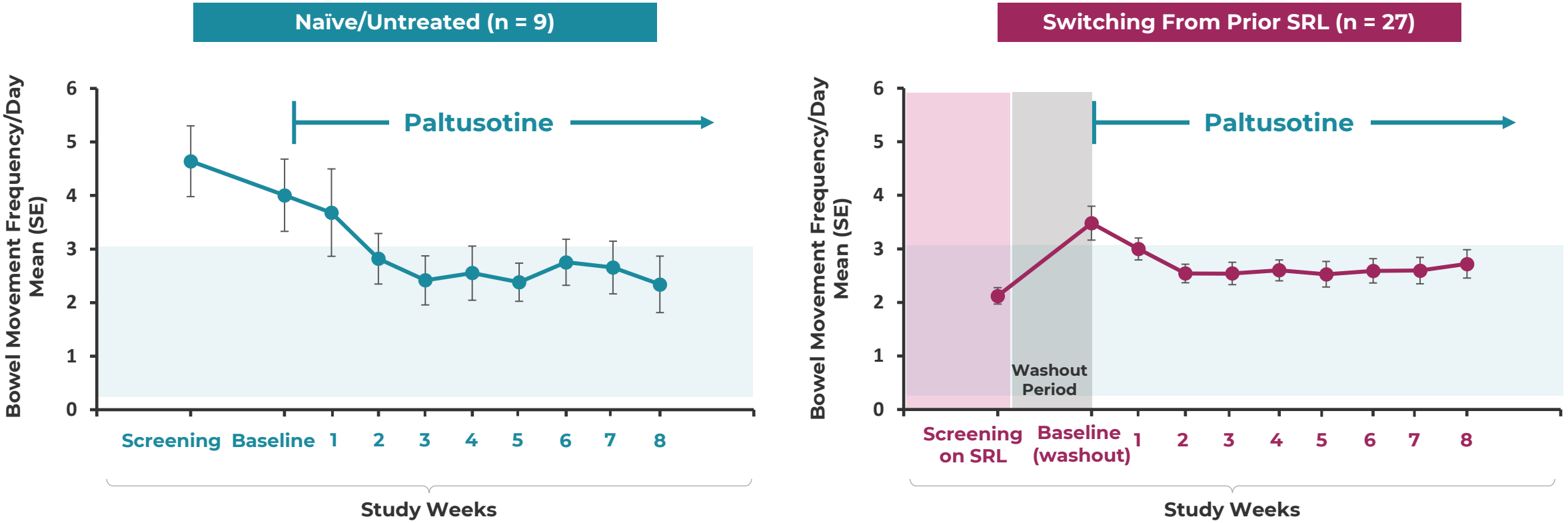
Paltusotine Showed Improvements in Flushing Frequency in Majority of Subjects

Change from Baseline to Last Week of Treatment
(Patients with at Least 2 Weeks of RTP Data, Ordered by Baseline Value)



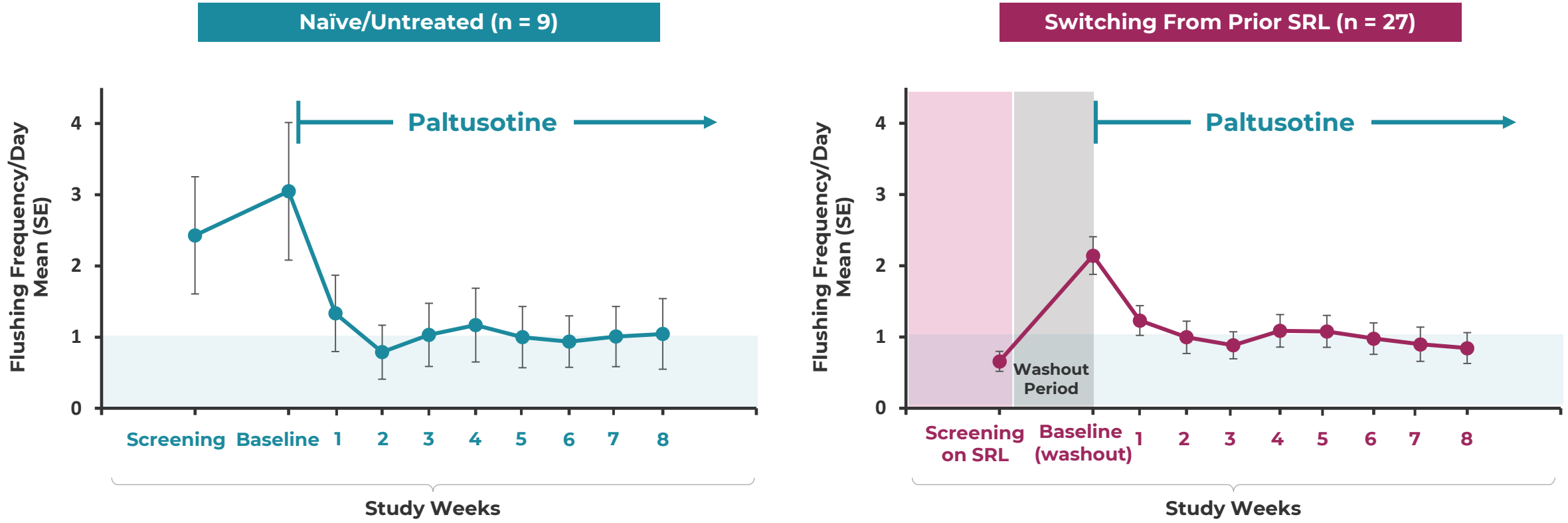
End of each arrow represents the data from the last available week of treatment for each of the 35 subjects, including that from early dropouts. RTP = Randomized Treatment Phase.

Rapid Improvements in Bowel Movement Frequency Were Observed Within 2 Weeks of Treatment and Were Sustained Through Week 8



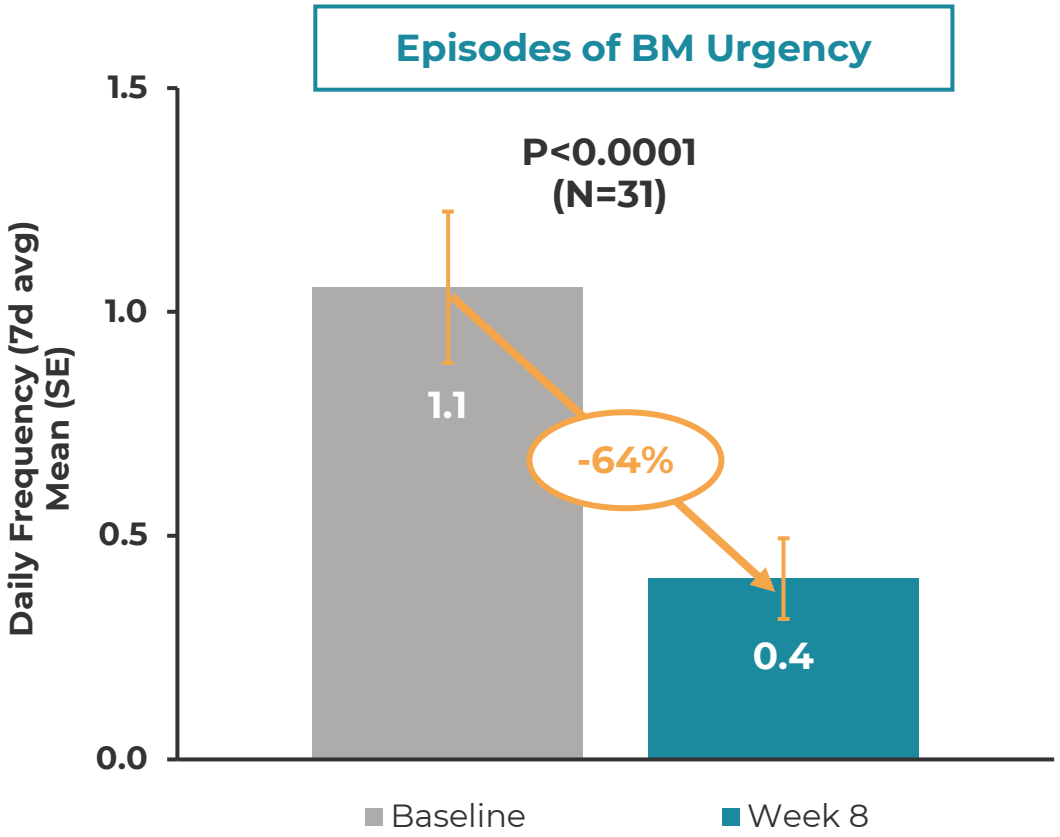
Frequency measure is based on the 14-day average during the screening period and 7-day average prior to baseline on all other timepoints.
SRL = somatostatin receptor ligand.

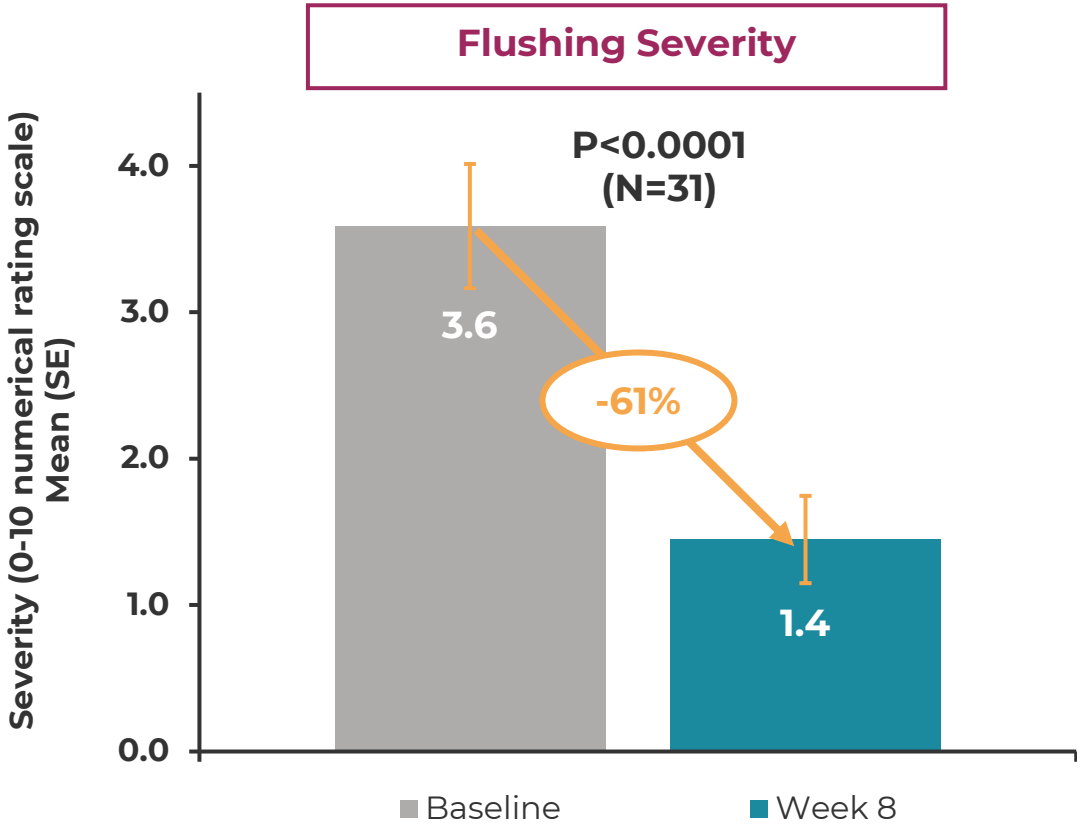
Rapid Improvements in Flushing Frequency Were Observed Within 2 Weeks of Treatment and Were Sustained Through Week 8



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.

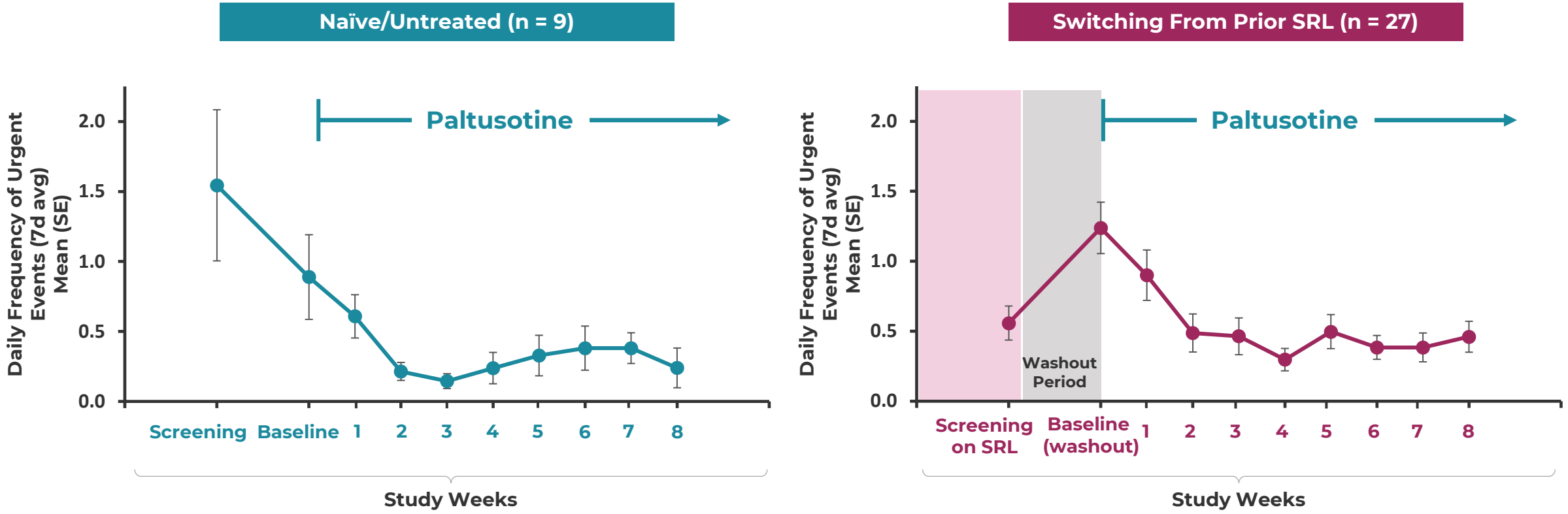
Paltusotine Also Reduced the Severity of Key Carcinoid Syndrome Symptoms





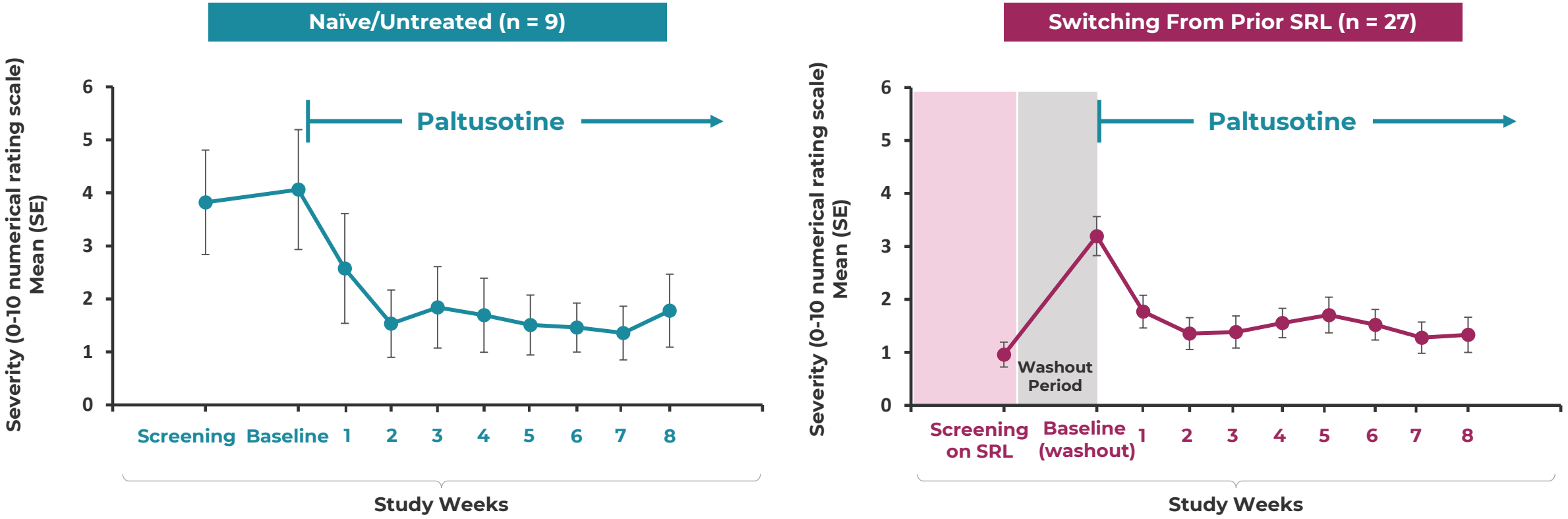
N=31 subjects with data through the Randomized Treatment Period; one subject who discontinued in the RTP dosed with paltusotine and had diary data through week 8 of the RTP; BM = bowel movement.

Rapid Improvements in Episodes of BM Urgency Were Observed Within 2 Weeks of Treatment and Were Sustained Through Week 8



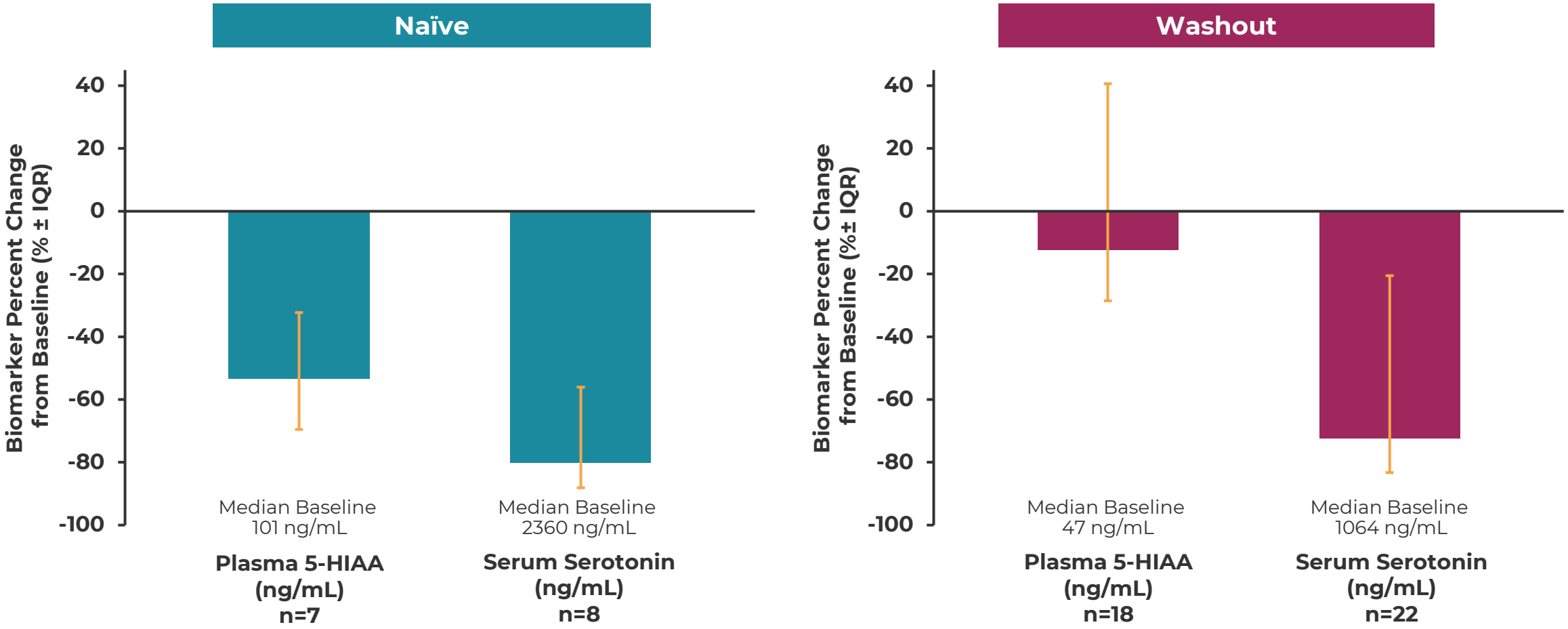
Frequency measure is based on the 14-day average during the screening period and 7-day average prior to baseline on all other timepoints.
BM = bowel movement; SRL = somatostatin receptor ligand.

Rapid Improvements in Flushing Severity Were Observed Within 2 Weeks of Treatment and Were Sustained Through Week 8



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.

Paltusotine Suppressed Serotonin Levels, a Key Biomarker in Carcinoid Syndrome Patients



Baseline is last value prior to start of randomized treatment, i.e., Week 1, or Screening 1 for naïve subjects if Week 1 was missing; IQR = Interquartile range is the spread of the middle half of a data set; The upper limit of normal for Plasma 5-HIAA is 22 ng/mL. The upper limit of normal for Serum Serotonin is 541 ng/mL.

Once Daily Oral Paltusotine Showed Positive Results in Carcinoid Syndrome Patients

Summary: Phase 2 Results Support Proceeding to a Phase 3 Program

- Rapid and sustained reductions were observed in frequency and severity of bowel movements and flushing episodes with 40 mg and 80 mg
- Paltusotine was generally well-tolerated with no severe or serious treatment related adverse events
- Overall PK profile was consistent with prior studies
- Serotonin and 5HIAA levels provided additional evidence for activity of paltusotine in carcinoid syndrome

Next Steps: Engage with FDA and Prepare for Phase 3 Start

- Plan to discuss the results and align on a Phase 3 study design
- Begin preparations to enable the initiation of Phase 3 by the end of the year

Paltusotine is an investigational drug in clinical studies for the treatment of acromegaly and carcinoid syndrome.

Market Research Supports that Paltusotine's Emerging Profile can Address Unmet Needs for Carcinoid Syndrome

Oral Alternative

- HCPs note the **extensive training** required for nurses to correctly prepare and administer injectable SRLs and would welcome an **oral SRL with easier prep and administration**
- If SRLs are not administered properly, **patients may not receive the full dose,** missing the full benefit of the medication
- The **SRL injections can lead to significant injection site pain and granulomas**

*"Sometimes they don't thaw [the medication] long enough, they'll pinch the skin instead of flattening. And you get **injection granulomas** because the treatment wasn't delivered correctly, and the **patient doesn't get the maximum benefit of the treatment.**"*

- Med Onc, Academic

Symptom Control

- HCPs say **the level of symptom control demonstrated by paltusotine in phase 2 study was comparable** with their clinical experience with injectable SRLs
- Physicians appreciate that paltusotine **targeted both flushing and diarrhea** symptoms **without added safety concerns**

*"The **two main symptoms, the diarrhea and flushing, if that's getting better, that is a pretty good sign.** The flushing is the main one for me. There is not enough available therapy for that."*

- Med Onc, Community

Patient Preference

- HCPs predict they would offer paltusotine to all patients, and anticipate **most would prefer oral SRLs over injectables**
- Many patients are **injection averse,** or **live far away,** making it difficult to get to monthly appointments (especially elderly patients)

*"Patients who live far from the clinic, and **they want to come to the clinic less frequently**. Or if they said, 'I can't take this injection' or **'I don't want to get injections,'** we can consider [Paltusotine]."*

- Med Onc, Community

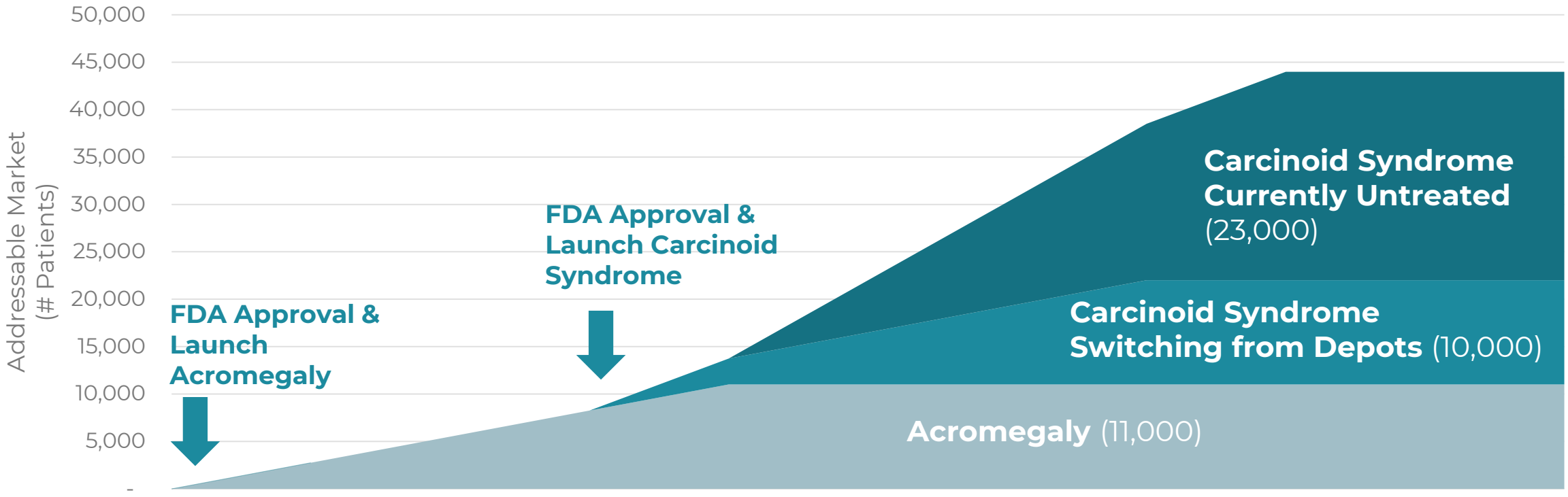
Source: *Primary qualitative market research conducted with US Oncologists*

Paltusotine is an investigational drug in clinical studies for the treatment of acromegaly and carcinoid syndrome.

Strategy to Enable Paltusotine to Serve a Greater Number of Patients

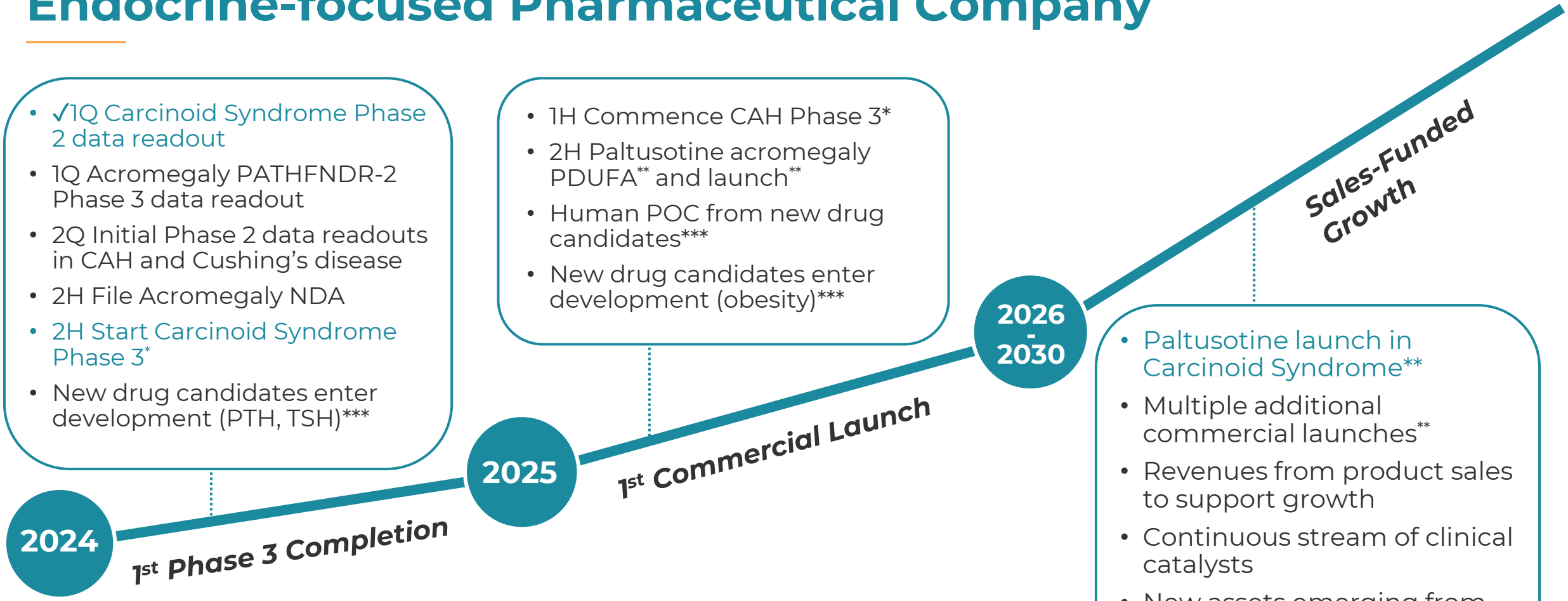
Paltusotine Strategic Objectives:

- Build HCP Experience with Acromegaly
- Phase 3 Study Design Supporting Both Switching and Untreated Carcinoid Syndrome Patients
- Build HCP Experience in Carcinoid Syndrome



Paltusotine is an investigational drug in clinical studies for the treatment of acromegaly and carcinoid syndrome.

Crinetics is Building the Premier **Fully Integrated Endocrine-focused Pharmaceutical Company**



- ✓1Q Carcinoid Syndrome Phase 2 data readout
- 1Q Acromegaly PATHFNDR-2 Phase 3 data readout
- 2Q Initial Phase 2 data readouts in CAH and Cushing's disease
- 2H File Acromegaly NDA
- 2H Start Carcinoid Syndrome Phase 3*
- New drug candidates enter development (PTH, TSH)***

- 1H Commence CAH Phase 3*
- 2H Paltusotine acromegaly PDUFA** and launch**
- Human POC from new drug candidates***
- New drug candidates enter development (obesity)***

- Paltusotine launch in Carcinoid Syndrome**
- Multiple additional commercial launches**
- Revenues from product sales to support growth
- Continuous stream of clinical catalysts
- New assets emerging from discovery into development

Strategic Approach to **Growing Long-term Value**

*Pending alignment with FDA **Pending NDA submission, acceptance and regulatory approval
***Pending identification, creation and clinical development of new drug candidates for additional diseases

CAH: congenital adrenal hyperplasia; PTH: parathyroid hormone; TSH: thyroid stimulating hormone; POC: proof of concept

Q&A

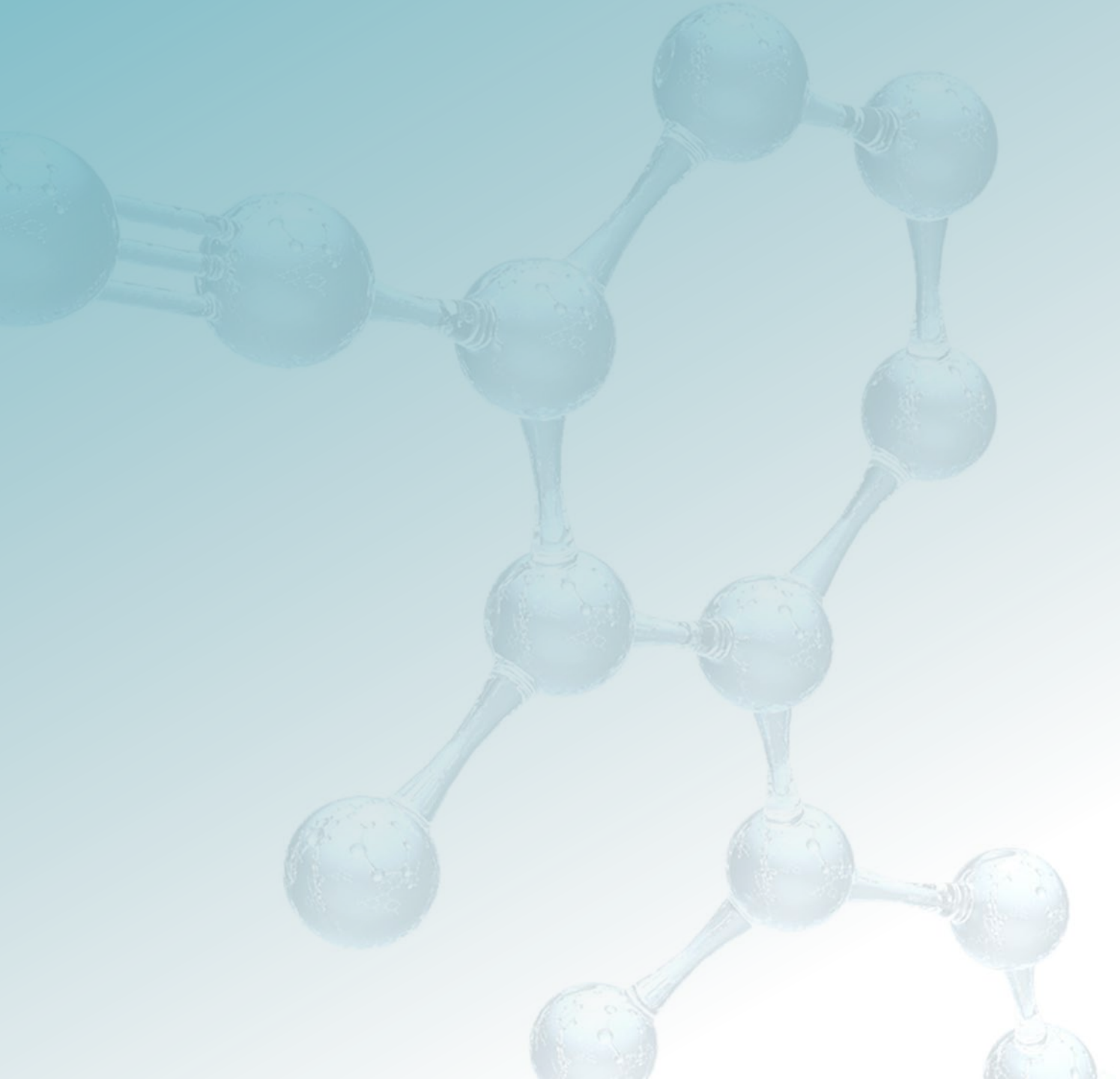
Scott Struthers, Ph.D.
Founder and Chief Executive Officer

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

Alan Krasner, M.D.
Chief Endocrinologist

Jim Hassard
Chief Commercial Officer

Crinetics Pharmaceuticals



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Thank You