Crinetics Pharmaceuticals

PATHFNDR-1

Paltusotine Acromegaly Therapy Featuring a Non-Invasive Daily Regimen

TOPLINE RESULTS FROM PALTUSOTINE PHASE 3 PATHFNDR-1 STUDY

A Randomized, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Paltusotine in Subjects with Acromegaly Treated with Long-acting Somatostatin Receptor Ligands

SAFE HARBOR STATEMENT

This presentation contains forward-looking statements. Crinetics Pharmaceuticals, Inc. (“Crinetics”) 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 potential benefits of paltusotine for acromegaly patients and patients with carcinoid syndrome; the potential for the PATHFNDR program to support registration of paltusotine for all acromegaly patients who require pharmacotherapy; the expected timing of topline data from the PATHFNDR-2 study and the Phase 2 and Phase 3 studies in patients with carcinoid syndrome and the expected timing of the submission of a new drug application for paltusotine for the treatment of acromegaly and related open label extension studies. In some cases, you can identify forward-looking statements by terms such as “may,” “believe,” “anticipate,” “could,” “should,” “estimate,” “expect,” “intend,” “plan,” “project,” “will,” “forecast,” “laying the foundation,” “aspiring,” “target” and similar terms.

These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, without limitation: topline data that we report may change following a more comprehensive review of the data related to the clinical studies and such data may not accurately reflect the complete results of a clinical study, and the FDA and other regulatory authorities may not agree with our interpretation of such results; the risk that preliminary results of preclinical studies or clinical studies do not necessarily predict final results and that one or more of the clinical outcomes may materially change as patient enrollment continues, following more comprehensive reviews of the data, and as more patient data become available; potential delays in the commencement, enrollment and completion of clinical studies and the reporting of data therefrom; the FDA or other regulatory agencies may require additional clinical studies of paltusotine or suggest changes to our planned Phase 3 clinical studies prior to and in support of the approval of a New Drug Application or applicable foreign regulatory approval; the COVID-19 pandemic may disrupt our business and that of the third parties on which we depend, including delaying or otherwise disrupting our clinical studies and preclinical studies, manufacturing and supply chain, or impairing employee productivity; our dependence on third parties in connection with product manufacturing, research and preclinical and clinical testing; the success of our clinical studies, nonclinical studies and preclinical studies for paltusotine; regulatory developments or price restrictions in the United States and foreign countries; unexpected adverse side effects or inadequate efficacy of our product candidates that may limit their development, regulatory approval and/or commercialization; our ability to obtain and maintain intellectual property protection for our product candidates; we may use our capital resources sooner than we expect; and other risks described under the heading “Risk Factors” in documents we file from time to time with the Securities and Exchange Commission (“SEC”). Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. All forward-looking statements are qualified in their entirety by this cautionary statement, which is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and, except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight 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.

PATHFNDR[1] Met the Primary and All Secondary Endpoints and Paltusotine Was Well-Tolerated

Paltusotine Acromegaly Therapy Featuring a Non-Invasive Daily Regimen

PRIMARY ENDPOINT

- ✓ **83% of participants on paltusotine maintained IGF-1 ≤ 1.0xULN vs 4% on placebo (p<0.0001)**

SECONDARY ENDPOINTS (paltusotine arm vs. placebo)

- ✓ **Change from baseline in IGF-1 (p<0.0001)**
- ✓ **Change from baseline in Acromegaly Symptoms Diary score (p=0.02)**
- ✓ **Proportion of participants who maintained GH <1.0 ng/mL (p=0.0003)**

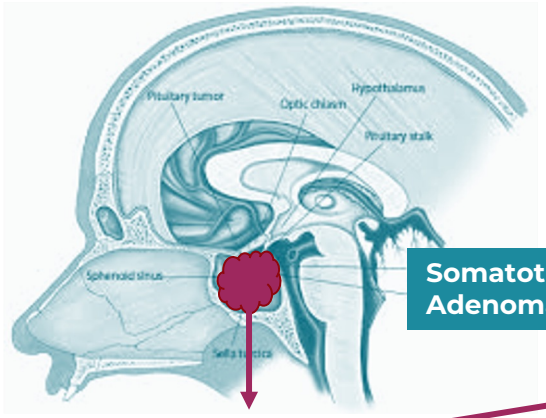
SAFETY

- ✓ **Paltusotine was well-tolerated with no severe or serious adverse events**
- ✓ **Paltusotine demonstrated no new safety signals**

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

What is Acromegaly?

Acromegaly is caused by a benign pituitary tumor secreting excess growth hormone (GH)
Uncontrolled acromegaly is debilitating and increases risk of early death



Somatotroph Adenoma

GH

Somatostatin Receptor Ligands (SRLs) inhibit GH secretion

Liver

IGF-I

Excess GH secretion by the pituitary gland causes excess IGF-1 secretion by the liver

- **Changed Facial Features**
- **Prognathism**
- **Enlarged Hands**
- **Carpel Tunnel**
- **Arthritis**

- **Hypertension**
- **Hypopituitarism**
- **Hepatomegaly**
- **Impaired Glucose**
- **Thyroid Hypertrophy**

- **Headache**
- **Vision Defects**
- **Perspiration**
- **Joint Pain**
- **Swelling**
- **Respiratory Issues**

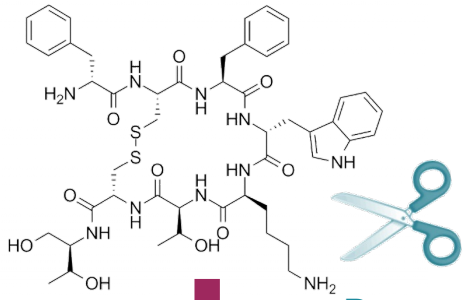




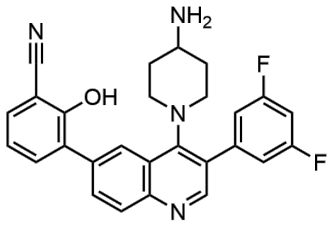

Sources: http://www.fipapatients.org; Bex M, Abs R, T'Sjoen G, et al. Eur J Endocrinol. 2007;157(4):399-409

Paltusotine Was Designed as the First Once-Daily, Oral, Selectively Targeted SST2 Agonist

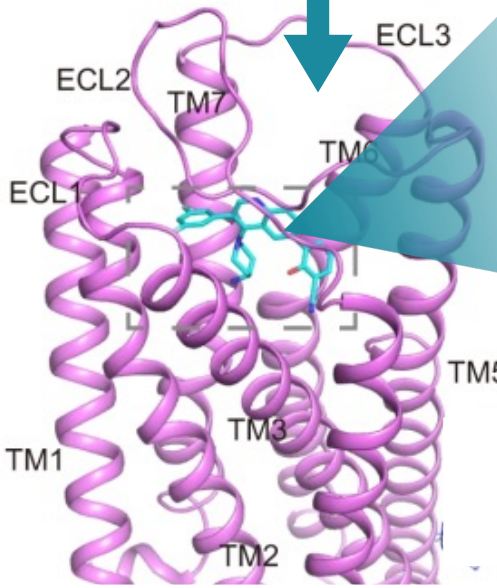
octreotide (peptide)



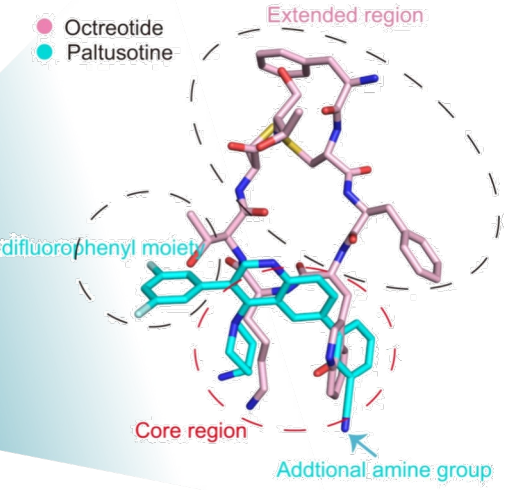
paltusotine (nonpeptide)



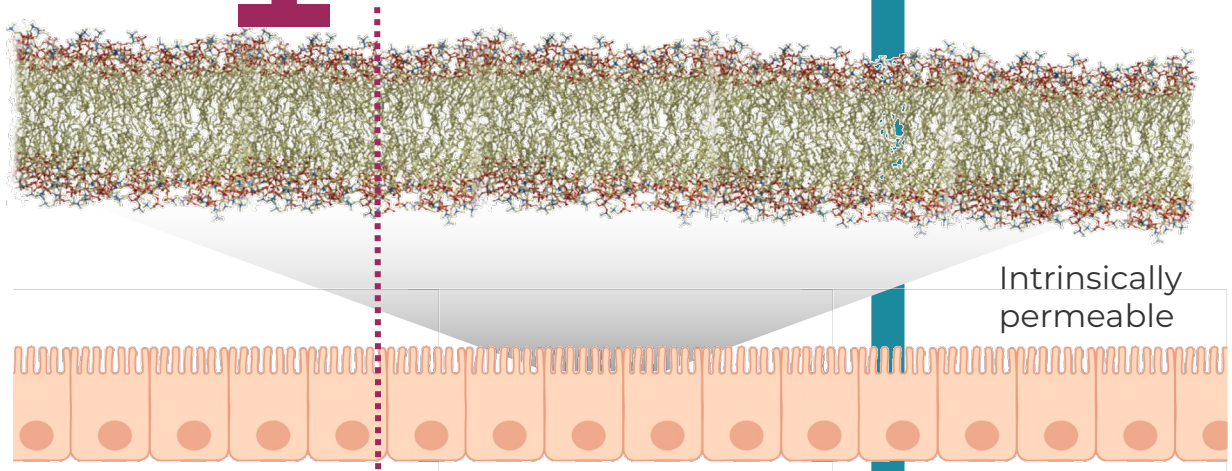
Peptides and nonpeptides share a common receptor binding site



SST2 Receptor



Proteases



Intrinsically permeable

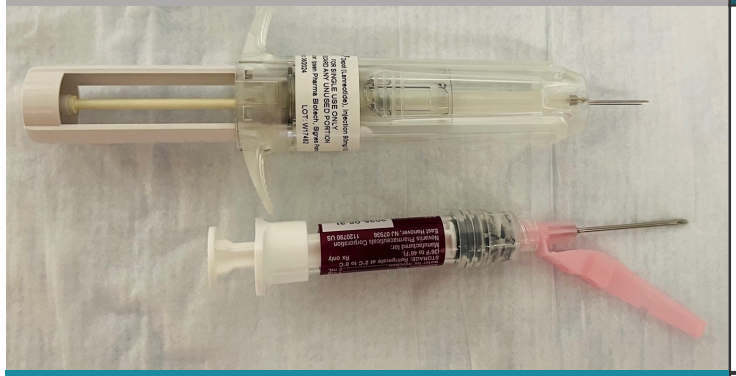
oral bioavailability 0.5%
half-life: ~2 hrs.

Blood Stream

oral bioavailability 70%
half-life: ~30 hrs.

Sources: Madan et al. Pituitary, (2022) 25:328-339; Heo, Yoon et al. eLife (2022);0:e76823; Zhao et al. Nature Commun, (2023) 14, 962

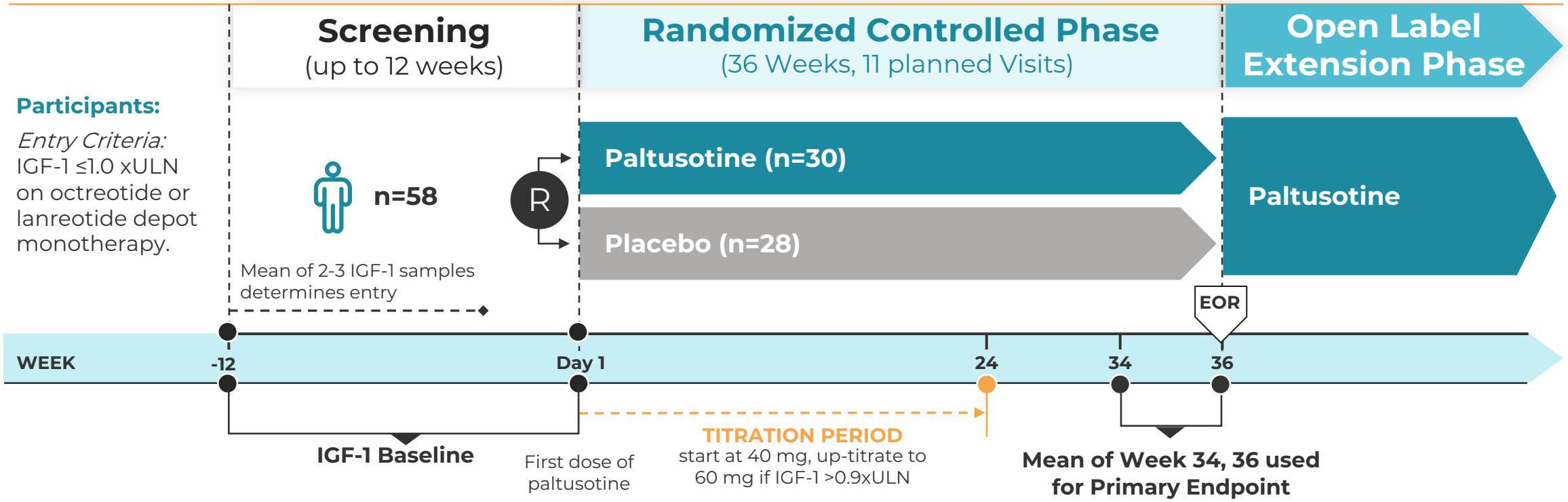
Goal for Paltusotine:
Help People to Focus on Living Life

Current Standard of Care	Disease Control	Tolerability	Patient Experience
	**Poor symptom control:** worsening of symptoms at the end of each injection cycle[1,2]	**Treatment-related injection site reactions** reported by 77% of patients on monthly SRLs[3]	Depot SRL injections are **painful and often need to be administered in a doctor's office**
Potential Benefits of Paltusotine*			
	**Reliable, consistent and durable IGF-1 control**	**No injections** **Well tolerated** with no severe or serious adverse events	**Once daily oral tablet** has potential to reduce strain on daily routine and healthcare system

* If paltusotine receives regulatory approval. Clinical studies to support applications for regulatory approval are ongoing.

SRL: Somatostatin receptor ligand; Sources: 1. Geer et al. BMC Endocrine Disorders, (2020) 20:117; 2. Strasburger et al. European Journal of Endocrinology, (2016) 174; 3. Fleseriu et al. Frontiers in Endocrinology; March 2021, Vol.12

Evaluated Participants Switching from Standard of Care Depots to Once Daily Oral Paltusotine



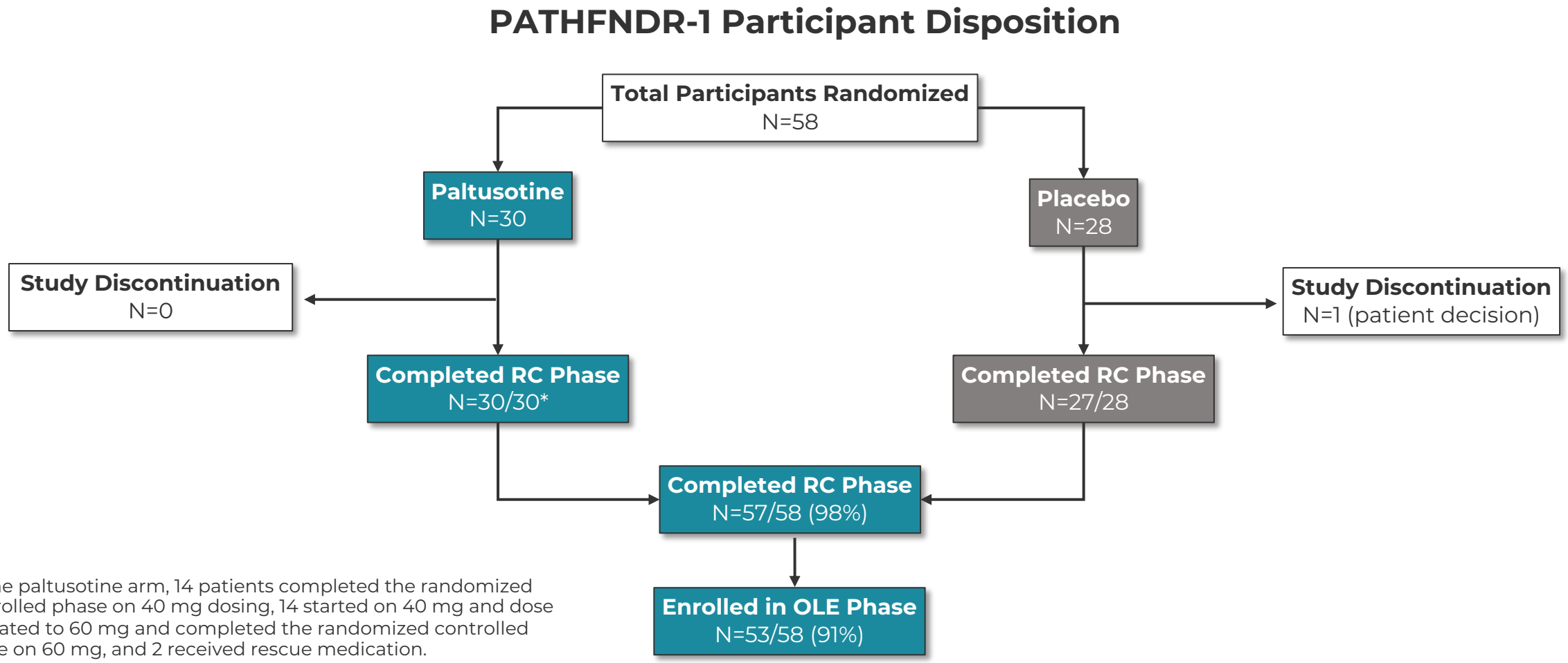
Primary Endpoint: Proportion of patients with IGF-1 ≤1.0 xULN (mean of samples from weeks 34 and 36)

IGF-1 Baseline: Mean of 3-4 IGF-1 samples (including Day 1 sample) prior to start of study drug dosing.

EOR: End of Randomized Controlled Phase. If participant is rescued, then last observation prior to rescue is used for EOR value.

Rescue: Participant received injected SRL and was classified as a non-responder if there were two consecutive IGF-1 ≥ 1.3 xULN on 60 mg *AND e*xacerbation of acromegaly clinical signs/symptoms as determined by the investigator.

98% of Participants Completed the Randomized Controlled Phase of PATHFNDR-1 and 91% Enrolled in the Open Label Extension (OLE) Phase



*In the paltusotine arm, 14 patients completed the randomized controlled phase on 40 mg dosing, 14 started on 40 mg and dose escalated to 60 mg and completed the randomized controlled phase on 60 mg, and 2 received rescue medication.

Participant Characteristics

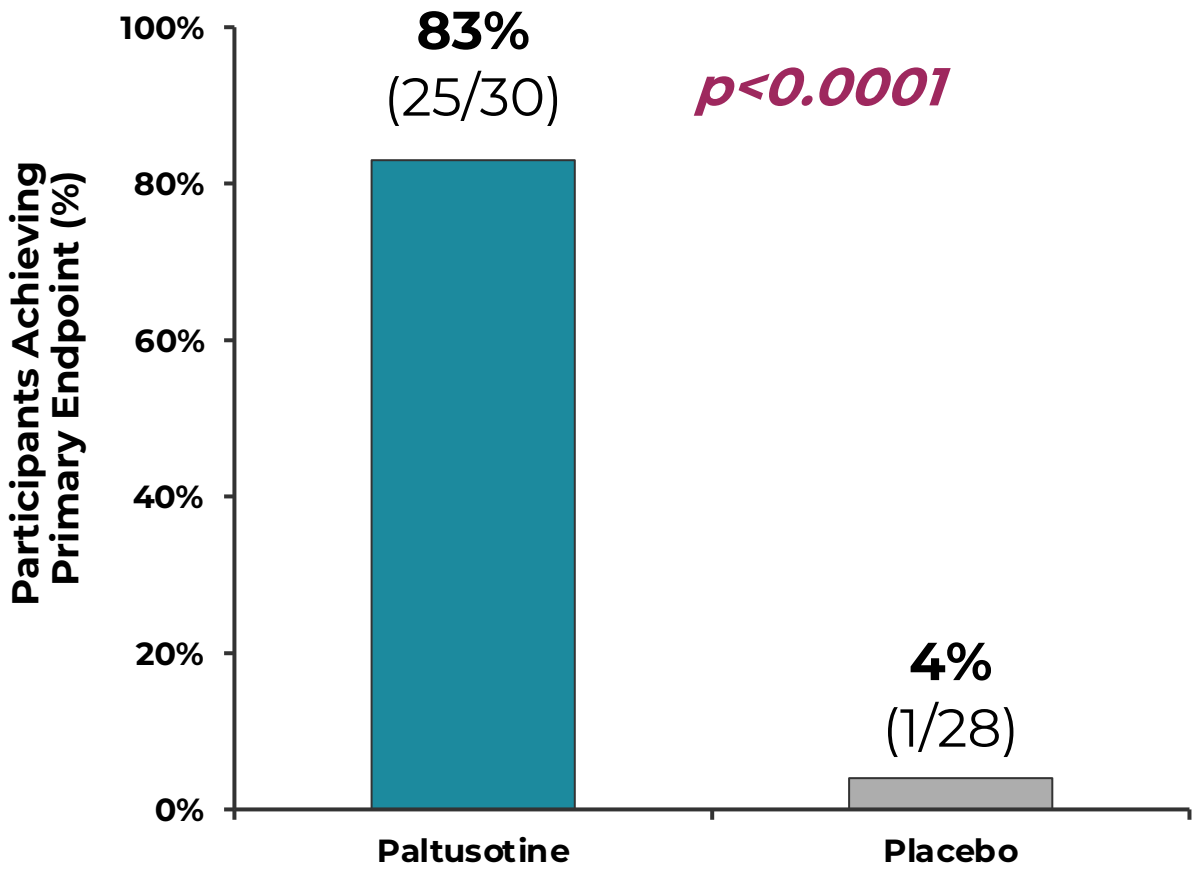
Participant Characteristics	Paltusotine N=30	Placebo N=28	Overall N=58
Female, n (%)	**15 (50%)**	**17 (61%)**	**32 (55%)**
Age at informed consent - Mean (SD), years	**55.9 (14.6)**	**53.9 (12.9)**	**54.9 (13.7)**
Weight - Mean (SD), kg	**83.7 (18.6)**	**73.2 (16.0)**	**78.6 (18.1)**
BMI - Mean (SD), kg/m^2	**29.9 (5.6)**	**27.6 (5.9)**	**28.8 (5.8)**
Geography, n (%)			
United States	6 (20%)	5 (18%)	11 (19%)
Europe and Israel	13 (43%)	12 (43%)	25 (43%)
Latin America	11 (37%)	11 (39%)	22 (38%)

Disease Characteristics

Disease Characteristics and Previous Treatment	Paltusotine N=30	Placebo N=28	Overall N=58
Duration since acromegaly diagnosis - Mean (SD), months	**187 (88)**	**121 (82)**	**155 (91)**
Pituitary surgery performed - n (%)	**26 (87%)**	**24 (86%)**	**50 (86%)**
Duration since pituitary surgery - Mean (SD), months	**172 (89)**	**102 (65)**	**138 (85)**
Baseline IGF-1 xULN - Mean (SD)	**0.83 (0.14)**	**0.82 (0.16)**	**0.83 (0.15)**
Baseline GH - Mean (SD), ng/mL	**0.92 (1.02)**	**0.89 (0.83)**	**0.90 (0.93)**
Prior SRL at time of screening			
Octreotide, n (%)	18 (60%)	16 (57%)	34 (59%)
Monthly Dose: 10 mg / 20 mg / ≥30 mg (n)	1 / 7 / 10	2 / 11 / 3	3 / 18 / 13
Lanreotide, n (%)	12 (40%)	12 (43%)	24 (41%)
Monthly Dose: 60 mg / 90 mg* / 120 mg (n)	2 / 4 / 6	1 / 5 / 6	3 / 9 / 12

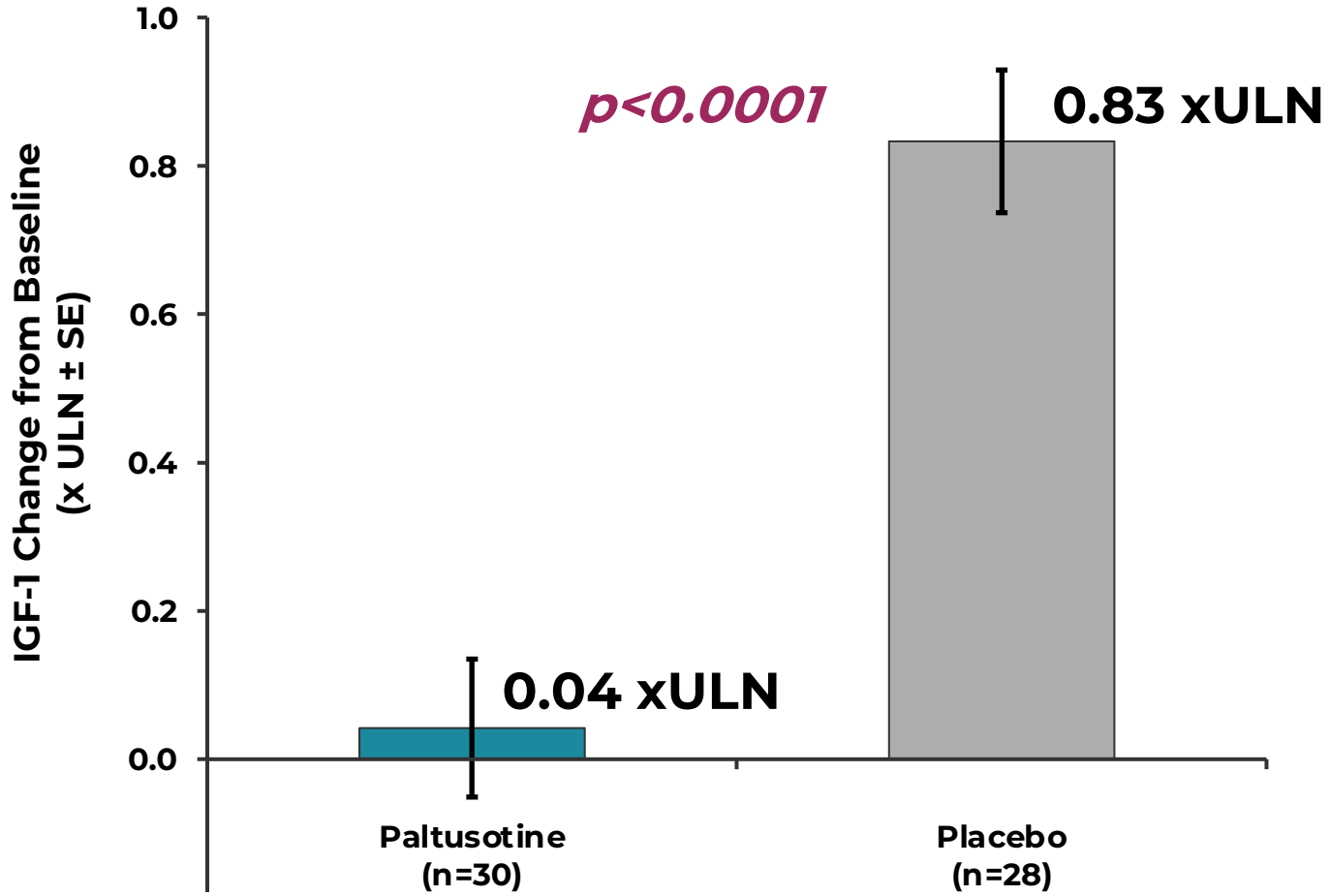
* 1 participant received 120 mg every 6 weeks and was considered part of the 90 mg group.

Primary Endpoint Achieved: 83% of Participants on Paltusotine Maintained IGF-1 ≤1.0 xULN



Participants who were rescued or stopped the assigned treatment before week 34 did not meet the protocol-defined primary endpoint.

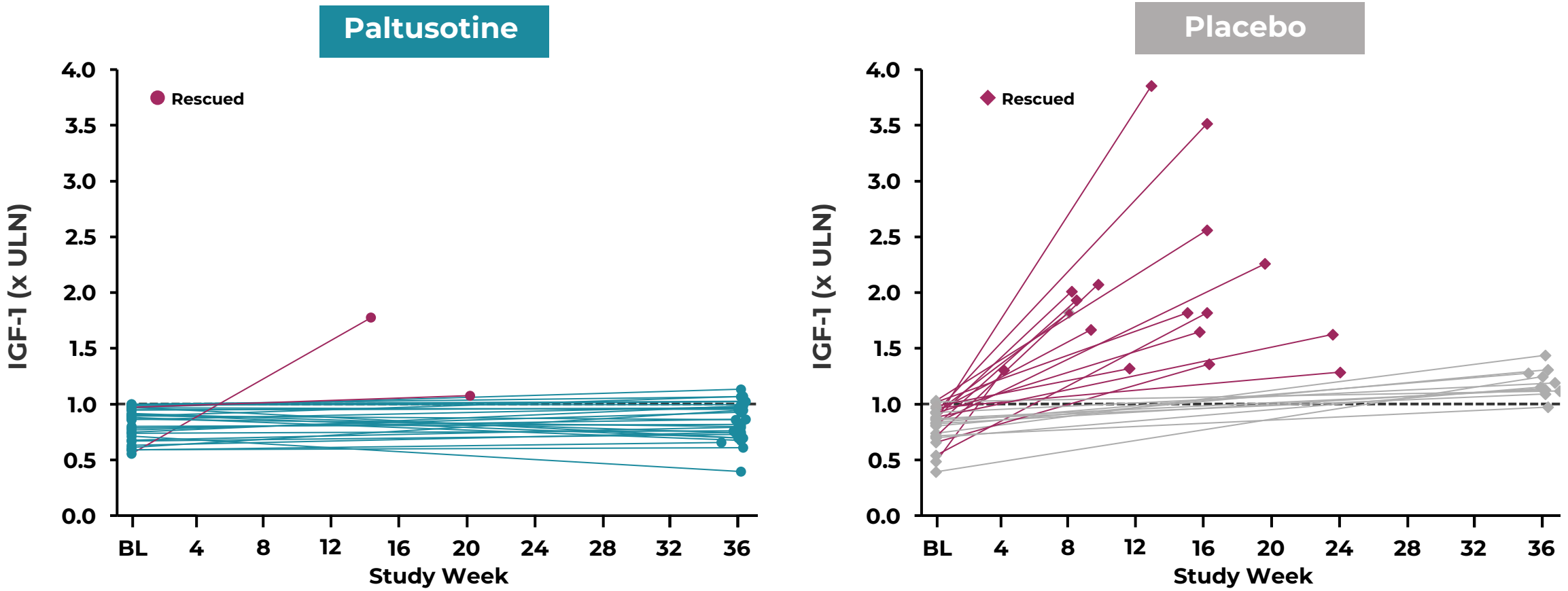
Secondary Endpoint #1 Achieved: Paltusotine Treatment Maintained Control of IGF-1



Least Squares (LS) Mean (± SE) is shown and estimated based on an analysis of covariance.
If participant was rescued, IGF-1 values measured just prior to rescue are used.

Participants on Paltusotine Maintained IGF-1 Levels

IGF-1 xULN at Baseline and End of Randomized Controlled Phase (EOR) for Each Participant



EOR: End of Randomized Controlled Phase. If participant was rescued, IGF-1 values measured prior to rescue are used.
Rescue: If there were two consecutive IGF-1 ≥ 1.3 xULN on 60 mg AND exacerbation of acromegaly clinical signs/symptoms as determined by the investigator.

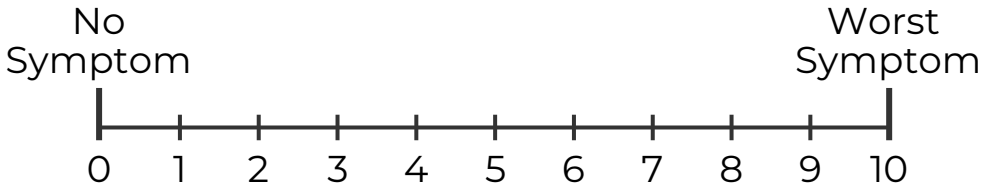
Patients Reported Symptom Severity Using the Acromegaly Symptoms Diary (ASD)

- ASD was developed in accordance with FDA guidance to evaluate symptoms of acromegaly in clinical studies*
- Seven symptoms were rated from 0 (no symptom) to 10 (worst symptom); total ASD score 0 to 70
- A daily checklist for symptoms was collected prior to and during study treatment

Symptoms Evaluated in the ASD

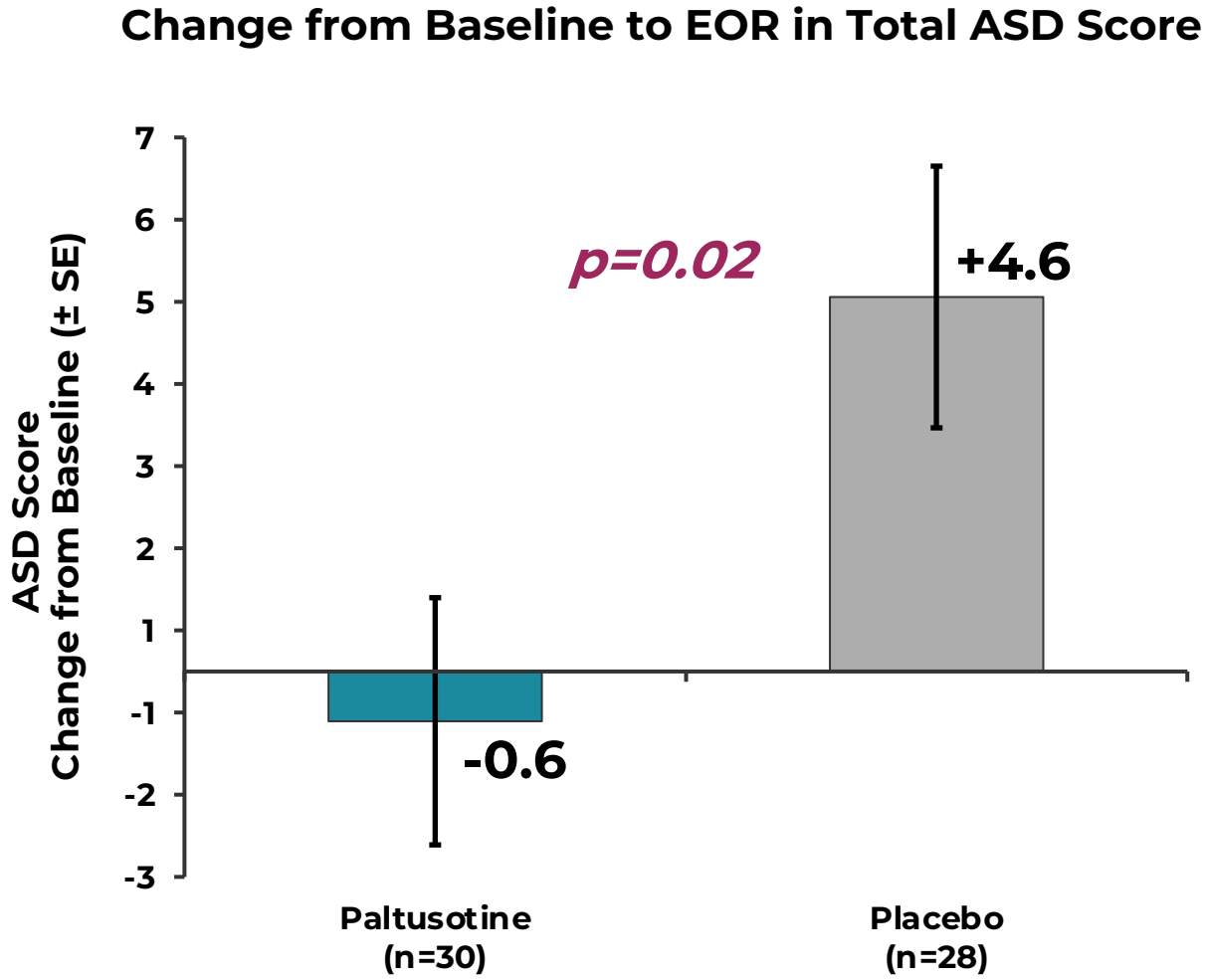
Headache pain
Joint pain
Sweating
Fatigue
Leg weakness
Swelling
Numbness/tingling
Total Score (0-70)

Numeric Scale (per symptom)



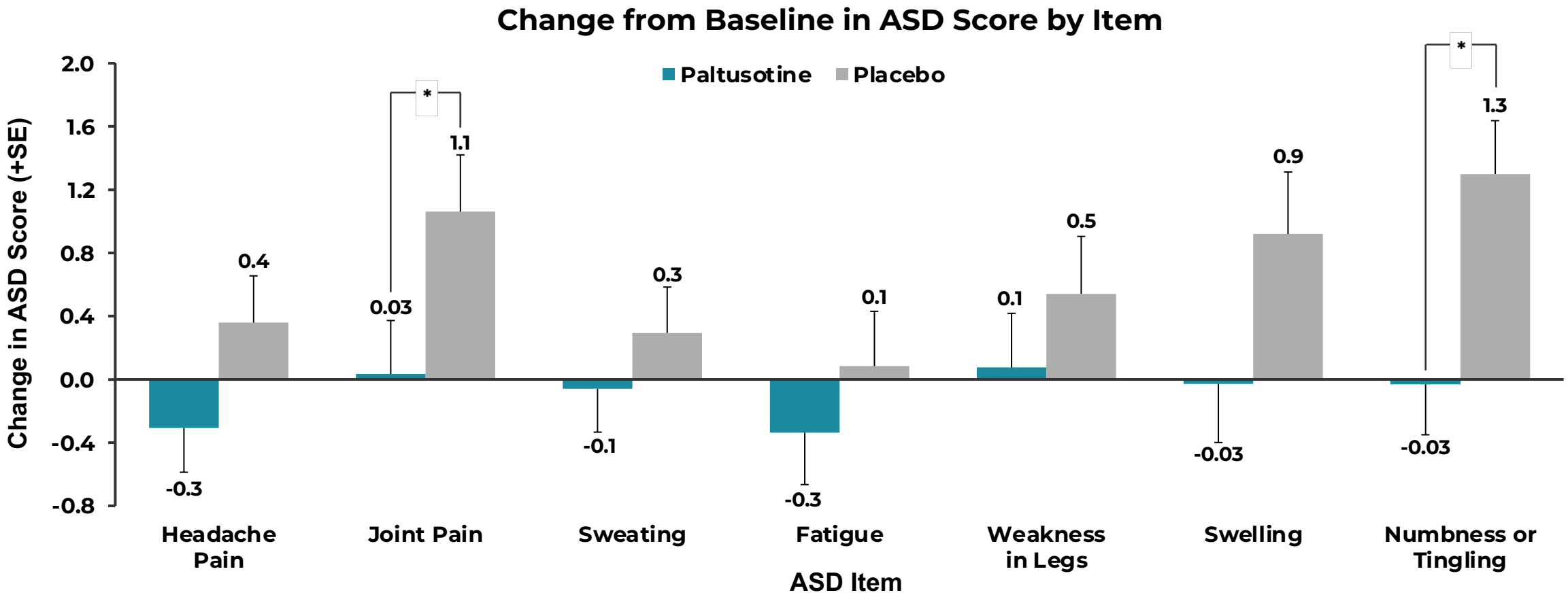
*Martin et al. Journal of Patient-Reported Outcomes (2023) 7:15; https://doi.org/10.1186/s41687-023-00541-7

Secondary Endpoint #2 Achieved: Paltusotine Treatment Maintained Control of Acromegaly Symptoms



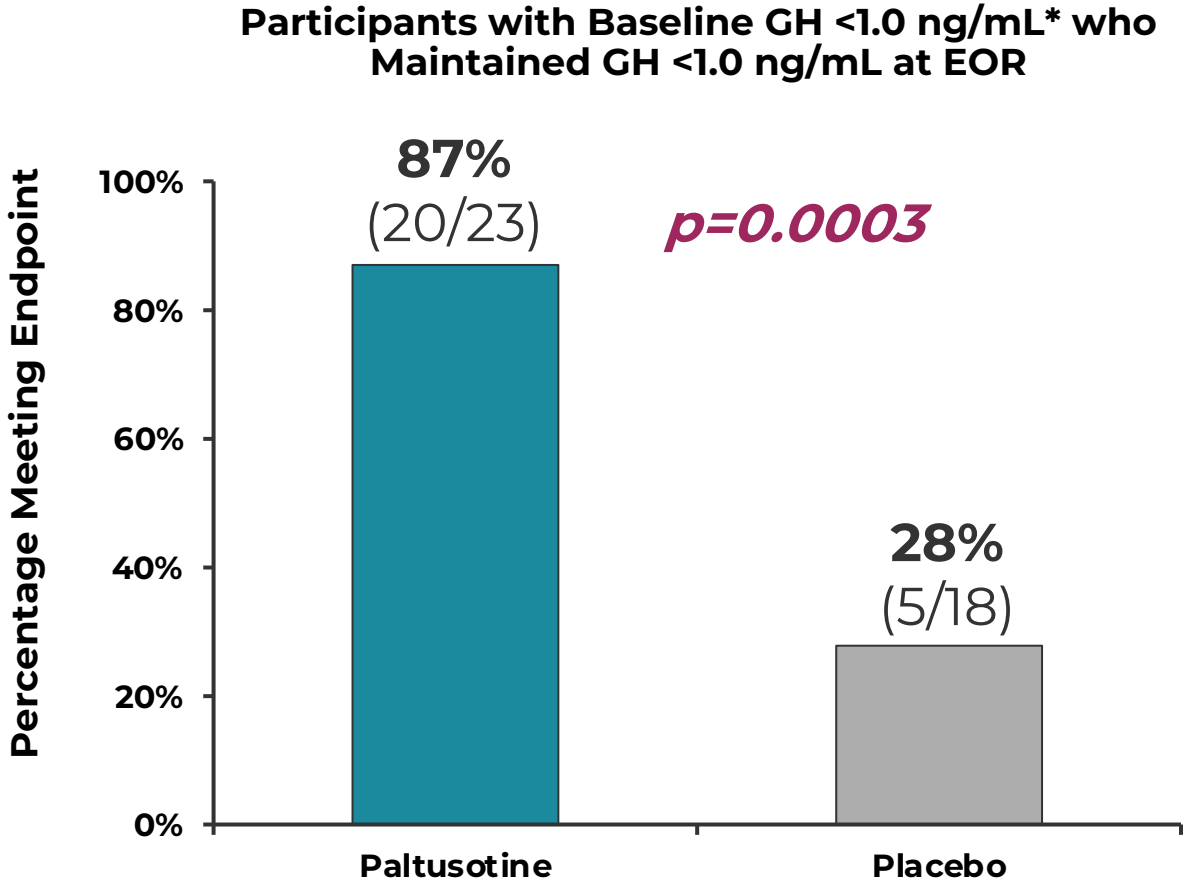
EOR: End of Randomized Controlled Phase. ASD scores measured prior to rescue or discontinuation are used. Baseline ASD scores were 13.2 for paltusotine and 10.9 for placebo.

Paltusotine Treatment Maintained Control Across All Individual Symptom Components of ASD



*p<0.05.
EOR: End of Randomized Controlled Phase, ASD scores measured prior to rescue or discontinuation are used. Each symptom is on a 0 (no symptom) to 10 (worst symptom) scale.

Secondary Endpoint #3 Achieved: Paltusotine Treatment Maintained Growth Hormone Control



*Endocrine Society Clinical Practice guidelines recommend target GH levels < 1.0 ng/mL; Katznelson et al. J Clin Endocrinol Metab 99: 3933–3951, 2014
Participants who were rescued or stopped the assigned treatment before week 34 did not meet the protocol-defined endpoint.
EOR: End of Randomized Controlled Phase
n: 23 out 30 paltusotine participants and 18 out of 28 placebo participants entered the study with a baseline GH <1.0 ng/mL

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

Treatment-Emergent Adverse Events	Paltusotine N=30 n (%)	Placebo N=28 n (%)
Any	**24 (80%)**	**28 (100%)**
Mild	14 (47%)	10 (36%)
Moderate	10 (33%)	15 (54%)
Severe	0	3 (11%)
Treatment-related	**11 (37%)**	**4 (14%)**
Serious		
Not treatment-related	0	1 (4%)
Treatment-related	0	0
Leading to dose reduction	**1 (3%)**	**0**
Leading to rescue	**2 (7%)**	**17 (61%)**
Leading to death	**0**	**0**

Severe TEAEs in placebo were arthralgia in 1 participant, peripheral swelling/fatigue/pain in extremity in 1 participant, and leukopenia in 1 participant.
Serious TEAE in placebo was acute cholecystitis.

PATHFNDR-1 Adverse Events Summary

Treatment Emergent Adverse Events ≥5%	Paltusotine N=30 n (%)	Placebo N=28 n (%)
Common Acromegaly Symptoms		
Arthralgia	8 (27%)	16 (57%)
Headache	6 (20%)	10 (36%)
Peripheral swelling	2 (7%)	10 (36%)
Fatigue	2 (7%)	5 (18%)
Muscular weakness	1 (3%)	3 (11%)
Paraesthesia	0	7 (25%)
Hyperhidrosis	0	4 (14%)
Common SRL Side Effects		
Diarrhoea	7 (23%)	4 (14%)
Abdominal pain	5 (17%)	3 (11%)
Nausea	3 (10%)	2 (7%)
Abdominal distension	2 (7%)	1 (4%)
Flatulence	2 (7%)	1 (4%)
Other		
Constipation	2 (7%)	4 (14%)
Urinary tract infection	2 (7%)	2 (7%)
Nasopharyngitis	2 (7%)	1 (4%)
Dyspnoea	1 (3%)	2 (7%)
Hyperglycaemia	1 (3%)	2 (7%)
Dizziness	1 (3%)	2 (7%)
Back pain	1 (3%)	2 (7%)
COVID-19	0	6 (21%)
Asthenia	0	4 (14%)
Pain in extremity	0	3 (11%)

Includes AEs occurring during rescue period. Rates were similar when rescue period is excluded.

The frequency of adverse events considered related to acromegaly was notably lower in participants treated with paltusotine compared to placebo (30% vs. 86% respectively).

PATHFNDR-1 Safety Summary

- Paltusotine was well-tolerated with no severe or serious adverse events reported in the active arm
- The most frequently (>10%) reported adverse events included arthralgia, diarrhea, headache, abdominal pain and nausea
- No safety signals were observed in vital signs, ECGs, or laboratory values during treatment with paltusotine
- No clinically significant changes were observed in pituitary tumor size as measured by MRI
- Safety results in PATHFNDR-1 comparable to that observed in entire clinical program to date

Crinetics' Approach to Address Unmet Needs of People with Acromegaly, Prescribers, and Healthcare Systems

As a trusted member of the global endocrine community, Crinetics aspires to bring the first once daily, oral selectively targeted SST2 agonist* to patients

For Patients

- Once daily oral
- Consistent symptom control
- Room temperature storage
- Home delivery
- Patient support services

For Physicians

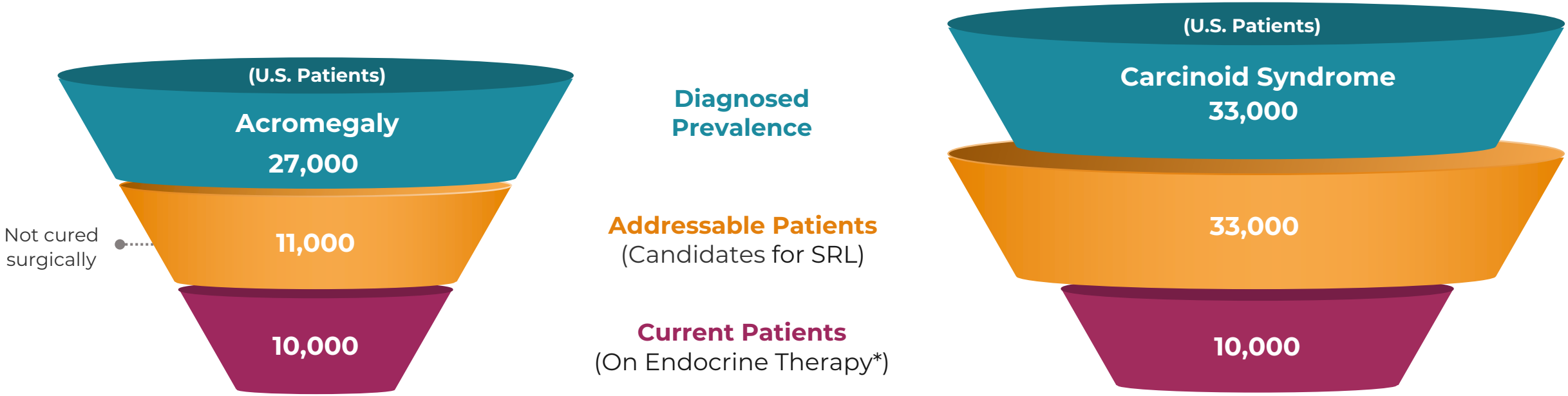
- Reliable, consistent, and durable IGF-1 control
- Simple dose selection
- Low drug interaction risk
- HCP support services

For the Healthcare System

- Potential reduced patient out-of-pocket costs
- At-home option reduces costs compared to in-office administration
- At-home option saves HCP resources

* If paltusotine receives regulatory approval. Clinical studies to support applications for regulatory approval are ongoing; HCP: Healthcare Provider.

Paltusotine: Initial Multi-Billion Dollar U.S. Market Opportunity in Acromegaly and Carcinoid Syndrome



$70K	Average Annual WAC for Injectables	$100K
$700M	Current Market for Endocrine Therapy (U.S.)	$1,000M
$800M	Total Addressable Market for Endocrine Therapy (U.S.)	$3,300M

*Endocrine therapy includes SRLs, dopamine agonists, and growth hormone antagonists
WAC: Wholesale acquisition cost; Sources: Company data on file

Anticipated Paltusotine Milestones

- **4Q23** Preliminary results from carcinoid syndrome Phase 2 study
- **1Q24** Results from PATHFNDR-2 Phase 3 study in untreated acromegaly patients
- **2024** Acromegaly NDA submission
- **2024** Anticipated carcinoid syndrome Phase 3 start
- **Ongoing:** Acromegaly open label extension studies
  - N > 120 and increasing
  - Some Phase 2 patients have been treated with paltusotine for up to 3 years

Q&A

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