Topline Results from Paltusotine Phase 3 PATHFNDR-2 Study

A Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Safety And Efficacy of Paltusotine in Subjects with Non-pharmacologically Treated Acromegaly

March 19, 2024

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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 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; the commercialization of paltusotine as the first once-daily, oral SRL for the treatment of acromegaly; the ability for paltusotine to effectively provide symptom control and biochemical control in acromegaly patients; and the commercial acceptance of paltusotine as a new medical treatment for acromegaly with improvements in treatment experience and access to care for patients and medical providers. 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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Phase 3 Study Met the Primary and All Secondary Endpoints and Paltusotine Was Well-Tolerated

PRIMARY ENDPOINT

- ✅ **56% of participants achieved IGF-1 ≤ 1.0xULN vs 5% on placebo (p<0.0001)**

SECONDARY ENDPOINTS

- ✅ **Change from baseline in IGF-1 (p<0.0001) – Key secondary endpoint**
- ✅ **67% achieved IGF-1 <1.3×ULN (p<0.0001)**
- ✅ **Change from baseline in Total Acromegaly Symptoms Diary (ASD) score (p=0.004)**
- ✅ **Proportion of subjects with GH <1.0 ng/mL at Week 22 (p<0.0001)**

SAFETY

- ✅ **Paltusotine was generally well-tolerated with no serious adverse events**
- ✅ **Paltusotine demonstrated no new safety signals**

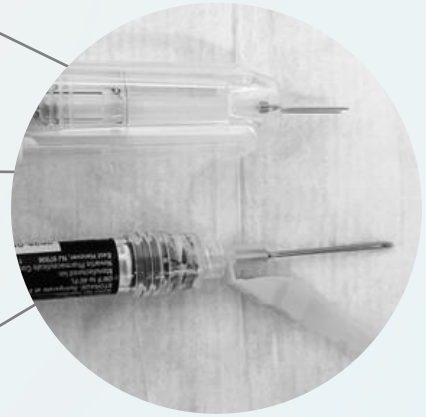
The PATHFNDR Program Provides a Uniquely Rich Data Set Assessing BOTH Biochemical AND Symptom Control in Acromegaly

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

*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.

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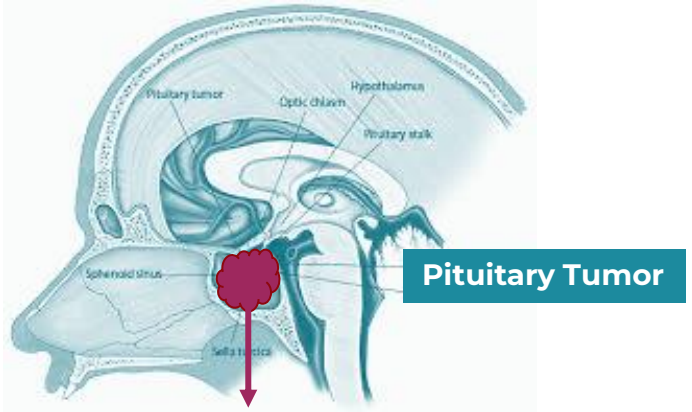
What is Acromegaly?

Acromegaly is caused by a benign pituitary tumor secreting excess growth hormone (GH)

Uncontrolled acromegaly is debilitating and increases risk of early death



Pituitary Tumor

GH

Somatostatin Receptor Ligands (SRLs)

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 Tolerance
- 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.

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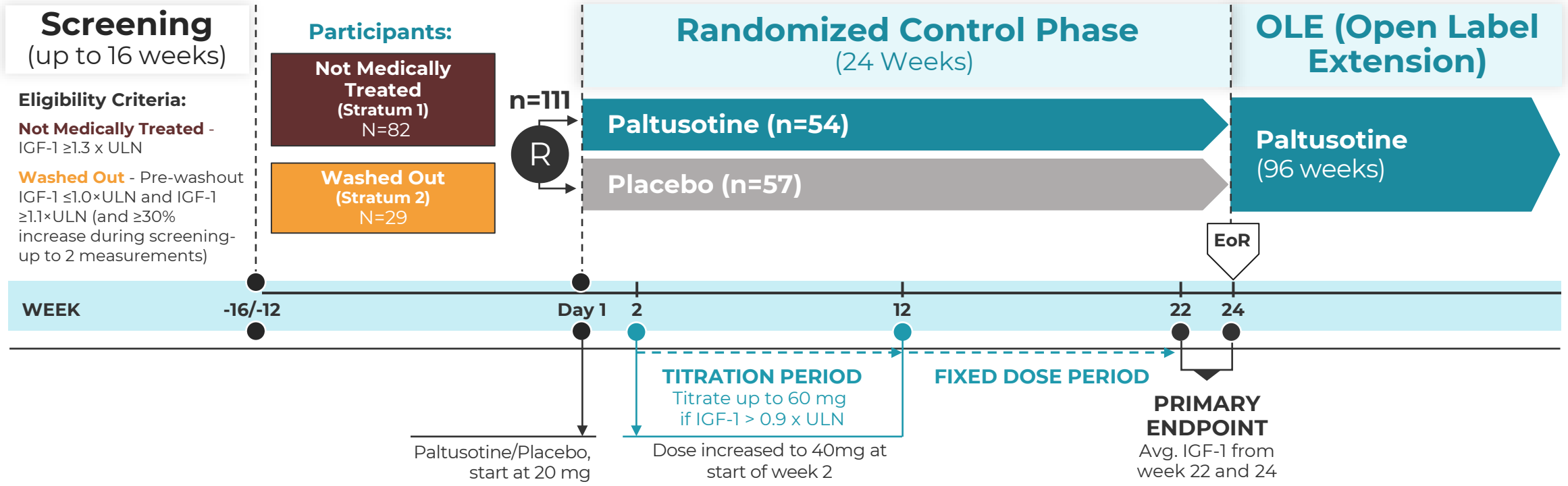
Evaluated Once Daily Oral Paltusotine in Non-pharmacologically Treated Acromegaly



Not Medically Treated (Stratum 1) – Medically Naïve: no prior medical therapy. **Previously Treated**: no medical therapy within 4 months prior to screening.

Washed Out (Stratum 2) – Controlled on octreotide or lanreotide for at least 3 months but agreed to stop injections during the screening period.

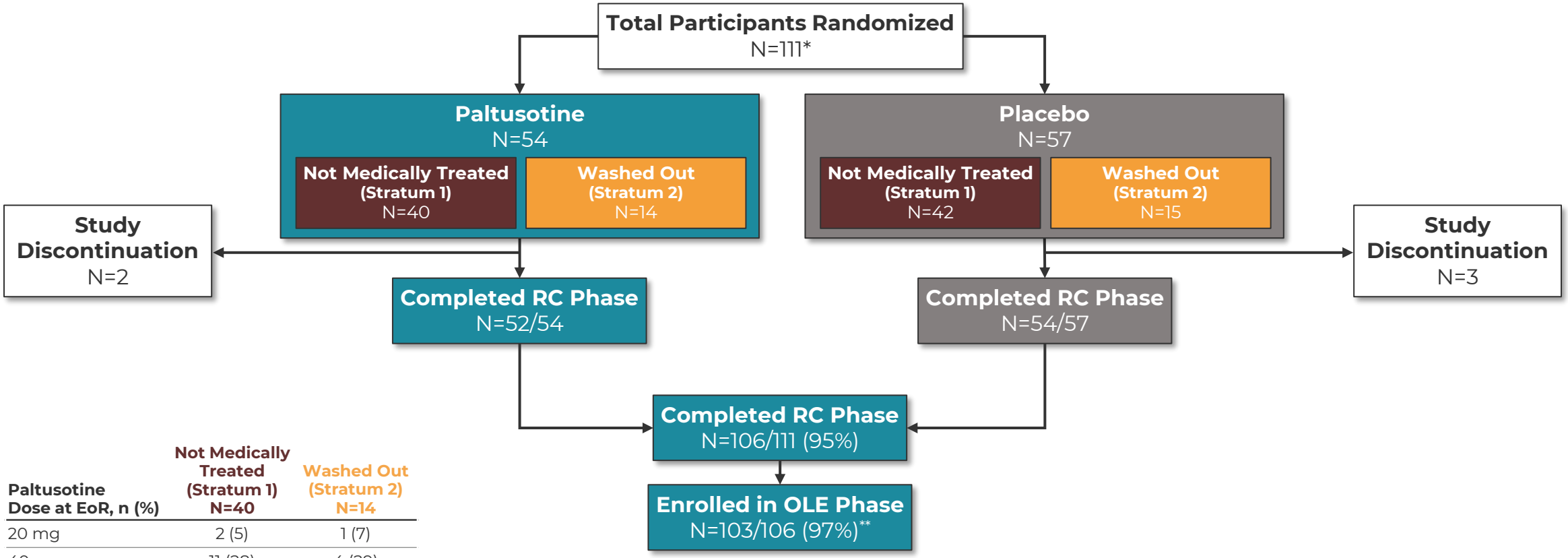
IGF-1 Baseline: defined as the average of pre-dose Day 1 IGF-1 and last IGF-1 value measured just prior to Day 1.

EoR: End of Randomized controlled phase. If participant was 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 ≥ 1.5x ULN on 60 mg *AND* exacerbation of acromegaly clinical signs/symptoms as determined by the investigator.

95% of Participants Completed the Randomized Control Phase of PATHFNDR-2 and 97% Enrolled in the Open Label Extension

PATHFNDR-2 Participant Disposition



Paltusotine Dose at EoR, n (%)	Not Medically Treated (Stratum 1) N=40	Washed Out (Stratum 2) N=14
20 mg	2 (5)	1 (7)
40 mg	11 (28)	4 (29)
60 mg	27 (68)	9 (64)

RC = Randomized Control.
* 112 Participants randomized, one subject randomized in error and never dosed.
** An additional 11 participants directly enrolled into the OLE, after confirming eligibility.

Participant Characteristics

Participant Characteristics	Paltusotine N=54	Placebo N=57	Overall N=111
Female, n (%)	**26 (48%)**	**33 (58%)**	**59 (53%)**
Age at informed consent - Mean (SD), years	**47.5 (13.6)**	**45.9 (12.3)**	**46.7 (12.9)**
Weight - Mean (SD), kg	**86.1 (19.9)**	**82.4 (18.7)**	**84.2 (19.3)**
BMI - Mean (SD), kg/m^2	**29.6 (5.4)**	**28.7 (5.2)**	**29.1 (5.3)**
Geographic region, n (%)			
Latin America	19 (35%)	17 (30%)	36 (32%)
Europe and Israel	14 (26%)	18 (32%)	32 (29%)
China	8 (15%)	15 (26%)	23 (21%)
India	7 (13%)	4 (7%)	11 (10%)
United States	6 (11%)	3 (5%)	9 (8%)

BMI=Body Mass Index

Disease Characteristics and Previous Treatment

Disease Characteristics and Previous Treatment	Paltusotine N=54	Placebo N=57	Overall N=111
Duration since acromegaly diagnosis - Mean (SD), months	**97.9 (95.7)**	**77.1 (69.4)**	**87.2 (83.5)**
Pituitary surgery performed - n (%)	**50 (93%)**	**49 (86%)**	**99 (89%)**
Pituitary Radiation - n (%)*	**2 (4%)**	**3 (5%)**	**5 (5%)**
Baseline IGF-1 x ULN - Mean (SD)	**2.0 (0.81)**	**2.2 (1.10)**	**2.1 (0.97)**
Baseline GH - Mean (SD), Median, ng/mL	**3.0 (2.90), 2.1**	**9.4 (24.15), 2.3**	**6.3 (17.64), 2.3**
Prior SRL at time of screening(Stratum 2)**			
Octreotide, n (%)***	6 (11%)	11 (19%)	17 (15%)
Monthly Dose: 10 mg / 20 mg / ≥30 mg (n)	0 / 3 / 3	1 / 4 / 6	1 / 7 / 9
Lanreotide, n (%)	8 (15%)	3 (5%)	11 (10%)
Monthly Dose: 60 mg / 90 mg / 120 mg (n)	1 / 2 / 5	2 / 0 / 1	3 / 2 / 6

* Pituitary radiation therapy performed >3 years before screening.
** Washed out subjects were controlled on medical therapy for at least 3 months but agreed to washout for 4 months prior to beginning study treatment.
***One subject washed out from oral octreotide taking 60 mg/day is not included.

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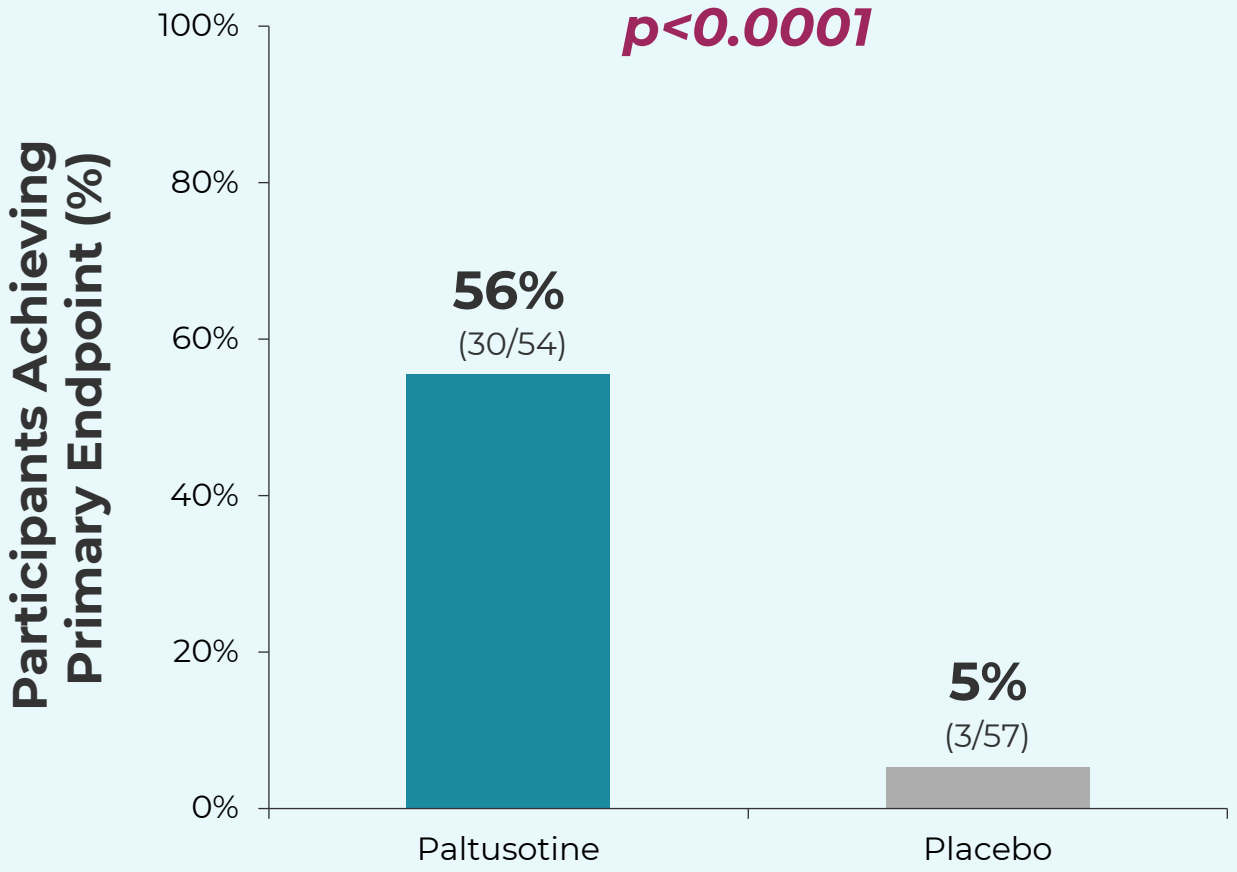
Primary Endpoint Met: 56% of Participants on Paltusotine Achieved IGF-1 ≤1.0xULN



Participants who were rescued or stopped the assigned treatment before week 24 were considered not to have met the primary endpoint.

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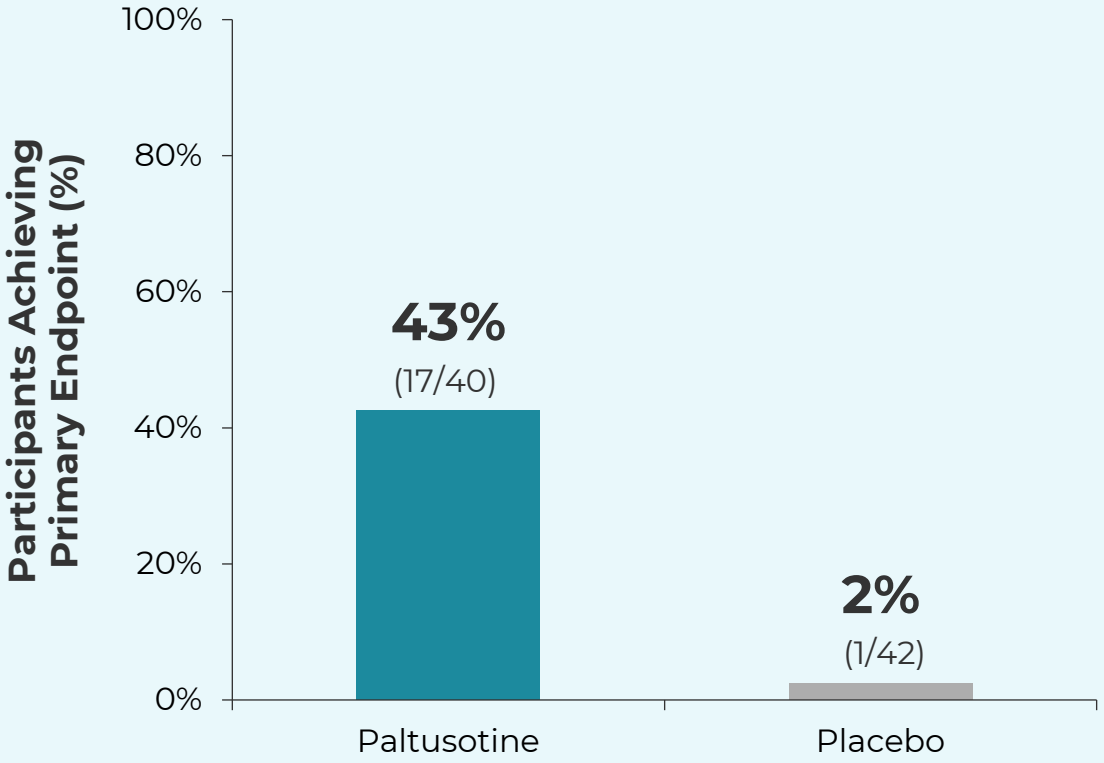
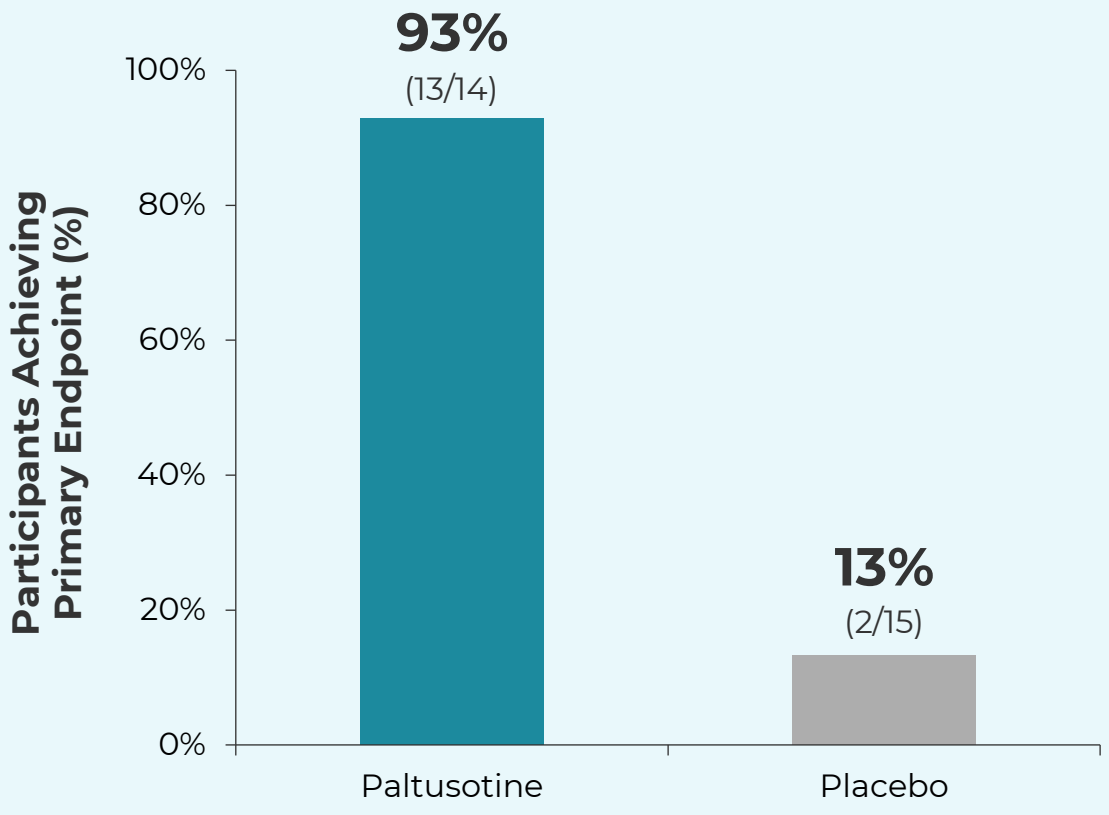
Paltusotine Achieved Statistically Significant Responses (IGF-1 ≤1.0xULN) in Both Patient Populations

Not Medically Treated
(Stratum 1)
p<0.0001



Washed Out
(Stratum 2)
p<0.0001



11 Participants who were rescued or stopped the assigned treatment before week 24 were considered not to have met the primary endpoint.

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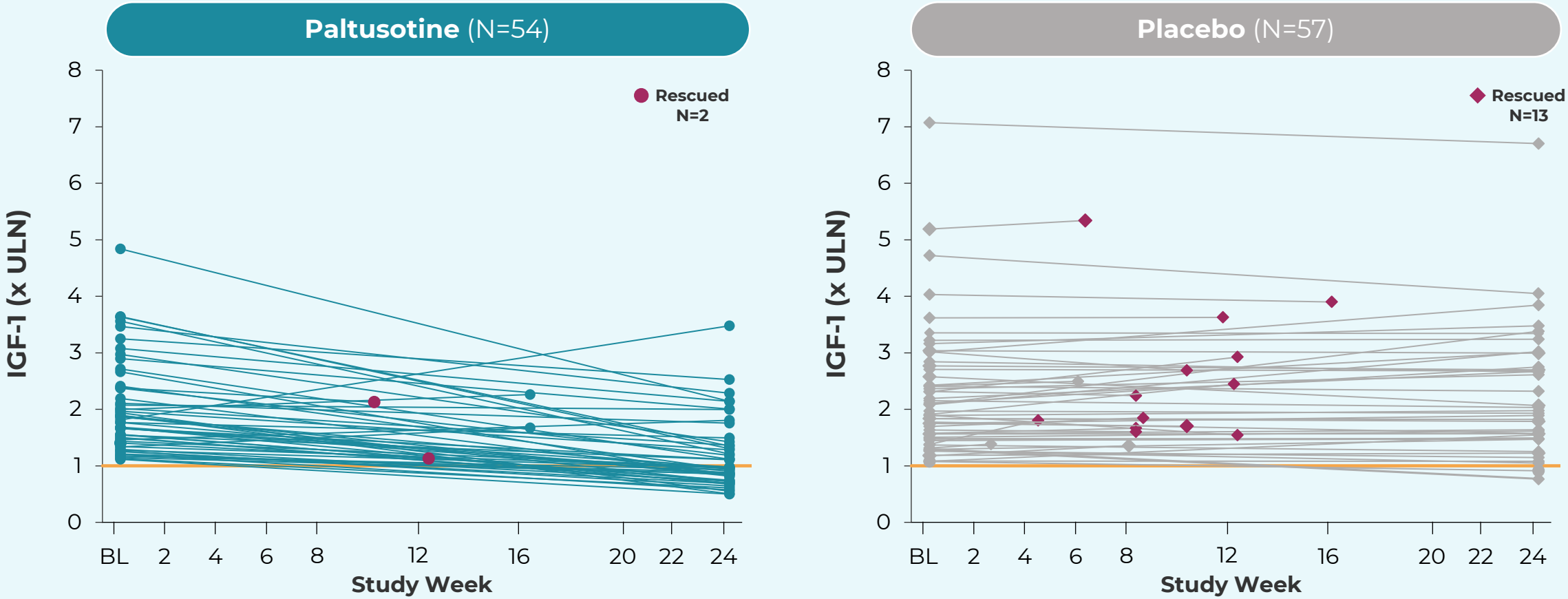
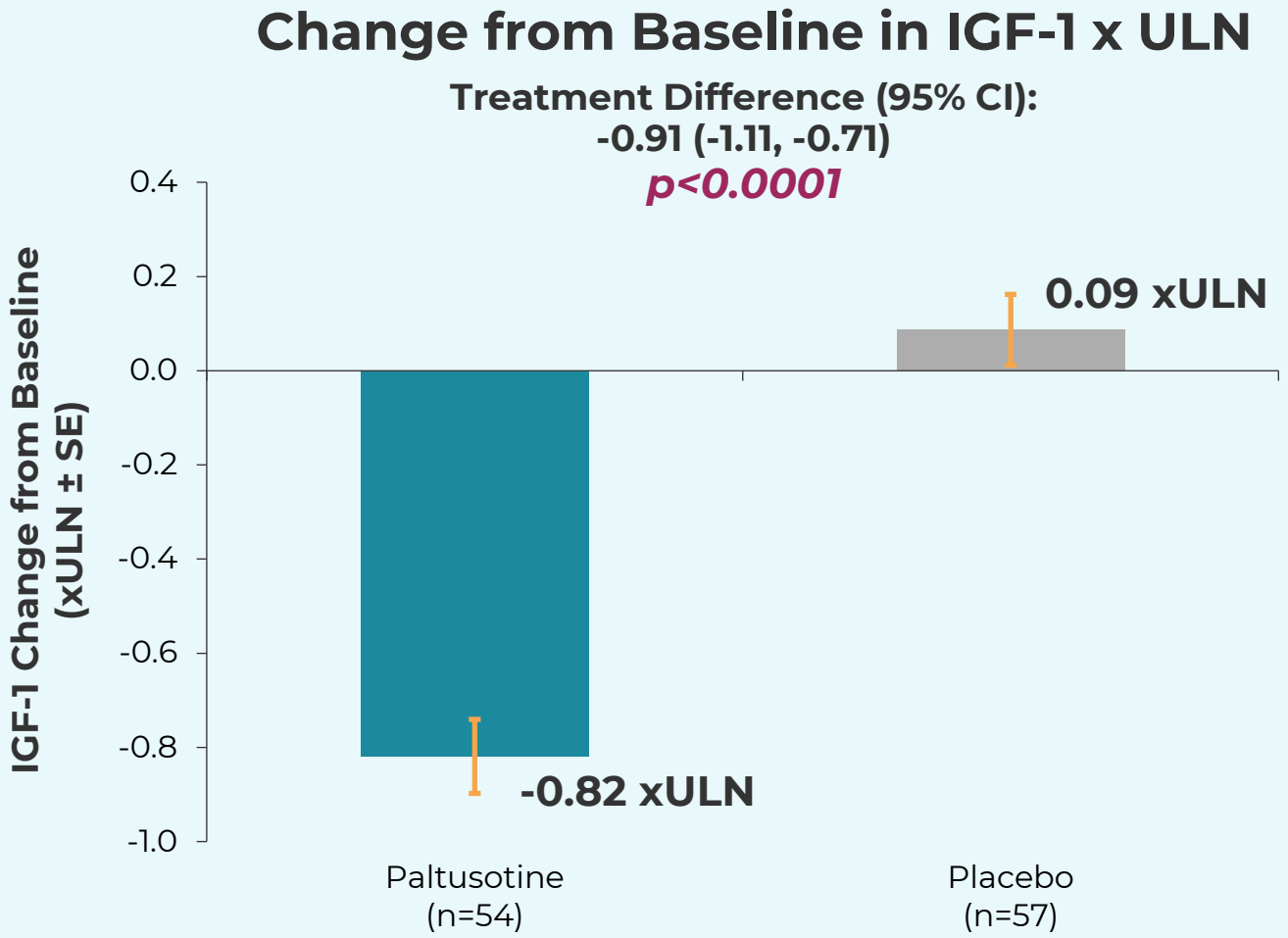
Paltusotine Reduced IGF-1 Levels in 50/54 (93%) of Participants

IGF-1 x ULN at Baseline and End of Randomized Control Phase (EoR) for Each Participant



IGF-1 values measured prior to rescue or discontinuation are used.

Key Secondary Endpoint Achieved: Paltusotine Treatment Significantly Decreased IGF-1 Levels



Least Squares (LS) Mean (± SE) is shown and estimated based on an analysis of covariance.
IGF-1 values measured prior to rescue or discontinuation are used.

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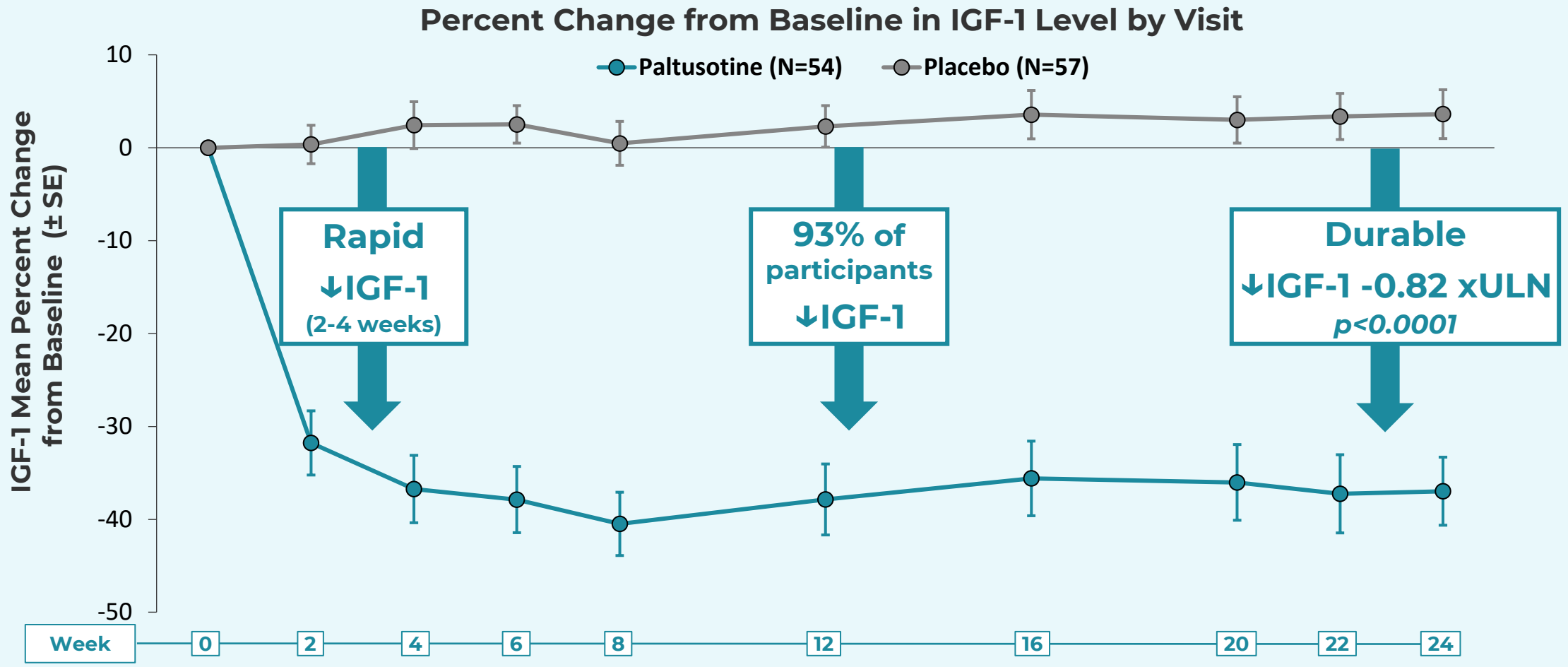
Paltusotine Treatment Rapidly (Within 2-4 Weeks) and Durably Decreased IGF-1 Levels



IGF-1 values measured prior to rescue or discontinuation are carried forward

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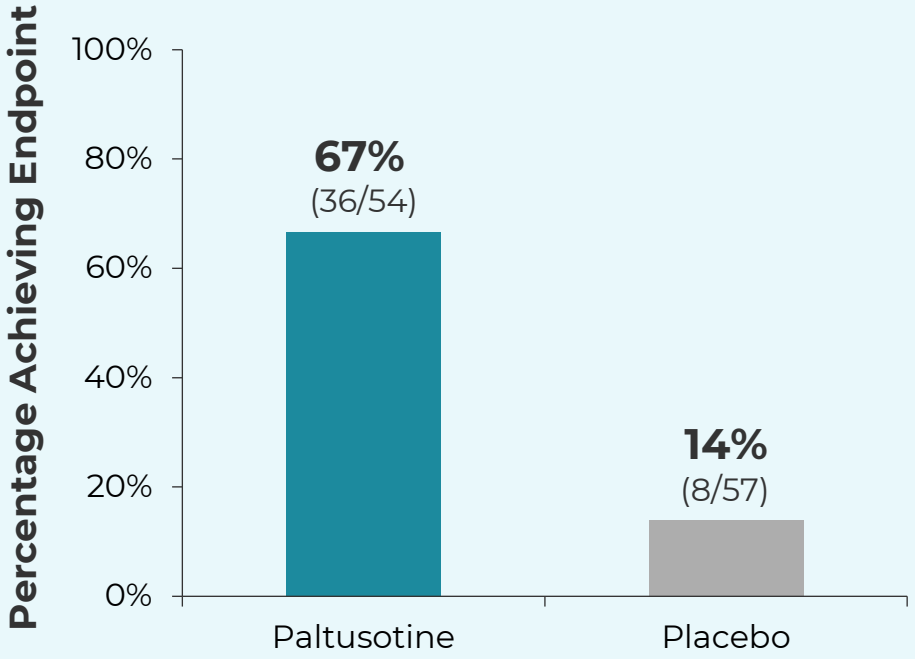
Secondary Endpoint #2 Met: 67% of Participants Achieved IGF-1 <1.3×ULN with Paltusotine

Participants who Achieved IGF-1 <1.3×ULN at EoR

Overall

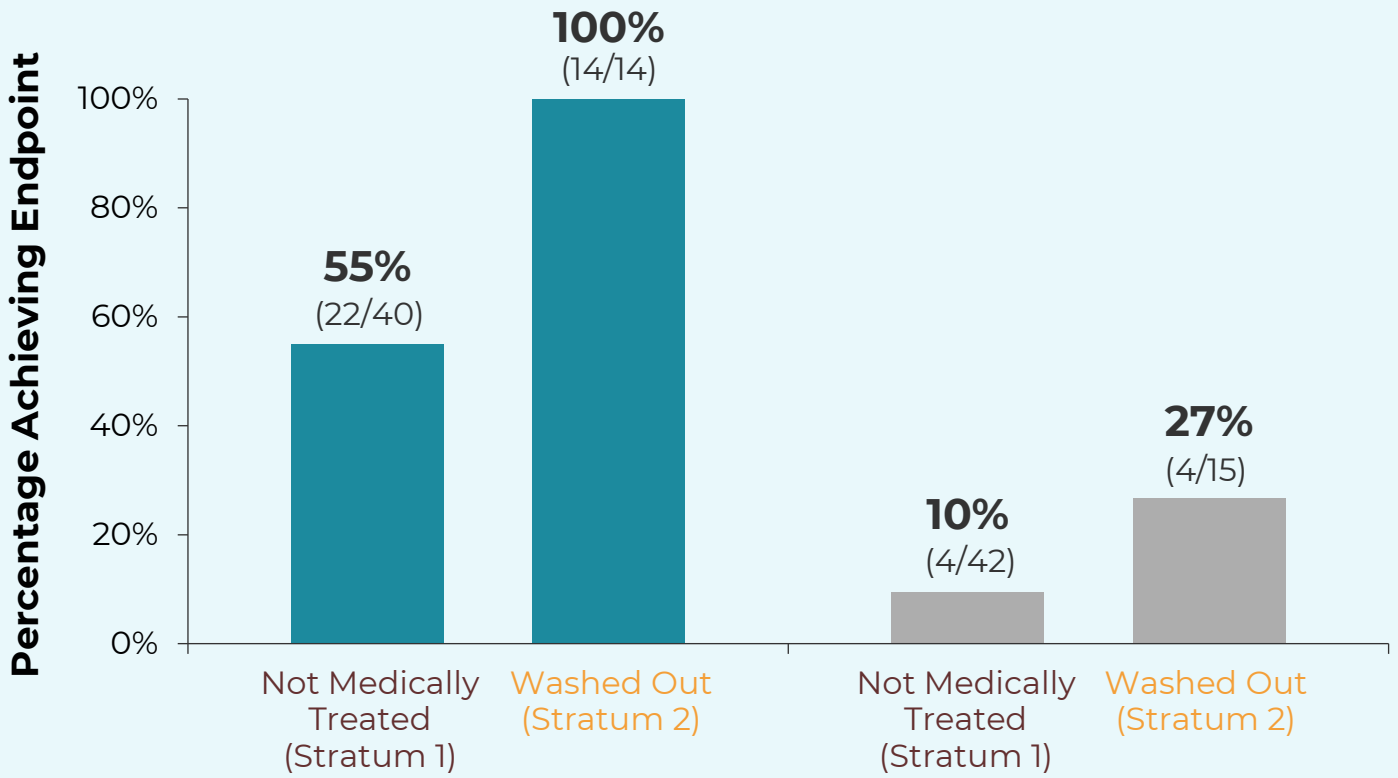
p<0.0001



Paltusotine

Placebo

p<0.0001 in both strata vs. placebo



EoR: End of Randomized control phase; Participants who were rescued or stopped the assigned treatment before week 24 were considered not to have met the endpoint.

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

- ASD was developed in accordance with FDA guidance to evaluate symptoms of acromegaly in clinical trials*
- Each symptom was rated from 0 (no symptom) to 10 (worst symptom), Total 0 to 70
- A daily checklist for symptoms was collected for participants 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.

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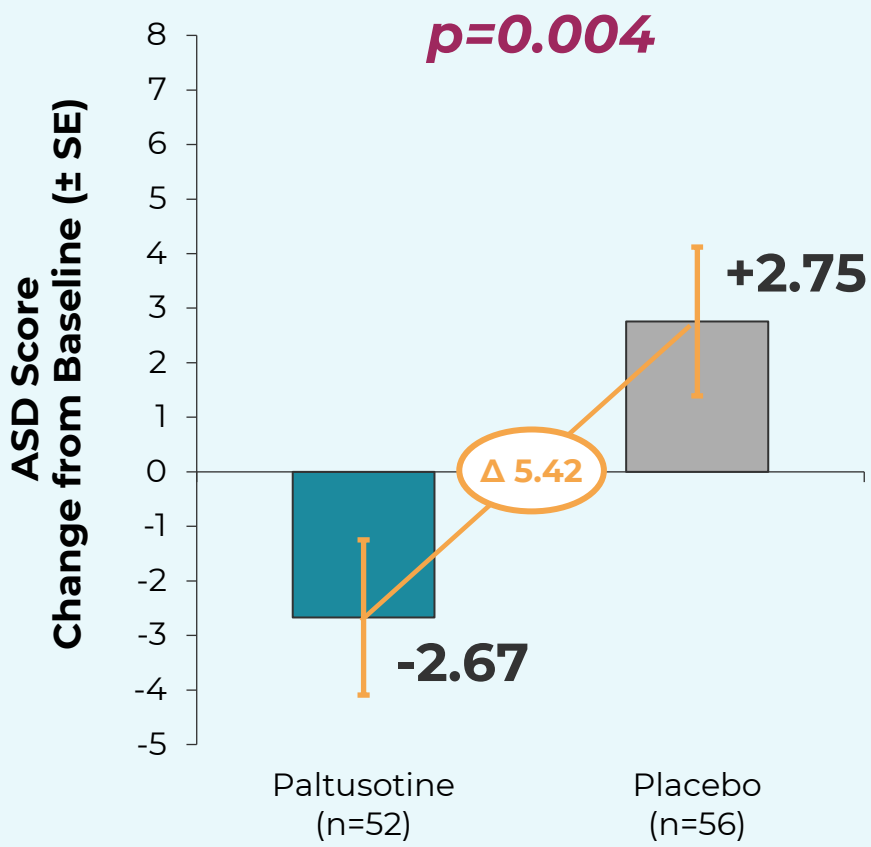
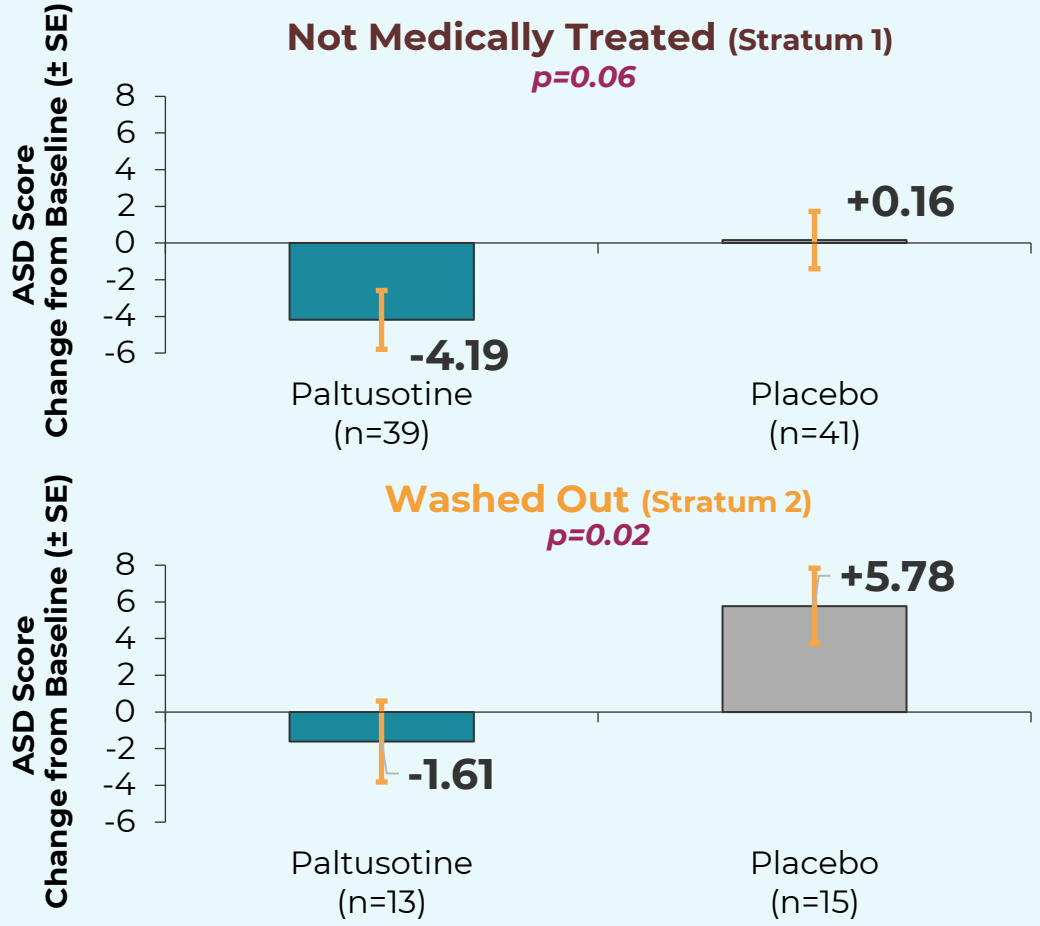
Secondary Endpoint #3 Achieved: Paltusotine Treatment Improved Acromegaly Symptoms

Change from Baseline to EoR in Total ASD Score





Least Squares (LS) Mean is estimated based on an analysis of covariance.
EoR: End of Randomized control phase. ASD scores measured prior to rescue or discontinuation are used.

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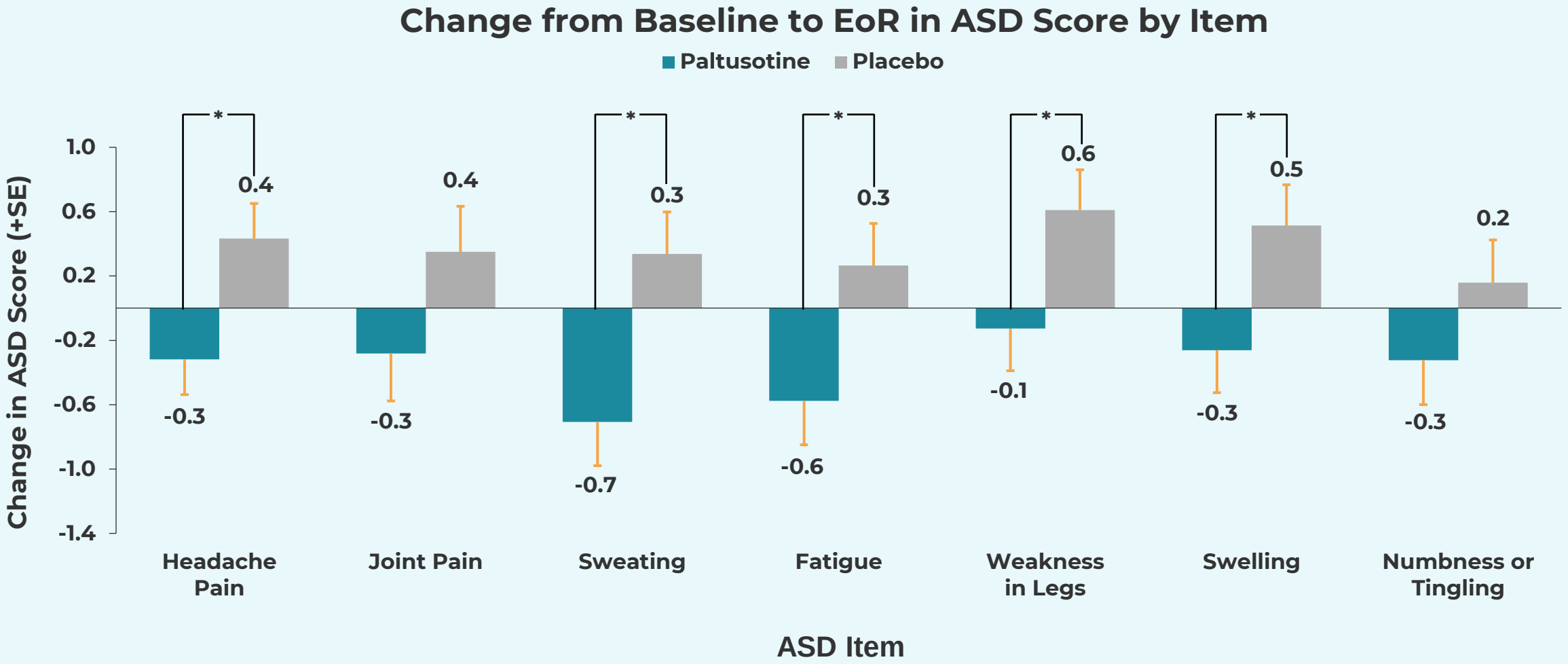
Paltusotine Treatment Improved All Individual Symptom Components of ASD



* p<0.05. P-value is estimated based on an analysis of covariance.
Least Squares (LS) Mean is presented and estimated based on an analysis of covariance.
EoR: End of Randomized Control Phase, ASD scores measured prior to rescue or discontinuation are used.
Each symptom is on a 0 (no symptom) to 10 (worst symptom) scale.

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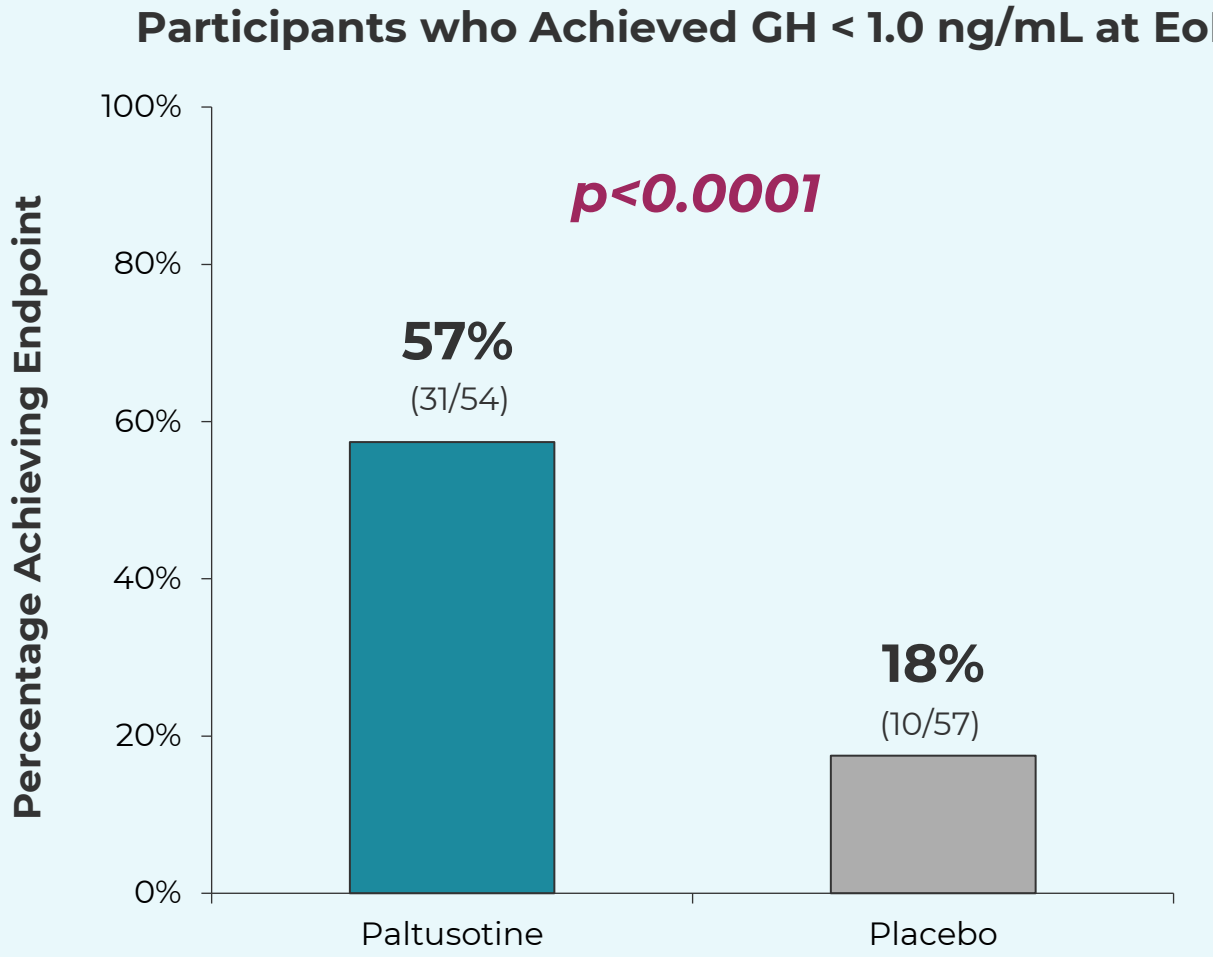
Secondary Endpoint #4 Met: Paltusotine Treatment Achieved Target Growth Hormone Levels in 57% of Subjects



Participants who are rescued or stop the assigned treatment before week 22 did not meet endpoint. GH was measured prior to randomization and at W22, as a mean of 5 separate blood levels measured within a 3 hour period. EoR: End of randomized control phase.

Paltusotine was Generally Well-Tolerated with No Serious Adverse Events

Treatment-Emergent Adverse Events (TEAEs)	Paltusotine N=54 n (%)	Placebo N=57 n (%)
Any	**49 (91%)**	**49 (86%)**
Mild	47 (87%)	45 (79%)
Moderate	15 (28%)	26 (46%)
Severe	2 (4%)	5 (9%)
Treatment-related	**26 (48%)**	**15 (26%)**
Serious	**0**	**1 (2%)**
Not treatment-related	0	1 (2%)
Treatment-related	0	0
Leading to dose reduction	**3 (6%)**	**1 (2%)**
Leading to rescue	**2 (4%)**	**13 (23%)**
Leading to death	**0**	**0**

Paltusotine Demonstrated No New Safety Signals

TEAEs with an Incidence of ≥5% in Total Participants

TEAE	Paltusotine N=54 n (%)	Placebo N=57 n (%)
Diarrhoea	18 (33%)	10 (18%)
Headache	**11 (20%)**	**19 (33%)**
Arthralgia	**6 (11%)**	**13 (23%)**
Abdominal pain	6 (11%)	2 (4%)
Paresthesia	**5 (9%)**	**3 (5%)**
Nausea	5 (9%)	2 (4%)
Abdominal discomfort	5 (9%)	1 (2%)
Upper respiratory tract infection	4 (7%)	10 (18%)
Fatigue	**3 (6%)**	**8 (14%)**
Dyspepsia	3 (6%)	6 (11%)
Anemia	3 (6%)	5 (9%)
Back pain	3 (6%)	4 (7%)
Urinary tract infection	3 (6%)	4 (7%)
Asthenia	3 (6%)	3 (5%)
Peripheral swelling	**2 (4%)**	**6 (11%)**
Hyperhidrosis	**1 (2%)**	**5 (9%)**

- Safety profile in PATHFNDR-2 comparable to that observed in clinical program to date
- TEAEs (**bold**) are symptoms known to be associated with acromegaly

Includes AEs occurring during rescue period. Rates were similar when rescue period is excluded AE's commonly associated with symptoms of acromegaly are shown in bold.

PATHFNDR-2 Safety Summary

- Paltusotine was generally well-tolerated with no serious adverse events reported
- The most frequently (>10%) reported adverse events included diarrhoea, headache, arthralgia, and abdominal pain
- No new safety signals were observed in adverse events, vital signs, ECGs, or laboratory values during treatment with paltusotine
- Paltusotine treatment was associated with stable or reduced pituitary tumor size, as measured by MRI

Ongoing Open Label Extension Studies:
Currently ~225 participants treated up to 4yrs

PATHFNDR Program Provides a Uniquely Rich Data Set Assessing *BOTH* Biochemical *AND* Symptom Control in Acromegaly

Paltusotine data now support NDA filing for broad use in acromegaly

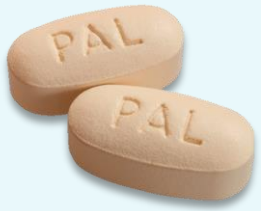
- Previously, ***PATHFNDR-1*** met all pre-specified endpoints in **maintenance of control when switching from SRLs**
- Today, ***PATHFNDR-2*** met all pre-specified endpoints in **patients not medically treated** who had elevated IGF-1 levels at baseline

First commercial launch for Crinetics, pending FDA approval of paltusotine for acromegaly

Aspiration: *to launch an important new medical treatment for acromegaly patients and medical providers:*

- ***The first once-daily, oral SRL***
- ***Reducing treatment burden***
- ***Reducing access barriers***
- ***Delivering rapid, durable, and consistent control***

Today → **2H24** → **2025**



Acromegaly NDA submission
Carcinoid syndrome Phase 3 start
pending alignment with FDA

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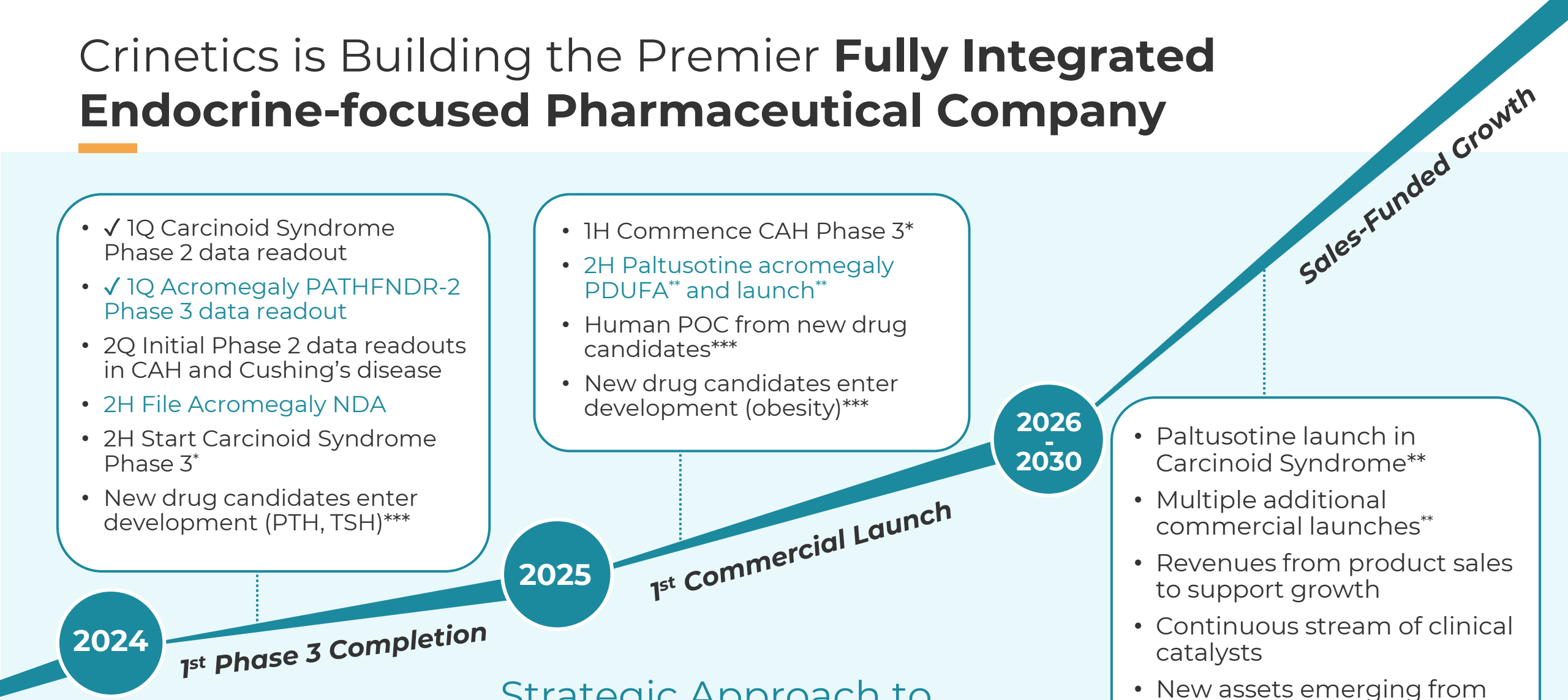
Crinetics is Building the Premier **Fully Integrated Endocrine-focused Pharmaceutical Company**



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.

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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

Marc Wilson
Chief Financial Officer

Jim Hassard
Chief Commercial Officer

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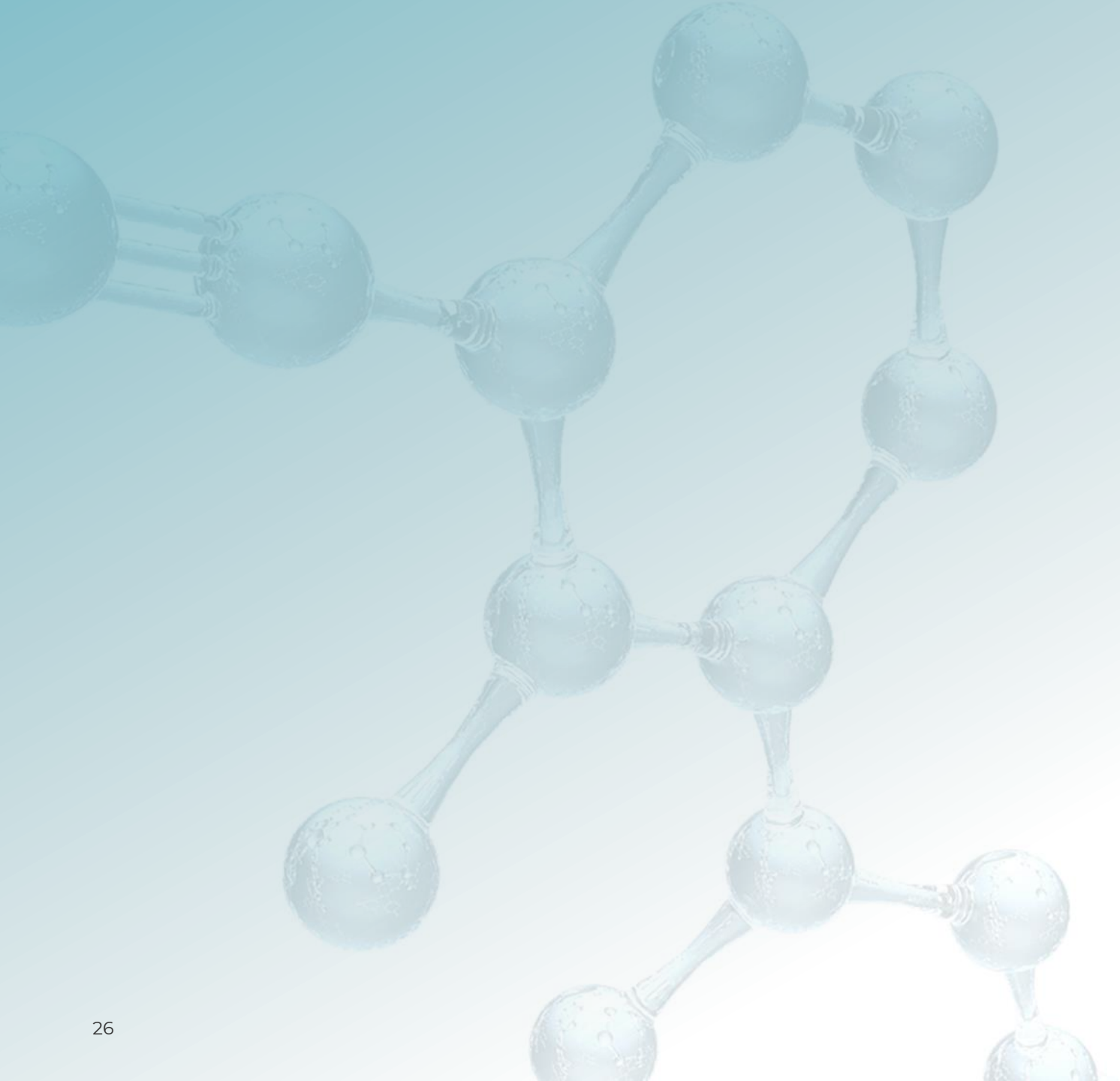

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Thank You