Efficacy and Safety of Once-Daily Oral Paltusotine in Patients With Acromegaly: Up to 2 Years in the PATHFNDR-1 and PATHFNDR-2 Open-Label Extension Studies

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Background and objective

BACKGROUND

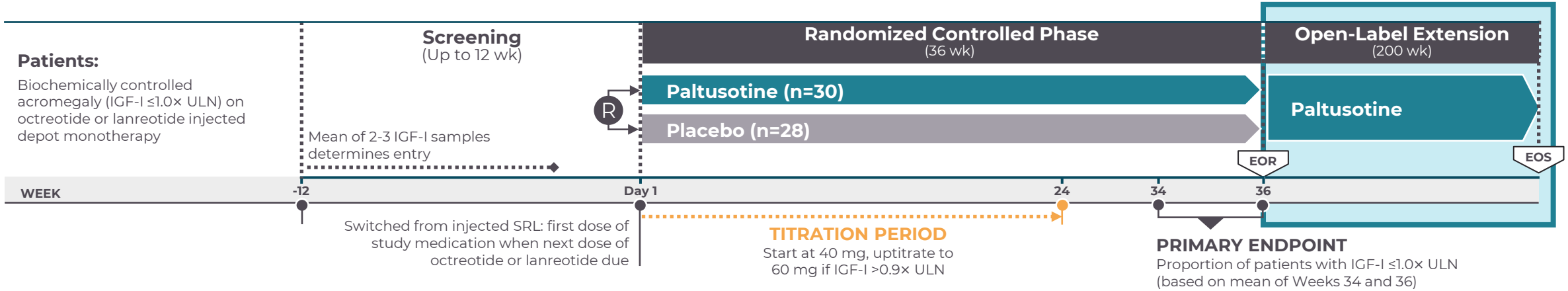
- Paltusotine (PALSONIFY™) is a nonpeptide, selective somatostatin 2 receptor agonist
- Paltusotine is approved in the United States and Europe as a once-daily oral treatment for adults with acromegaly
- In phase 3 trials, paltusotine was well tolerated and associated with both biochemical and symptom control
    - PATHFNDR-1: patients with biochemically controlled acromegaly who switched from monthly SRL injections[1]
    - PATHFNDR-2: patients with acromegaly that was medically untreated and biochemically uncontrolled at randomization[2]

OBJECTIVE

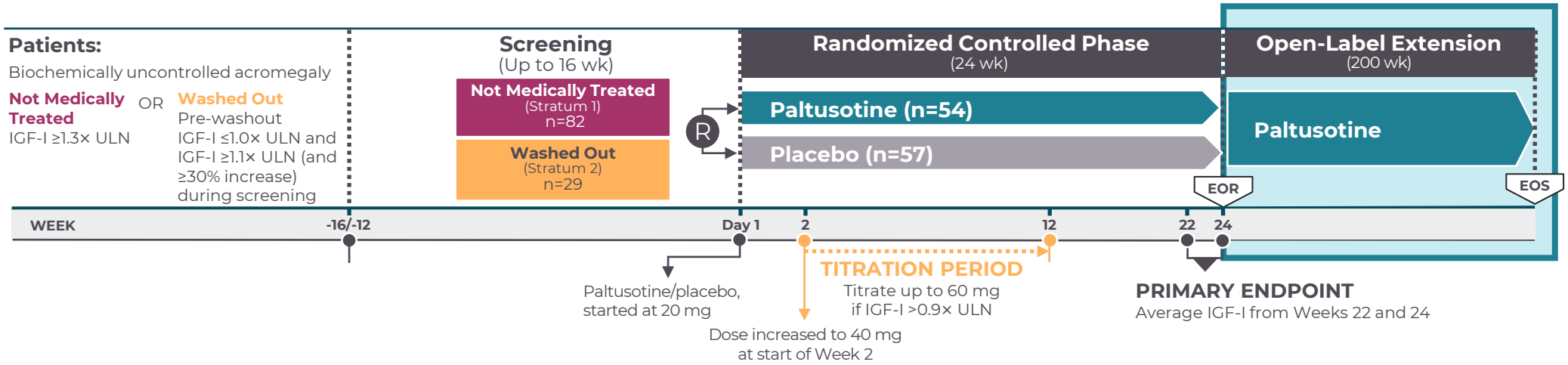
To evaluate the long-term efficacy and safety of paltusotine in the phase 3 PATHFNDR-1 and PATHFNDR-2 open-label extension studies

1. Gadelha MR, et al. *J Clin Endocrinol Metab*. 2024;110(1):228-237. **2.** Biller BMK, et al. *J Clin Endocrinol Metab*. 2026;111(4):e1050-e1063.

PATHFNDR-1 study design[1]



PATHFNDR-2 study design[2]



Not Medically Treated (Stratum 1) – Medically naive: 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.

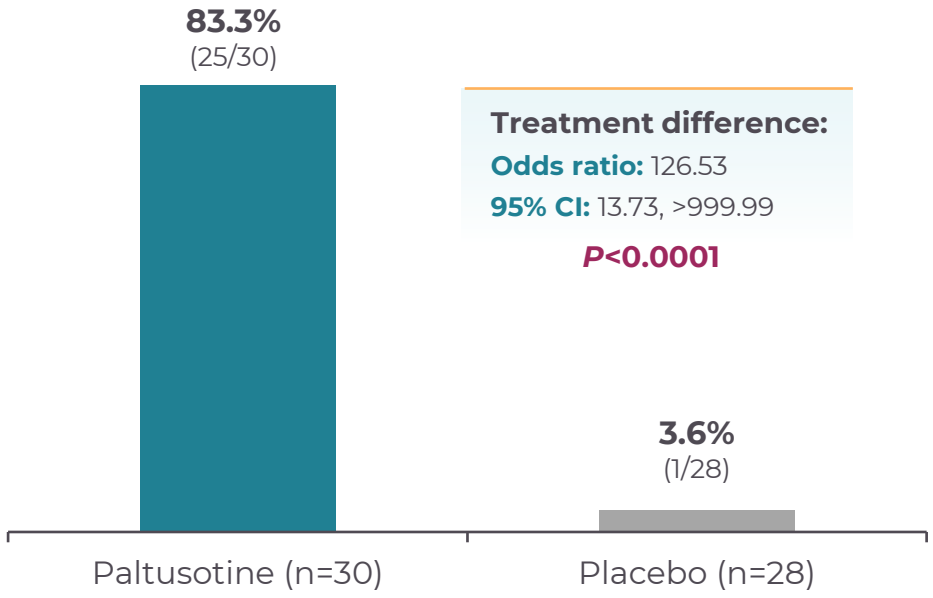
EOR = end of the randomized controlled phase; EOS = end of study; R = randomization.

1. Gadelha MR, et al. *J Clin Endocrinol Metab*. 2025;110(1):228-237. **2.** Biller BMK, et al. *J Clin Endocrinol Metab*. 2026;111(4):e1050-e1063.

PATHFNDR-1: Biochemical control outcomes in patients switching from injected depot SRLs to paltusotine

Primary Endpoint[1]

Patients With IGF-I ≤1.0× ULN at EOR

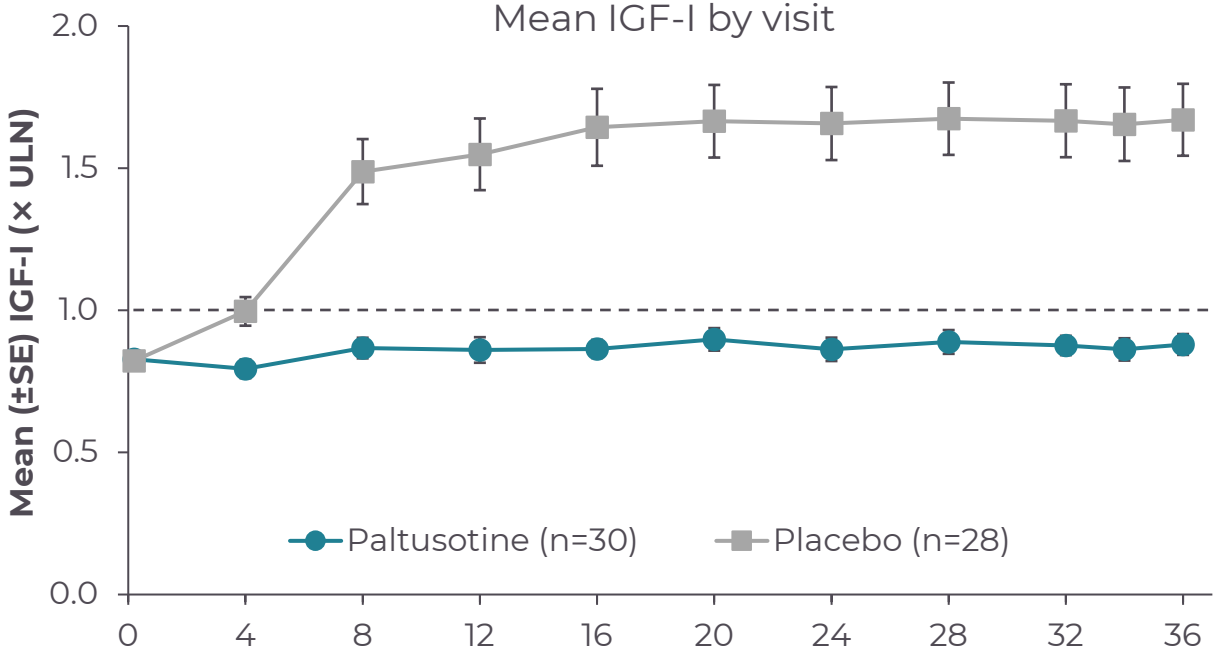


Treatment difference:
Odds ratio: 126.53
95% CI: 13.73, >999.99
***P*<0.0001**

PRIMARY ENDPOINT **Maintained IGF-I ≤1.0× ULN**

Exploratory Endpoint[2]

Mean IGF-I by visit



Only 1 patient taking paltusotine in PATHFNDR-1 had an IGF-I above 1.1× ULN at the end of randomized treatment[1]

Last observation carried forward for patients who received rescue medication or discontinued from the study.

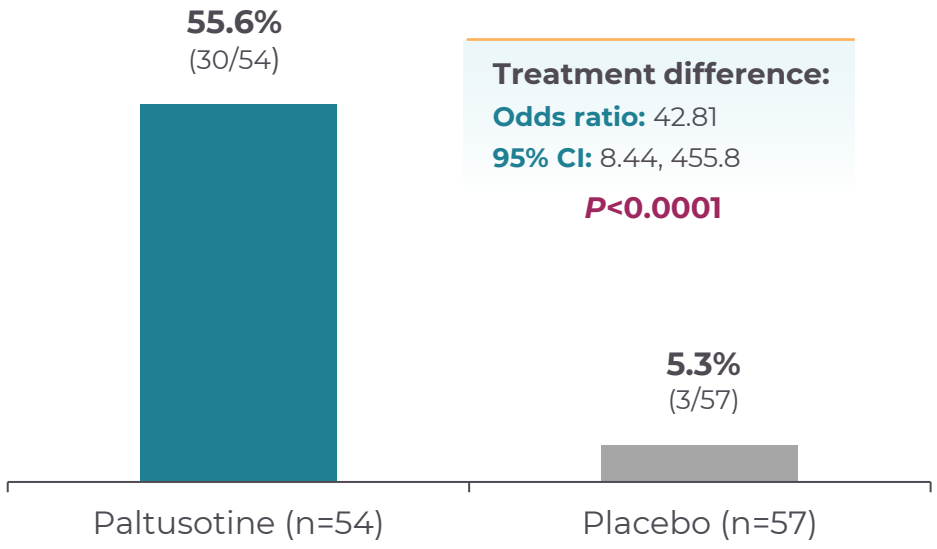
EOR = end of the randomized controlled phase.

1. Gadelha MR, et al. *J Clin Endocrinol Metab*. 2025;110(1):228-237. **2.** Biller BMK, et al. Presented at ENDO 2025; San Francisco, CA; July 12-15, 2025.

PATHFNDR-2: Biochemical control outcomes in medically untreated patients treated with paltusotine

Primary Endpoint[1]

Patients With IGF-I ≤1.0× ULN at EOR

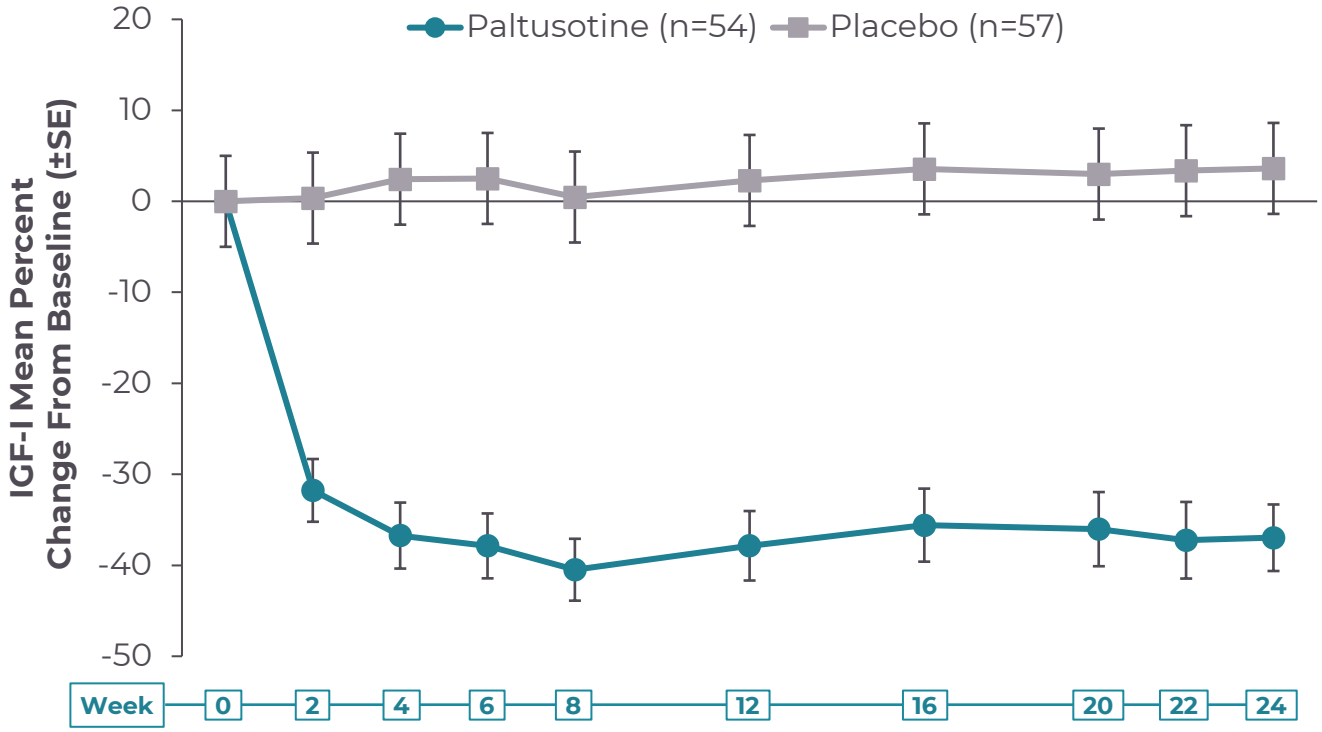


Treatment difference:
Odds ratio: 42.81
95% CI: 8.44, 455.8
***P*<0.0001**

PRIMARY ENDPOINT **Achieved IGF-I ≤1.0× ULN**

Exploratory Endpoint[2]

Mean Percent Change From Baseline in IGF-I Level by Visit

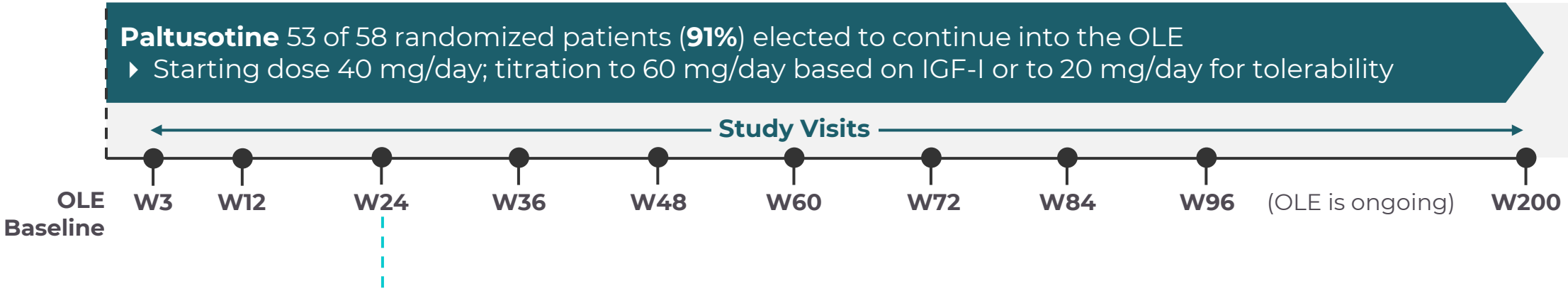


Last observation carried forward for patients who received rescue medication or discontinued from the study.

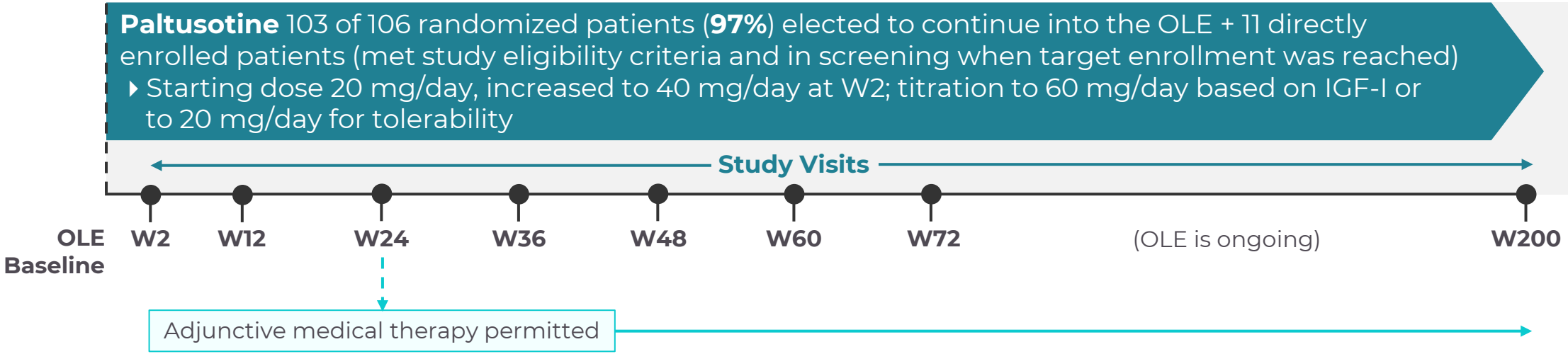
EOR = end of the randomized controlled phase.

1. Biller BMK, et al. *J Clin Endocrinol Metab.* 2026;111(4):e1050-e1063. **2.** Biller BMK, et al. Presented at ENDO 2024; Boston, MA; June 1-4, 2024.

PATHFNDR-1 open-label extension



PATHFNDR-2 open-label extension



Efficacy data: PATHFNDR-1 through W96; PATHFNDR-2 through W72
Safety data: Through data cutoff date (September 2025)

Open-label extension endpoints

EFFICACY

- IGF-I levels and GH levels
  - Measured centrally using Immunodiagnostic Systems iSYS immunoassays
  - Single-measurement GH
- Acromegaly Symptom Diary (ASD)[1]
  - Developed in accordance with FDA guidance
  - Administered at study visits

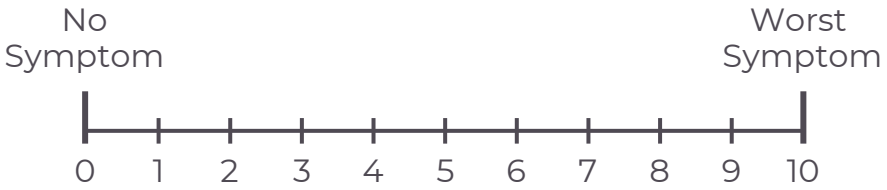
SAFETY

- Adverse event monitoring throughout
- Clinical laboratory tests, ECG at study visits
- Pituitary MRI (~every 1-2 years)
- Biliary/gallbladder ultrasound (~every 2 years or if symptoms)

Acromegaly Symptom Diary Core Symptoms[1]
Headache
Joint pain
Sweating
Fatigue
Leg weakness
Swelling
Numbness/tingling

Total Score (0-70)

Numeric Scale (per symptom)



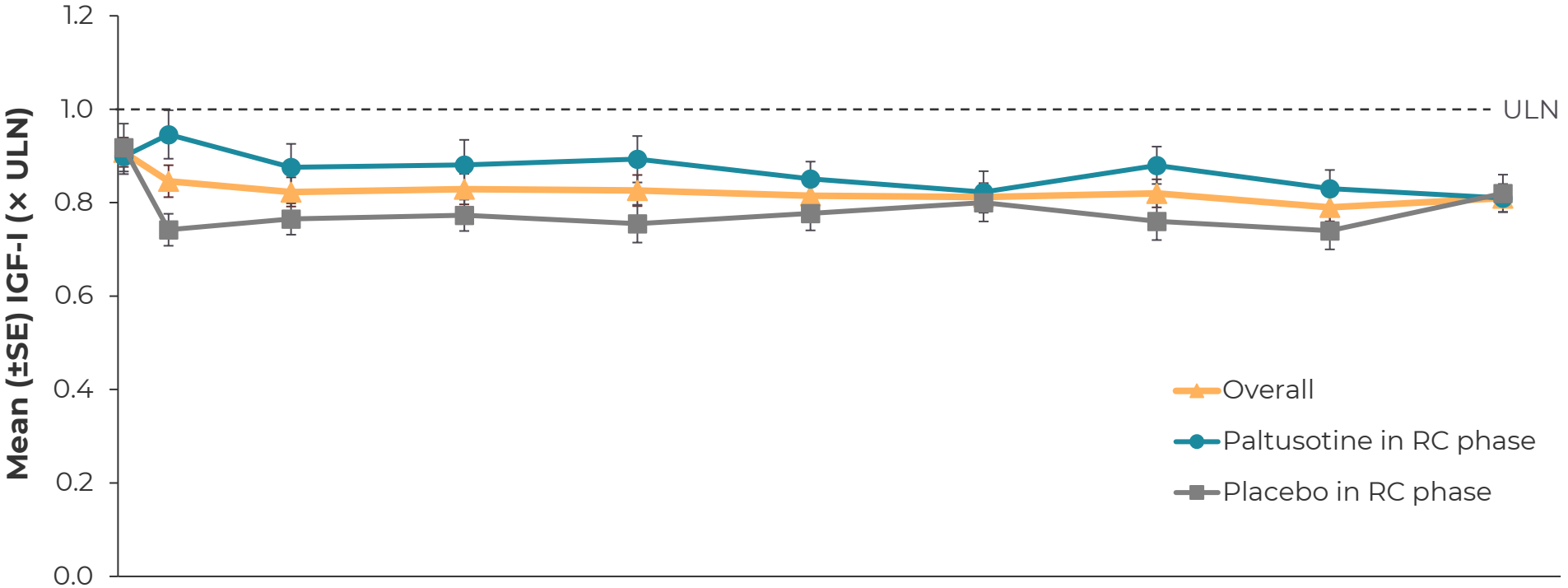
1. Martin S, et al. *J Patient Rep Outcomes*. 2023;7(1):15.

Paltusotine dose and adjunctive medication

	PATHFNDR-1 OLE (n=53)	PATHFNDR-2 OLE (n=114)
Paltusotine dose at last assessment, n (%)*		
20 mg/day	0	3 (2.6)
40 mg/day	15 (28.3)	20 (17.5)
60 mg/day	38 (71.7)	91 (79.8)
Adjunctive medication, n (%)*	1 (1.8)	18 (15.8)
Bromocriptine	0	6 (5.3)
Cabergoline	1 (1.8)	12 (10.5)

*As of the data cutoff date.

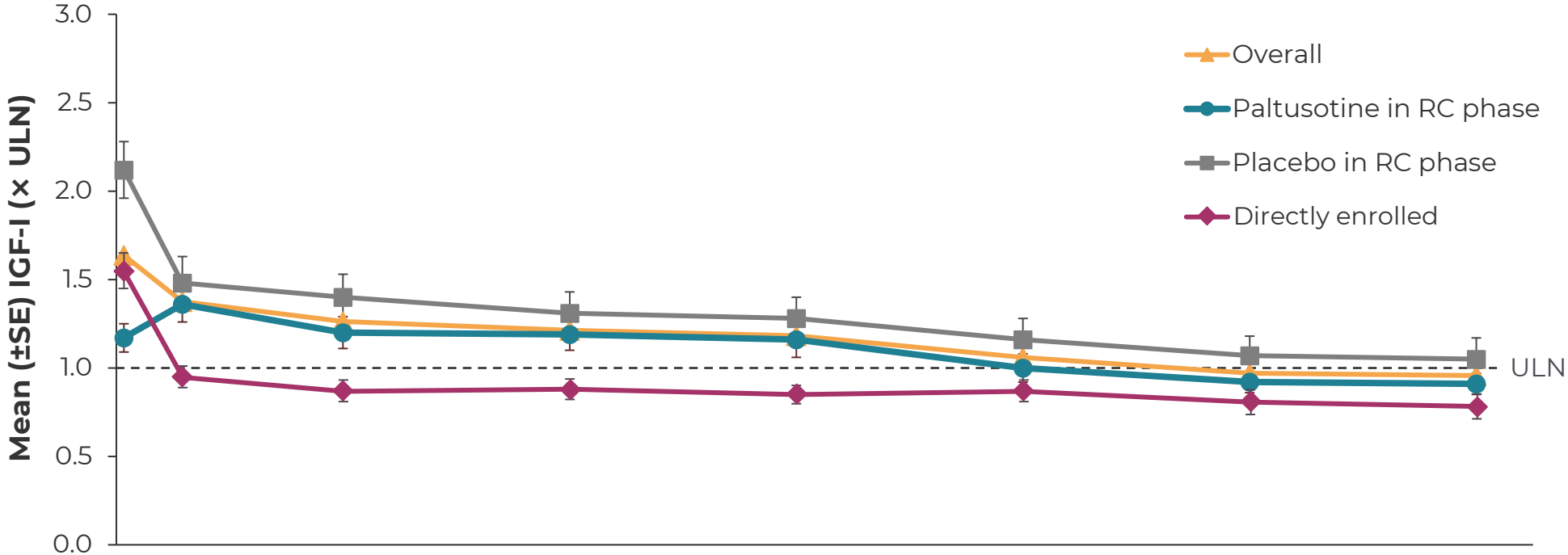
PATHFNDR-1 OLE: Durable IGF-I control with paltusotine



	OLE Baseline	OLE Week 3	OLE Week 12	OLE Week 24	OLE Week 36	OLE Week 48	OLE Week 60	OLE Week 72	OLE Week 84	OLE Week 96
Paltusotine in RC phase, n	27	26	27	27	26	26	26	25	26	25
Placebo in RC phase, n	26	25	25	25	25	24	24	23	23	22

OLE baseline = Study Week 36 (end of the RC phase).
RC = randomized controlled.

PATHFNDR-2 OLE: Paltusotine demonstrated rapid and durable IGF-I reduction



	OLE Baseline	OLE Week 2	OLE Week 12	OLE Week 24	OLE Week 36	OLE Week 48	OLE Week 60	OLE Week 72
Overall, n	114	113	113	108	105	98	88	78
Paltusotine in RC phase, n	51	50	51	49	48	43	40	36
Placebo in RC phase, n	52	52	52	49	47	45	38	33
Directly enrolled, n	11	11	10	10	10	10	10	9

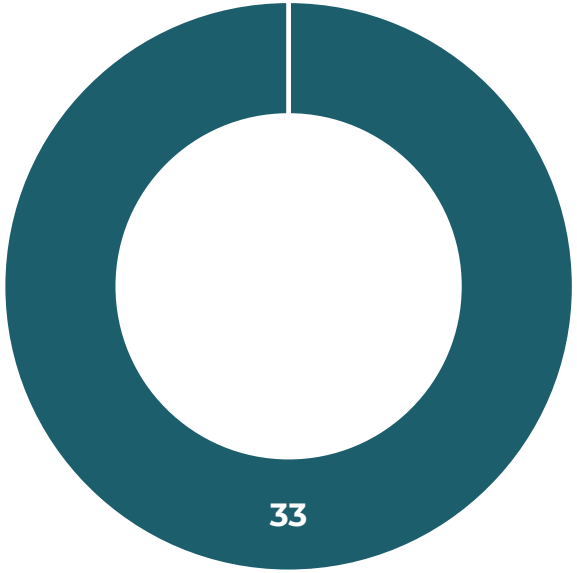
OLE baseline = Study Week 24 (end of the RC phase).
RC = randomized controlled.

Other efficacy outcomes

- In the PATHFNDR-1 OLE, GH levels were maintained during treatment with paltusotine
- In the PATHFNDR-2 OLE, GH levels were reduced in patients newly treated with paltusotine and were maintained in patients previously treated with paltusotine in the randomized controlled phase
- In both OLE studies, Acromegaly Symptom Diary scores were stable from OLE baseline through the last timepoint assessed

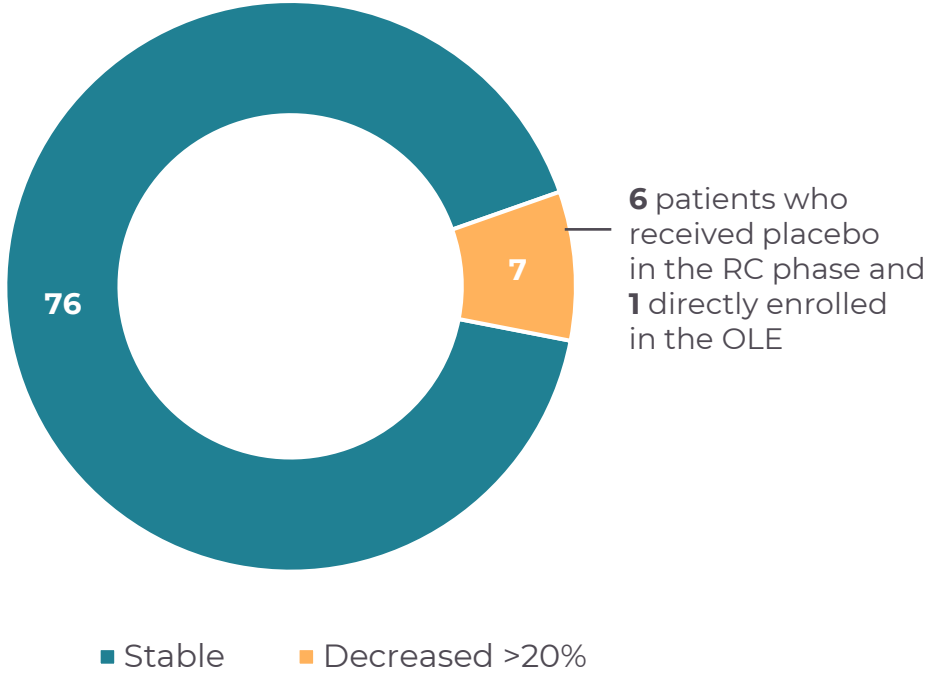
Pituitary tumor volume relative to OLE baseline

PATHFNDR-1 OLE (n=33)



Patients with available MRI scans at OLE Week 48

PATHFNDR-2 OLE (n=83)



Patients with available MRI scans at OLE Week 24

RC = randomized controlled.

Pooled PATHFNDR-1 OLE and PATHFNDR-2 OLE: Summary of adverse events

Adverse Event, n (%)	Pooled OLE Population (n=167)
Most common AEs (incidence >10%)	
Diarrhea	26 (15.6)
Headache	19 (11.4)
Arthralgia	19 (11.4)
Urinary tract infection	17 (10.2)
Serious AE, treatment-related	6 (3.6)*
AE leading to study discontinuation	4 (2.4)†

*3 patients with cholelithiasis, 1 patient with biliary colic and sinus arrest, 1 patient each with bile duct stone or gastritis.
†1 patient each with acute combined drug intoxication, lipase increased, pituitary tumor, or ventricular arrhythmia.

Conclusions

- During long-term treatment (median follow-up of ~2 years), once-daily oral paltusotine demonstrated sustained efficacy and was well tolerated in patients who switched from an injected depot SRL and in those who were medically untreated and biochemically uncontrolled when paltusotine was initiated
- The long-term safety profile was consistent with that observed in the randomized controlled trials, with no new safety findings

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Thank You