Once-Daily Oral Paltusotine in the Treatment of Patients With Biochemically Uncontrolled Acromegaly: Interim Results of the PATHFNDR-2 Open-Label Extension

MON-069

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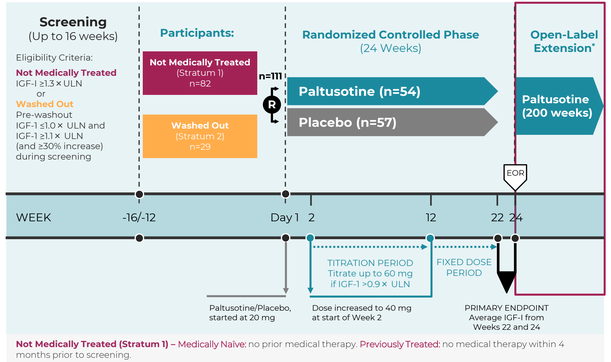
BACKGROUND

- Paltusotine is a non-peptide, selective somatostatin 2 (SST2) receptor agonist in development as a once-daily oral treatment for patients with acromegaly or carcinoid syndrome[1]
- PATHFNDR-2 was a randomized, double-blind, placebo-controlled trial that demonstrated a rapid and durable response for paltusotine in medically untreated patients with biochemically uncontrolled acromegaly

STUDY DESIGN

- The ongoing PATHFNDR-2 open-label extension (OLE) is evaluating the efficacy and safety of longer-term treatment with paltusotine
  - OLE starting dose of 20 mg/day, titrated to 40 mg/day based on tolerability at OLE Week 2, and optional titration to 60 mg/day based on IGF-I levels
  - Adjunctive acromegaly medication (eg, cabergoline, pegvisomant) is permitted beginning at OLE Week 24 at the investigator's discretion
  - MRI scans are performed locally and read by a central radiologist

PATHFNDR-2 Study Design



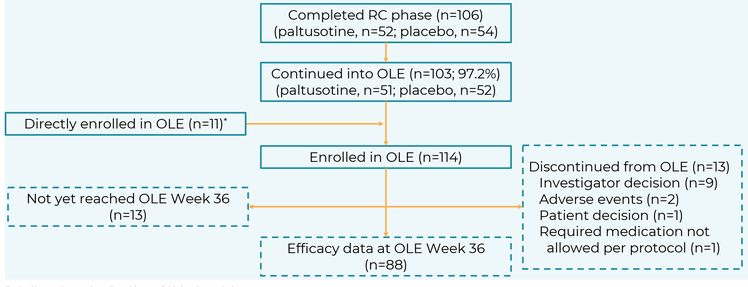
Not Medically Treated (Stratum 1) – Medically Naïve: no prior medical therapy. Previously Treated: no medical therapy within 4 months prior to screening.

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

*Data cutoff for this interim analysis: September 1, 2024.
EOR = end of randomized controlled phase; R = randomization.

RESULTS

Patient Disposition



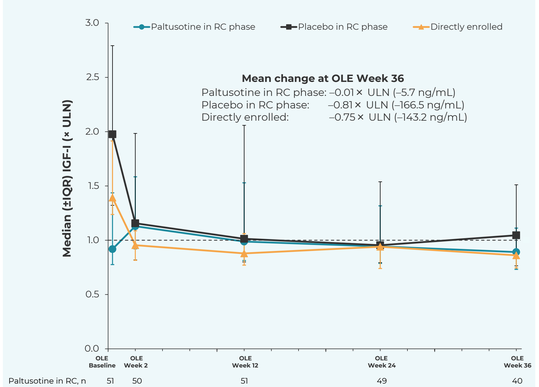
Dashed boxes show patient disposition as of this interim analysis.
*Met eligibility criteria for RC phase; were in screening process when target enrollment reached.
OLE = open-label extension; RC = randomized controlled.

Patient Characteristics

Parameters	Paltusotine in RC (n=51)	Placebo in RC (n=52)	Directly Enrolled (n=11)	All Patients (n=114)
Age, years, mean (SD)	47.5 (13.3)	45.5 (11.7)	58.4 (8.6)	47.7 (12.7)
Female, n (%)	26 (51.0)	29 (55.8)	4 (36.4)	59 (51.8)
Time since diagnosis, years, mean (SD)	8.0 (8.1)	6.0 (5.2)	14.9 (5.5)	7.8 (7.1)
Prior pituitary surgery, n (%)	47 (92.2)	45 (86.5)	10 (90.9)	102 (89.5)
Prior pituitary radiation, n (%)	2 (3.9)	3 (5.8)	0	5 (4.4)
OLE baseline IGF-I, × ULN, mean (SD)	1.17 (0.57)	2.12 (1.12)	1.55 (0.34)	1.64 (0.96)
Received rescue medication in RC, n	1	12	–	–

OLE baseline = Study Week 24 (end of the randomized controlled phase).
OLE = open-label extension; RC = randomized controlled.

IGF-I Levels Were Decreased in Patients Newly Treated With Paltusotine and Maintained in Previously Treated Patients

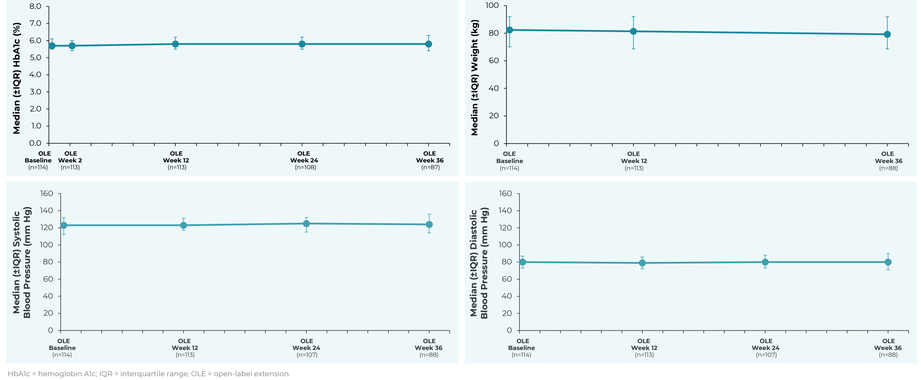


Paltusotine in RC, n	51	50	51	49	40
Placebo in RC, n	52	52	52	49	39
Directly enrolled, n	11	11	10	10	9

Adjunctive medications were started after OLE Week 24 and before the OLE Week 36 efficacy assessment in 3 patients (paltusotine in RC phase: n=1 cabergoline; placebo in RC phase: n=1 cabergoline, n=1 bromocriptine).
OLE baseline = Study Week 24 (end of the randomized controlled phase).
IQR = interquartile range; OLE = open-label extension; RC = randomized controlled.

- GH levels were reduced in patients newly treated with paltusotine and maintained in previously treated patients
- Acromegaly Symptom Diary scores were stable from OLE baseline through OLE Week 36

HbA1c, Blood Pressure, and Weight Were Stable During Treatment With Paltusotine (All Patients)



HbA1c = hemoglobin A1c; IQR = interquartile range; OLE = open-label extension.

CONCLUSIONS

- During treatment with once-daily oral paltusotine, IGF-I levels decreased rapidly in patients who had received placebo during the RC phase and patients with elevated IGF-I who were directly enrolled into the OLE
- Previously observed decreases in IGF-I were sustained in patients who continued on paltusotine
- Paltusotine was well tolerated during longer-term treatment

SAFETY

Adverse Events: Open-Label Extension

AEs, n (%)	Paltusotine in RC phase (n=51)	Placebo in RC phase (n=52)	Directly Enrolled (n=11)	Overall (n=114)
Any AE	42 (82.4)	47 (90.4)	10 (90.9)	99 (86.8)
Treatment-related SAE*	3 (5.9)	0	0	3 (2.6)
AE leading to discontinuation†	0	2 (3.8)	0	2 (1.8)
Most common AEs (incidence >5% in the overall patient population)				
Diarrhea	2 (3.9)	11 (21.2)	1 (9.1)	14 (12.3)
Hyperglycemia	6 (11.8)	5 (9.6)	2 (18.2)	13 (11.4)
Urinary tract infection	6 (11.8)	5 (9.6)	0	11 (9.6)
Headache	4 (7.8)	5 (9.6)	1 (9.1)	10 (8.8)
Arthralgia	4 (7.8)	4 (7.7)	0	8 (7.0)
Upper respiratory tract infection	3 (5.9)	5 (9.6)	0	8 (7.0)
Cholelithiasis	5 (9.8)	2 (3.8)	0	7 (6.1)

*Cholelithiasis and gastritis in 1 patient each; sinus arrest and biliary colic in 1 patient.
†Mild lipase increase and aggressive pituitary tumor in 1 patient each.

- At OLE Week 24 (last available timepoint), 7 of 83 patients had a reduction in pituitary tumor volume of >20% from OLE baseline: 6 patients who had received placebo in the RC phase and 1 directly enrolled patient

REFERENCE

1. Zhao J, et al. *ACS Med Chem Lett*. 2023;14(1):66-74.

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