Efficacy and Safety of Once-Daily Oral Paltusotine in Medically Untreated Patients with Acromegaly: Results from the Phase 3, Randomized, Placebo-Controlled PATHFNDR-2 Study

MON-694

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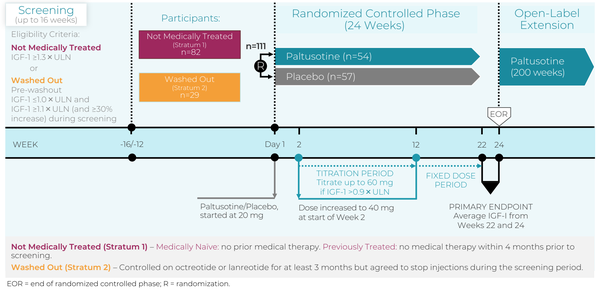
BACKGROUND

- Paltusotine is a once-daily, non-peptide, selective SST2 receptor agonist in development as oral treatment for patients with acromegaly or carcinoid syndrome[1]
- PATHFNDR-1: previous randomized, placebo-controlled trial
  - Maintenance of biochemical and symptom control in patients with acromegaly switched from injected depot SRL to once-daily paltusotine[2]

METHODS

- PATHFNDR-2: randomized, double-blind, placebo-controlled trial of paltusotine in medically untreated patients with active acromegaly
- IGF-I and GH measured centrally using IDS iSYS immunoassays
- Acromegaly Symptom Diary completed daily[3]
- Fixed sequential testing performed for primary and secondary endpoints

Study Design: PATHFNDR-2



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.

EOR = end of randomized controlled phase; R = randomization.

REFERENCES

1. Zhao J, et al. *ACS Med Chem Lett.* 2023;14(1):66-74. **2.** Gadela MR, et al. *Endocrine Abstracts.* 2023;94:399. **3.** Martin S, et al. *J Patient Rep Outcomes.* 2023;7(1):15.

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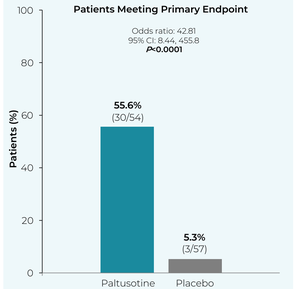
RESULTS

Patient Characteristics

Parameters	Paltusotine (n=54)	Placebo (n=57)
Age, years, mean (SD)	47.5 (13.6)	45.9 (12.3)
Female sex, n (%)	26 (48.1)	33 (57.9)
Time since diagnosis, months, mean (SD)	97.9 (95.7)	77.1 (69.4)
Prior pituitary surgery, n (%)	50 (92.6)	49 (86.0)
Prior pituitary radiation, n (%)	2 (3.7)	3 (5.3)
Baseline IGF-I, ×ULN, mean (SD)	2.0 (0.8)	2.2 (1.1)
Baseline GH, ng/mL, mean (SD), median*	3.0 (2.9), 2.1	9.4 (24.1), 2.3
Prior injected SRL (stratum 2)		
Octreotide, n (%)	6 (11.1)	11 (19.3)
Monthly dose: 10 mg/20 mg/≥30 mg, n	0/3/3	1/4/6
Lanreotide, n (%)	8 (14.8)	3 (5.3)
Monthly dose: 60 mg/90 mg/120 mg, n	1/2/5	2/0/1

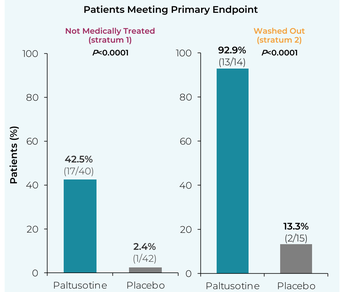
*GH measured as the mean from 5 samples collected within a 3-hour period. GH = growth hormone; IGF-I = insulin-like growth factor-I; SRL = somatostatin receptor ligand; ULN = upper limit of normal.

Primary Endpoint: Patients with IGF-I ≤1.0 × ULN at EOR

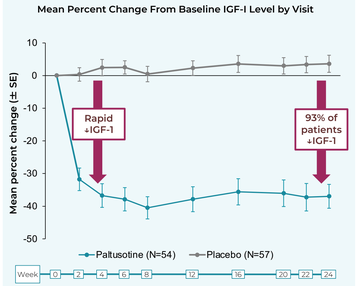


Based on mean of 2 measurements (Weeks 22 and 24). Participants who were rescued or stopped the assigned treatment before Week 24 considered not to have met the primary endpoint. EOR = end of randomized controlled phase.

Primary Endpoint by Stratum

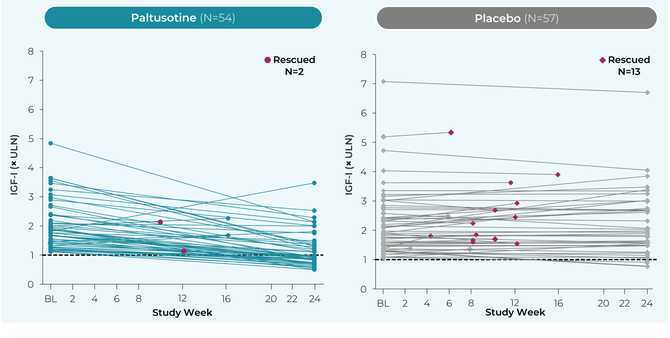


Rapid and Durable IGF-I Decrease

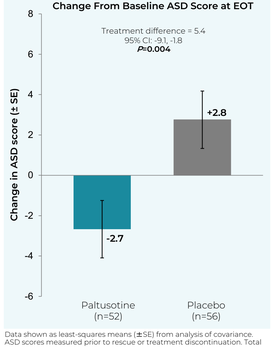


IGF-I values measured prior to rescue or discontinuation are carried forward.

IGF-I Change in Individual Patients

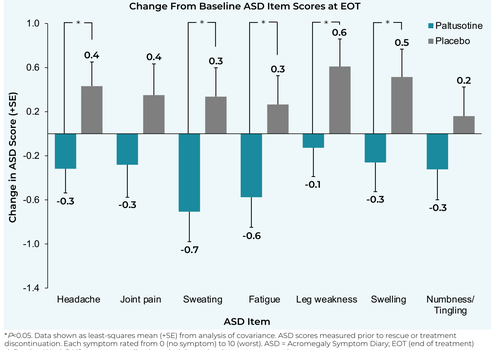


Secondary Endpoint: Change in ASD Total Score



Data shown as least-squares means (±SE) from analysis of covariance. ASD scores measured prior to rescue or treatment discontinuation. Total score range: 0-70. ASD = Acromegaly Symptom Diary; EOT (end of treatment) defined as Week 24 if no rescue medication administered, or last assessment prior to rescue.

Acromegaly Symptom Diary Components



*P<0.05. Data shown as least-squares mean (+SE) from analysis of covariance. ASD scores measured prior to rescue or treatment discontinuation. Each symptom rated from 0 (no symptom) to 10 (worst). ASD = Acromegaly Symptom Diary; EOT (end of treatment) defined as Week 24 if no rescue medication administered, or last assessment prior to rescue.

- Key secondary endpoint: mean change from baseline IGF-I of -0.82 × ULN with paltusotine versus +0.09 × ULN with placebo (treatment difference = -0.91; 95% CI: -1.11, -0.71; *P*<0.0001)
- Secondary endpoint: IGF-I <1.3 × ULN at end of randomized controlled phase in 66.7% of patients on paltusotine versus 14.0% on placebo (OR: 18.32; 95% CI: 5.64, 79.16; *P*<0.0001)
- Secondary endpoint: GH <1.0 ng/mL at Week 22 in 57.4% of patients on paltusotine versus 17.5% on placebo (OR: 7.59; 95% CI: 2.78, 23.48; *P*<0.0001)

CONCLUSIONS

- Paltusotine demonstrated rapid and sustained response in patients with active acromegaly
- This is the second randomized, placebo-controlled trial demonstrating biochemical and symptom control of acromegaly during treatment with once-daily oral paltusotine
- Paltusotine was generally well tolerated with no new safety signals

Summary of Adverse Events

Adverse Events, n(%)*	Paltusotine (n=54)	Placebo (n=57)
Diarrhea	18 (33.3)	10 (17.5)
Headache	**11 (20.4)**	**19 (33.3)**
Arthralgia	**6 (11.2)**	**13 (22.8)**
Abdominal pain	6 (11.1)	2 (3.5)
Upper RTI	4 (7.4)	10 (17.5)
Fatigue	**3 (5.6)**	**8 (14.0)**
Dyspepsia	3 (5.6)	6 (10.5)
Peripheral swelling	**2 (3.7)**	**6 (10.5)**

*Incidence >10% (either group). Adverse events in bold are symptoms known to be associated with acromegaly. RTI = respiratory tract infection.

- Greater proportion of patients taking placebo experienced symptoms known to be associated with acromegaly
- No serious adverse events in paltusotine-treated patients
- Safety profile comparable to that observed in paltusotine clinical program to date

For author affiliations and disclosures, please use the QR code.

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DISCLOSURES

BMKB reports being a PI of research grants from Crinetics and Ionis; and occasional consultant for Amolyt, Amryt, Camurus, Crinetics, and Recordati. AE reports being a PI/SI of research grants from Pfizer, Novartis, and Novo Nordisk; and a PI in clinical trials for Corcept Therapeutics, Crinetics Pharmaceuticals, Xeris Pharmaceuticals, and Recordati Rare Diseases. CLB reports receiving consulting fees, honoraria, and meeting support from Ipsen, Novo Nordisk, and Recordati; and serving on advisory boards for Novo Nordisk and Recordati. RSJ reports being a PI of a research grant from Crinetics. EH reports nothing to disclose. PKF reports being a PI of research grants from Crinetics and Corcept; a consultant for Regeneron and Quest Diagnostics; and an advisory board member for Amryt, Camurus, Crinetics, and Xeris. MF reports receiving occasional consulting fees from Camurus, Crinetics and Recordati; and being a PI of research grants from Crinetics. PJS reports being a PI of a research grant from Crinetics. M Bidlingmaier reports being a PI of research grants from Amolyt, Camurus, Chiasma, Crinetics, IDS, Ionis, Lumos, and OPKO; occasional consultant for Crinetics, Ionis, Novo Nordisk, Pfizer, Roche, and Sandoz; and speaker for Euroimmun, Novo Nordisk, and Pfizer. M Buchfelder reports being a PI of a research grant from Crinetics. CJS reports being a PI of a research grant from Crinetics to Charité Universitaetsmedizin; and occasional consultant/speaker for Amolyt Pharma, Crinetics, Debiopharm, Novo Nordisk, Pfizer, Recordati, and Sandoz-Hexal. MRG reports being a PI of research grants from Crinetics and Recordati; occasional consultant for Crinetics, Ipsen, Novo Nordisk, and Recordati; and speaker for Ipsen, Novo Nordisk, and Recordati. AC, BH, PJT, RSS, and AK are employees and stock shareholders of Crinetics Pharmaceuticals.