Paltusotine in the Treatment of Surgically Naïve Patients With Acromegaly: Post Hoc Analysis of Three Clinical Trials

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BACKGROUND

- Surgical resection of causative pituitary tumor is recommended first-line treatment for acromegaly[1] but fails to achieve cure in ~50% of patients[2]
- Some patients are not surgical candidates or refuse surgery, or surgery may be delayed[1]
- Paltusotine is a non-peptide selective SST2 receptor agonist in development as once-daily oral treatment for patients with acromegaly[3]

AIM

- To evaluate the efficacy and safety of paltusotine in patients with acromegaly who had no previous pituitary surgery

METHODS

- Post hoc analysis of 26 surgically naïve patients

Surgically Naïve Patients From One of Three Clinical Trials

	PATHFNDR-1	PATHFNDR-2	ACROBAT Advance
Study design	Randomized, placebo-controlled trial (phase 3)	Randomized, placebo-controlled trial (phase 3)	Single-arm, open-label extension study (phase 2, ongoing)
Patient population	Biochemically controlled (IGF-I ≤1.0× ULN) on injected depot SRL	Biochemically uncontrolled, no acromegaly medications at randomization	Biochemically controlled or uncontrolled on injected depot SRL ± adjunctive medication
Treatment	Switched (randomly assigned) to paltusotine or placebo	Randomly assigned to paltusotine or placebo	Paltusotine (switched from SRL-based regimen in parent study)
Treatment duration	36 weeks	24 weeks	Up to 3 years (this analysis)
Concomitant acromegaly medications	None	None	Add-on treatment with cabergoline or pegvisomant permitted

SRL = somatostatin receptor ligand.

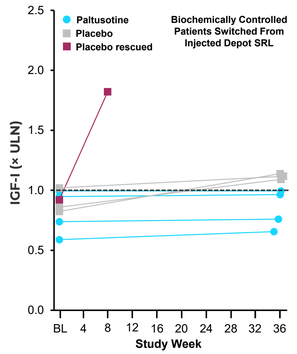
RESULTS

Patient Characteristics and Study Treatment

	PATHFNDR-1 (n=8)	PATHFNDR-2 (n=12)	ACROBAT Advance (n=6)
Age, years, mean (SD)	56.3 (13.1)	53.2 (10.8)	65.5 (4.4)
Female, n (%)	5 (62.5)	7 (58.3)	4 (66.7)
Paltusotine, n Placebo, n	4 4	4 8	6 --
Baseline IGF-I, ×ULN* Paltusotine Placebo	 0.82 (0.19) 0.91 (0.09)	 1.43 (0.24) 2.09 (0.72)	 1.09 (0.60-1.79) —
Paltusotine dose, n (%) 40 mg/day 60 mg/day	 2 (50.0) 2 (50.0)	 2 (50.0) 2 (50.0)	 3 (50.0) 3 (50.0)

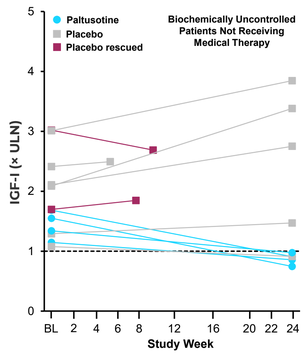
*Mean (SD) for PATHFNDR-1 and PATHFNDR-2; median (range) at parent study baseline for ACROBAT Advance.

PATHFNDR-1: IGF-I Level at Baseline and EOT* for Each Patient



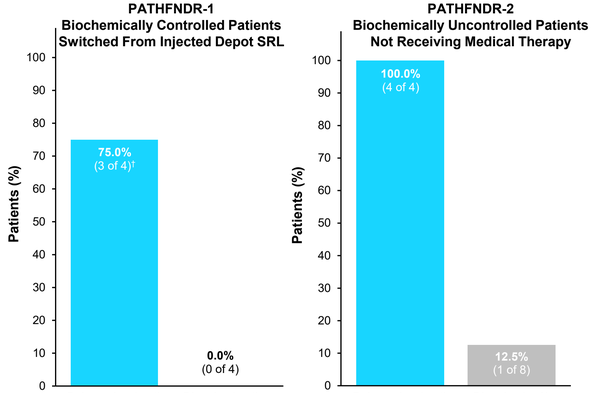
*EOT (end of treatment) defined as Week 36 if no rescue medication administered or last assessment prior to rescue. BL = baseline; EOT = end of treatment; IGF-I = insulin-like growth factor-I; ULN = upper limit of normal.

PATHFNDR-2: IGF-I Level at Baseline and EOT* for Each Patient



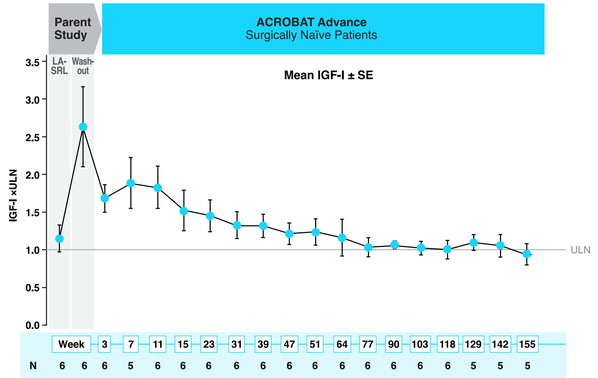
*EOT (end of treatment) defined as Week 24 if no rescue medication administered or last assessment prior to rescue. BL = baseline; EOT = end of treatment; IGF-I = insulin-like growth factor-I; ULN = upper limit of normal.

PATHFNDR-1 and PATHFNDR-2: Proportion of Patients With IGF-I ≤1.0× ULN*



*Based on average of Weeks 34 and 36 in PATHFNDR-1 and average of Weeks 22 and 24 in PATHFNDR-2, or the last assessment before rescue medication was administered (1 placebo patient was rescued in PATHFNDR-1; 2 placebo patients were rescued in PATHFNDR-2). †For one patient, IGF-I (average of Weeks 34 and 36) was 1.08× ULN; the Week 36 value (shown in the line graph) was 0.96× ULN.

ACROBAT Advance: Mean IGF-I Level During Open-Label Treatment With Paltusotine



LA-SRL parent study baseline; washout is the end of 4-week paltusotine washout period at the end of the parent study. During ACROBAT Advance, 3 of 6 patients received adjunctive therapy with cabergoline and 1 received cabergoline + pegvisomant. LA-SRL = long-acting somatostatin receptor ligand.

CONCLUSIONS

- Surgically naïve patients experienced rapid and durable treatment effects of paltusotine
- Paltusotine was well tolerated in surgically naïve patients
- Safety and efficacy in this limited sample of surgically naive patients was similar to that in the overall study population (primarily patients with prior surgery)
- These initial findings should be evaluated in future studies with larger sample sizes

Safety

- 1 paltusotine-treated patient discontinued study participation (ACROBAT Advance) due to inability to fulfill study requirements and procedures
- 3 paltusotine-treated patients (ACROBAT Advance) experienced serious adverse events (osteoarthritis, worsening coronary artery disease, renal oncocytoma) that were considered not related to study medication
- Radiology assessments showed tumor size stability in paltusotine-treated patients

REFERENCES

1. Fleseriu M, et al. *Lancet Diabetes Endocrinol.* 2022;10(11):804-826.
2. Starnoni D, et al. *Acta Neurochir.* 2016;158(11):2109-2121. 3. Zhao J, et al. *ACS Med Chem Lett.* 2023;14(1):66-74.

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AUTHOR DISCLOSURES

MM reports being a PI of research grants from Crinetics; receiving consulting fees, honoraria, and meeting support from Ipsen and Novo Nordisk; and serving on advisory boards for Novo Nordisk and Recordati. CB reports being a PI of research grants from Crinetics; receiving consulting fees, honoraria, and meeting support from Crinetics, Ipsen, Novo Nordisk, and Recordati; and serving on advisory boards for Crinetics and Recordati. RJ reports being a PI of research grants from Crinetics. PF reports being a PI of research grants from Corcept and Crinetics; a consultant for Quest Diagnostics and Regeneron; and an occasional advisory board member for Camurus, Chiesi, and Crinetics. CS reports being a PI of a research grant from Crinetics; and an occasional consultant/speaker for Amolyt Pharma, Crinetics, Novo Nordisk, Pfizer, Recordati, and Sandoz-Hexal. MB reports being a PI of research grants from Amolyt, Camurus, Chiasma, Crinetics, IDS, Ionis, Lumos, and OPKO; an occasional consultant for Crinetics, Ionis, Novo Nordisk, Pfizer, Roche, and Sandoz; and a speaker for Euroimmun, Novo Nordisk, and Pfizer. MG reports being a PI of research grants from Crinetics and Recordati; an occasional consultant for Camurus, Crinetics, Ipsen, Novo Nordisk, and Recordati; and a speaker for Camurus, Ipsen, Novo Nordisk, and Recordati. BB reports being a PI of research grants to Massachusetts General Hospital from Crinetics and Ionis; and an occasional consultant for Amolyt, Camurus, Chiesi, Crinetics, Pfizer, and Recordati. BH, AC, and LK are employees of Crinetics Pharmaceuticals.