Paltusotine Results in Improved Symptom Stability in Biochemically Controlled Acromegaly

SUN-043

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BACKGROUND

- The daily Acromegaly Symptom Diary (ASD)[1] was developed for use in accordance with FDA guidance to allow measurement of both symptom severity and day-to-day symptom variability in clinical trials
- Paltusotine is an oral, once-daily somatostatin receptor 2-specific agonist with high bioavailability in clinical development for treatment of acromegaly[2,3]
- PATHFNDR-1 is a phase 3, multinational, randomized, double-blind, placebo-controlled trial of 58 patients with IGF-I ≤1.0 × ULN while treated with depot octreotide or lanreotide who were randomized to switch to daily paltusotine or placebo[4]

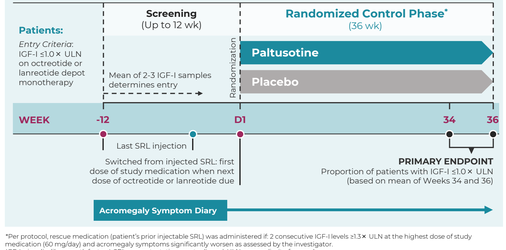
AIMS

- To compare the frequency of symptom exacerbations in a cohort of outpatients treated with injected depot SRLs (with varying degrees of biochemical control) to that in the biochemically controlled study population prior to enrollment in PATHFNDR-1
- To evaluate whether patients on injected depot SRLs would experience a reduction in the frequency of symptom exacerbations after switching to once-daily oral paltusotine while maintaining normal IGF-I levels

METHODS

- In PATHFNDR-1, participants completed the ASD on a daily basis beginning in the screening period (during which they received their last SRL injection) and throughout the randomized controlled period

PATHFNDR-1 Study Design



*Per protocol, rescue medication (patient's prior injectable SRL) was administered if: 2 consecutive IGF-I levels ≥1.3 × ULN at the highest dose of study medication (60 mg/day) and acromegaly symptoms significantly worsen as assessed by the investigator.
IGF-I = insulin-like growth factor-I; SRL = somatostatin receptor ligand; ULN = upper limit of normal.
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Acromegaly Symptom Diary

Daily Surveys

- 7 core acromegaly symptoms: headache, joint pain, sweating, fatigue, leg weakness, swelling, numbness/tingling
- 2 additional acromegaly symptoms: difficulty sleeping, difficulty with short-term memory
- Severity of each symptom rated for the previous 24 hours on a scale from 0 (no symptom) to 10 (worst symptom)

METHODS

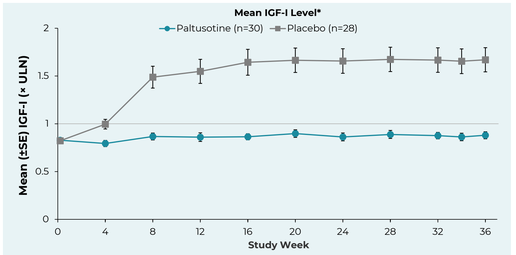
- Post hoc symptom analyses included PATHFNDR-1 participants who had adequate ASD data (at least 4 completed days during the screening period) and did not require rescue with injected SRLs
  - Symptom exacerbation was defined as a ≥2-point increase for any individual symptom score, comparing a 2-day average to the previous 2-day average
    - 2-point differences identified as clinically meaningful in a separate qualitative patient interview study (data on file)

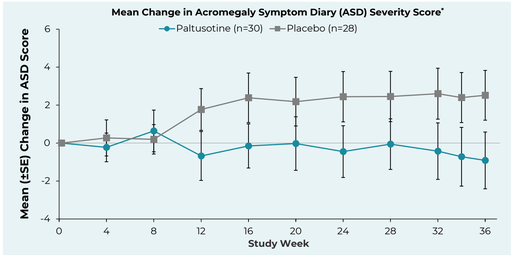
RESULTS

Biochemical and symptom severity control in PATHFNDR-1

- In PATHFNDR-1, IGF-I ≤1.0 × ULN (based on the mean of 2-3 measurements during the screening period) was required for enrollment
- After randomization, mean IGF-I levels were maintained throughout the treatment period in participants randomized to paltusotine and rose within 4 weeks in those taking placebo
- Symptom severity scores favored paltusotine from Week 12 through the remainder of the treatment period

PATHFNDR-1: IGF-I and Symptom Severity





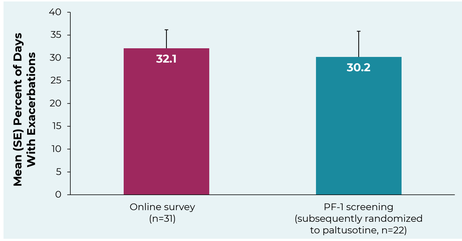
*Last observation carried forward (LOCF) for patients who received rescue medication or discontinued from the study.

RESULTS

Symptom exacerbation frequencies in the online survey cohort versus PATHFNDR-1 screening population

- In a previously reported online daily symptom survey study, outpatients with mixed biochemical control while treated with injected SRLs experienced symptom exacerbations 32.1% of days, on average (2.2 × /week)[5]
- In patients with normal IGF-I while treated with injected SRLs who completed the daily ASD during the screening period of PF-1, symptom exacerbations were experienced 30.2% of days, on average (2.1 × /week)

Acromegaly Symptom Exacerbation Frequency in Patients Treated With Injected SRLs

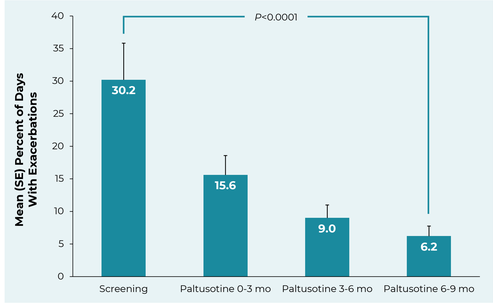


Online survey cohort had mixed biochemical control; PF-1 screening cohort had normal IGF-I.
PF-1 = PATHFNDR-1.

Change in symptom exacerbation frequency after switching from injected SRL to paltusotine

- Analysis of participants randomized to paltusotine in PATHFNDR-1 shows continued and significant reduction in symptom exacerbations over the treatment period

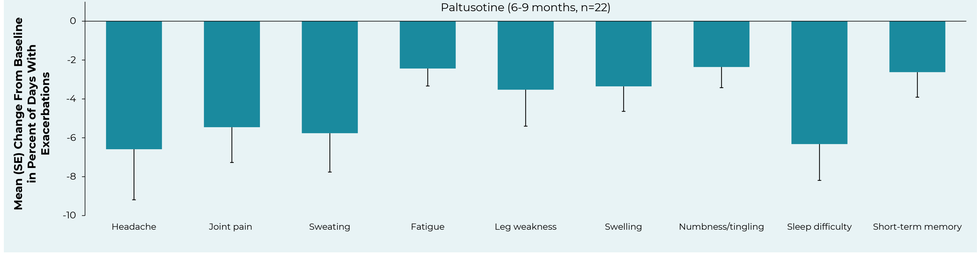
Overall Symptom Exacerbation Frequency in PATHFNDR-1 Participants Switching From Injected SRLs to Paltusotine (n=22)



Changes in individual symptom frequency with paltusotine

- Paltusotine treatment was associated with significantly greater reduction in symptom exacerbation frequency compared with placebo (linear regression model: difference = –7.3%; *P*=0.0167; controlling for baseline frequency)
- Paltusotine treatment was associated with reductions in symptom exacerbation frequency for all symptoms assessed

Change From Injected SRL Baseline in Individual Symptom Exacerbation Frequencies in Participants Treated With Paltusotine in PATHFNDR-1



CONCLUSIONS

- Patients with acromegaly treated with injected SRLs experience frequent symptom exacerbations, even when biochemically controlled
- In patients biochemically controlled with injected SRLs, switching to once-daily oral paltusotine was associated with stable biochemical control, stable symptom severity, and a significantly reduced frequency of symptom exacerbations
- Paltusotine treatment was associated with reductions in symptom exacerbation frequencies for all symptoms assessed
- A simple daily symptom-assessment tool provided important information pertaining to acromegaly disease control that was not apparent from IGF-I measurements

REFERENCES

1. Martin S, et al. *J Patient Rep Outcomes.* 2023;7(1):15. **2.** Madan A, et al. *Pituitary.* 2022;25(2):328-339. **3.** Zhao J, et al. *ACS Med Chem Lett.* 2022;14(1):66-74. **4.** Gadelha MR, et al. *J Clin Endocrinol Metab.* 2024;110(1):228-237. **5.** Geer EB, et al. Poster presented at the AACE Annual Meeting; May 15-17, 2025; Orlando, FL.

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DISCLOSURES

DC reports serving as a consultant for Amolyt, Crinetics Pharmaceuticals, Inc., and Novo Nordisk. TPQ, AC, YW, and AK are employees and shareholders of Crinetics Pharmaceuticals, Inc.

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