Effects of Paltusotine Treatment on Patient-Reported Symptoms of Acromegaly in Phase 3 Randomized Placebo-Controlled Studies (PATHFNDR-1 and PATHFNDR-2)

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INTRODUCTION

- Acromegaly is a chronic rare disease typically caused by a growth hormone (GH) secreting tumor in the pituitary[1]
- Injected depot administered somatostatin receptor ligands (SRLs) are considered first-line medical treatment for acromegaly[2]
- Paltusotine is an investigational nonpeptide somatostatin receptor 2 (SST2) agonist taken orally once daily for patients with acromegaly. Paltusotine was shown to result in significantly lower mean acromegaly symptom severity compared with placebo in two randomized, double-blind, phase 3 trials[3,4]
- **Objective:** To determine whether improvement or stabilization of acromegaly symptoms by paltusotine was consistent across the range of observed changes in symptom severity and patient history

METHODS

Data Source

Adult patients with acromegaly were enrolled in 1 of 2 randomized, blinded, placebo-controlled phase 3 studies to evaluate safety and efficacy of paltusotine:

- PATHFNDR-1 (PF-1): Included a 36-week randomized controlled (RC) period among 58 patients with acromegaly who were biochemically controlled on injected SRLs and randomized to switch to paltusotine or placebo[4]
- PATHFNDR-2 (PF-2): Included a 24-week RC period among 111 patients with acromegaly. Prior to the study, patients were not pharmacologically treated and therefore biochemically uncontrolled.[5] Prior to randomization to paltusotine or placebo, all patients were either:
  - Medically naïve or last treated ≥4 months prior to screening (IGF-1 ≥1.3 x ULN)
  - Controlled on injected SRLs and willing to wash out of treatment until IGF-1 ≥ 1.1 x ULN during the screening period
- Both studies included rescue criteria for patients who had unacceptable biochemical and worsening symptom control

Acromegaly Symptom Diary (ASD)[5]

- Evaluates 7 core symptoms of acromegaly: headache, joint pain, sweating, fatigue, leg weakness, swelling, and numbness/tingling
- Symptoms are rated on an 11-point numeric scale ranging from 0 (no symptom) to 10 (worst symptom) over the past 24 hours
- In both studies, patients completed the ASD daily from screening through the RC phase
- Both PF-1 and PF-2 evaluated change in ASD total score as a pre-specified secondary endpoint

Analyses

- Empirical cumulative distribution functions (eCDFs) were plotted using the full analysis set from each study to show the cumulative percentage of patients at each level of change in the weekly average ASD total score from baseline to EOR
- EOR was defined per protocol as 1) the value at the end of RC for patients who completed the RC phase without intercurrent events or 2) the last available value on or before the intercurrent event for patients who had intercurrent events (e.g., taking rescue medication or early discontinuation).
- Separate functions were plotted for treatment and placebo groups. For PF-2, the treatment group was further stratified based on treatment history

RESULTS

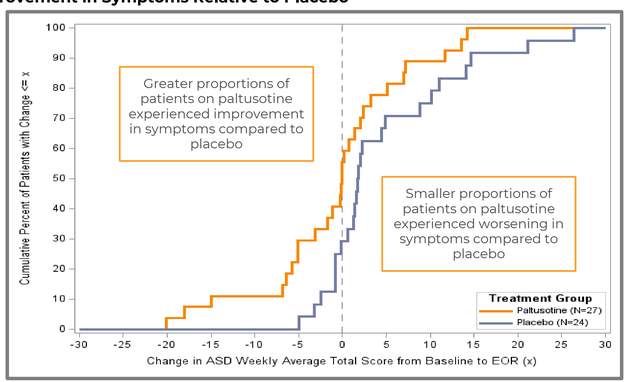
Demographic and Clinical Characteristics of the Analytic Samples

	CRN00808-09/PATHFNDR-1			CRN00808-08/PATHFNDR-2		
	Total (N=51)	Paltusotine (N=27)	Placebo (N=24)	Total (N=108)	Paltusotine (N=52)	Placebo (N=56)
Age, Mean ± SD						
Screening	55.9 ± 13.6	56.6 ± 14.3	55.2 ± 13.0	46.6 ± 13.1	47.5 ± 13.8	45.7 ± 12.3
Sex, N (%)						
Female	28 (54.9%)	13 (48.2%)	15 (62.5%)	59 (54.6%)	26 (50.0%)	33 (58.9%)
Male	23 (45.1%)	14 (51.9%)	9 (37.5%)	49 (45.4%)	26 (50.0%)	23 (41.1%)
Treatment History,[a] N (%)						
Medically Naive	--	--	--	45 (41.7%)	21 (40.4%)	24 (42.9%)
Previously Treated	--	--	--	35 (32.4%)	18 (34.6%)	17 (30.4%)
Washed Out	--	--	--	28 (25.9%)	13 (25.0%)	15 (26.8%)
IGF-1 ULN, Mean ± SD						
Baseline	0.8 ± 0.14	0.8 ± 0.14	0.8 ± 0.16	2.1 ± 0.95	2.0 ± 0.71	2.2 ± 1.11
ASD Weekly Average Total Score, Mean ± SD						
Baseline	11.8 ± 12.01	12.7 ± 12.15	10.9 ± 12.03	16.5 ± 14.83	17.5 ± 16.27	15.5 ± 13.43
EOR	13.7 ± 12.06	11.9 ± 10.45	15.7 ± 13.60	15.6 ± 14.94	13.6 ± 13.40	17.6 ± 16.12
Change from Baseline to EOR	1.9 ± 8.49	-0.8 ± 8.32	4.8 ± 7.85	-0.8 ± 10.61	-3.9 ± 9.95	2.0 ± 10.48

Abbreviations: ASD, Acromegaly Symptoms Diary; EOR, End of Randomization; IGF-1; Insulin-like growth factor 1; SD, standard deviation; ULN, upper limit of normal.

[a]PF-1 patients were all controlled on long-acting somatostatin receptor ligands at the start of the study.

Figure 1. PF-1: Greater Proportions of Patients Treated with Paltusotine Experienced Improvement in Symptoms Relative to Placebo



Negative change scores indicate improvement in acromegaly symptom severity; positive change scores indicate decline. Solid vertical line at 0 represents no change. A change score of -3 represents the lower bound of a meaningful within-patient change threshold range.

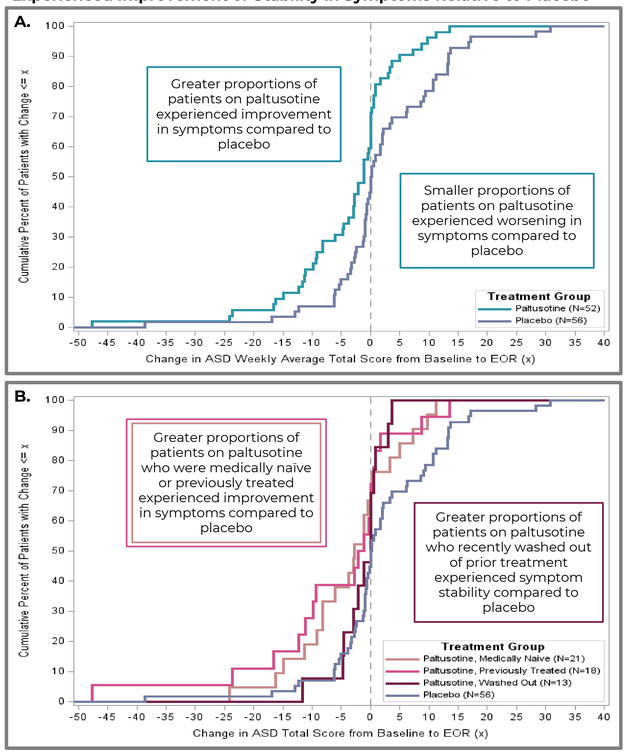
Abbreviations: ASD, Acromegaly Symptoms Diary; eCDF, empirical cumulative distribution function; EOR, End of Randomization; PF-1, PATHFNDR-1.

PATHFNDR-1: Paltusotine vs Placebo (Figure 1)

- Although the study was designed to evaluate disease maintenance, greater proportions of acromegaly patients biochemically controlled with injected SRLs who were switched to paltusotine experienced symptom improvement than patients on placebo
- 33% of patients who switched to paltusotine experienced ≥3-point improvement on the ASD total score, relative to 8% of patients on placebo

Key Takeaway: Greater proportions of patients treated with paltusotine experienced less acromegaly symptom burden compared to placebo, regardless of the magnitude of the symptom effect, treatment history, or state of biochemical disease control.

Figure 2. PF-2: Greater Proportions of Patients Treated with Paltusotine Experienced Improvement or Stability in Symptoms Relative to Placebo



Negative change scores indicate improvement in acromegaly symptom severity; positive change scores indicate decline. Solid vertical line at 0 represents no change. A change score of -3 represents the lower bound of a meaningful within-patient change threshold range.

Abbreviations: ASD, Acromegaly Symptoms Diary; eCDF, empirical cumulative distribution function; EOR, End of Randomization; PF-2, PATHFNDR-2.

Figure 2A. PATHFNDR-2: Paltusotine vs Placebo

- Overall, greater proportions of patients who initiated paltusotine experienced improvement in symptom severity relative to placebo

Figure 2B. PATHFNDR-2: Paltusotine According to Treatment History vs Placebo

- Greater proportions of patients who were medically naive or who had discontinued medical therapy in the distant past (≥ 4 months prior to screening) experienced improvement in symptoms when treated with paltusotine relative to placebo
- Greater proportions of patients who were controlled on injected SRLs and discontinued treatment recently (i.e., washed out during the screening period of the study) experienced symptom stability on paltusotine relative to patients on placebo

CONCLUSIONS

- Compared to placebo, treatment with oral paltusotine was associated with reduced acromegaly symptom burden across the entire observed range of change in patient-reported symptom severity
- Greater proportions of symptom improvement relative to placebo were noted in both trials, including in patients who maintained biochemical control after switching from injections to paltusotine (PF-1) and in patients who improved biochemical control (PF-2)
- Findings demonstrate that paltusotine favorably impacts acromegaly symptom severity regardless of the magnitude of the symptom effect, treatment history, or state of biochemical disease control

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DISCLOSURES

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Crinetics Pharmaceuticals