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Paltusotine Results in Improved Symptom Stability in Biochemically Controlled Acromegaly

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ABSTRACT

Patients who require medical treatment for acromegaly frequently report breakthrough symptom exacerbations despite ongoing treatment and apparent biochemical control of the disease. We hypothesized that patients switched from injected long-acting octreotide or lanreotide (SRLs) to once-daily oral paltusotine would experience maintenance of biochemical and symptom severity control with reduced frequency of symptom exacerbations. PATHFNDR-1 was a previously reported 36-week randomized, placebo-controlled, double-blind, phase 3 trial of 58 patients with

IGF-I ≤ULN on treatment with SRLs. Retrospective analyses of daily Acromegaly Symptom Diary (ASD) data from PATHFNDR-1 were performed. The ASD measured the severity of 7 core and 2 exploratory acromegaly symptoms on 0-10 scales based on 24-hour recall times. Symptom exacerbation rates were defined as at least 2-point increases for any individual symptom score, comparing a 2-day average to the previous 2-day average. This analysis included 22 patients randomized to paltusotine who had adequate ASD data during the screening and study treatment periods. Mean change from baseline in IGF-I after switching from SRL to paltusotine was 0.02 ± 0.03× ULN. The coefficient of variation (CV) of IGF-I levels during stable dosing with paltusotine was 10.8%. During the screening period, in which all patients were treated with SRLs, the mean symptom exacerbation rate was 30.2% ± 5.63 of days, or >2 events/week. This was similar to rates previously observed in a separate online daily symptom survey study of patients treated with SRLs in clinical practice. Despite no change in IGF-I control, symptom exacerbation frequencies declined progressively to 6.2% ± 1.56 of days during stable dosing with paltusotine ($p < 0.0001$ compared with SRLs). The reduction in individual symptom exacerbation frequencies with paltusotine treatment was consistent across all acromegaly symptoms assessed. Changes in frequency of symptom exacerbation were variable in patients switching from SRLs to placebo, 17/28 (61%) of whom required rescue prior to completing the treatment period of the study. Total symptom severity scores moderately correlated with symptom variability ($r=0.5$, $p=0.0004$). However, IGF-I levels did not correlate with symptom severity scores ($p=0.838$) or symptom variability ($p=0.834$). In conclusion, medically treated patients with acromegaly experience frequent symptom exacerbations, even when biochemically controlled. Switching from SRLs to paltusotine was associated with stable biochemical control and significantly reduced frequency of symptom exacerbations. A simple

daily symptom-assessment tool provided important information pertaining to acromegaly disease control that was not apparent from IGF-I measurements.

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Disclosures

DC reports serving as a consultant for Crinetics Pharmaceuticals.

TPQ, AC, YW, and AK are employees and shareholders of Crinetics Pharmaceuticals.