Efficacy and Safety of Palovarotene in Fibrodysplasia Ossificans Progressiva: A Randomized, Placebo-Controlled, Double-Blind Study

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Background and Objectives

Fibrodysplasia Ossificans Progressiva (FOP) (OMIM #135100) is an ultra-rare, severely disabling disease characterized by the occurrence of episodic flare-ups and the accumulation of heterotopic ossification (HO) in skeletal muscle and soft tissues. Progressive HO formation leads to restricted movement, physical disability, and early death.

Palovarotene (PVO) is an orally bioavailable retinoic acid receptor gamma (RARγ) agonist that demonstrated dose-dependent reductions in HO formation in a number of injury-based mouse models of HO. The primary objective of this Phase 2 study (NCT02190747) was to evaluate whether PVO administered at the time of a flare-up reduced HO formation relative to placebo in subjects with FOP.

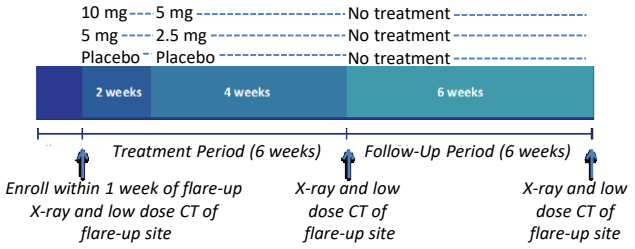
Main Eligibility Requirements

- Males/females at least 6 years old (and ≥20 kg) with clinically diagnosed FOP and R206H mutation.
- Onset of at least two of the six classic symptoms of a flare-up (pain, swelling, stiffness, decreased range of motion [ROM], stiffness, redness, warmth) confirmed by the Investigator within 1 week of starting study drug.
- Those with complete immobilization of the flare-up site or unable to undergo the imaging procedures were not eligible.

Study Design and Dosing Regimens

A multicenter, randomized, double-blind, sponsor-unblinded, placebo-controlled study in 40 subjects with FOP.

Two cohorts enrolled; dosing in Cohort 2 based on Data Monitoring Committee review of safety and efficacy findings in Cohort 1.



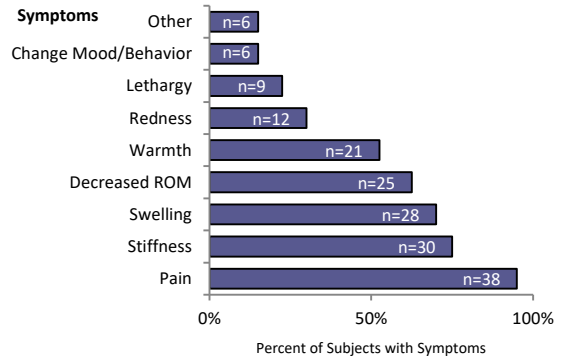
- Doses were adjusted according to subject weight in skeletally immature children.
- Presence and volume of new HO based on a Global Read process using pre-specified, standardized procedures (readers blinded to treatment).

Demographics and Baseline Disease

		Placebo (N=10)	5/2.5 mg (N=9)	10/5 mg (N=21)	All Subjects (N=40)
Age (years)	Mean ±SEM	21.2 ±4.3	17.9 ±2.9	22.8 ±2.2	21.3 ±1.7
	Min, max	9, 53	7, 29	9, 44	7, 53
Males	n (%)	3 (30.0)	3 (33.3)	12 (57.1)	18 (45.0)
Months since last flare-up	Mean ±SEM	5.4 ±1.4	18.7 ±12.3	14.1 ±5.6	13.0 ±4.0
	Min, max	0.4, 12.9	0.7, 114.6	0.2, 110.0	0.2, 114.6
Disposition					
Completed	n (%)	10 (100)	9 (100)	21 (100)	40 (100)

Results: Flare-up Characteristics

The most common flare-up locations were at the hip (40%), knee (23%), elbow (5%), and shoulder (5%).



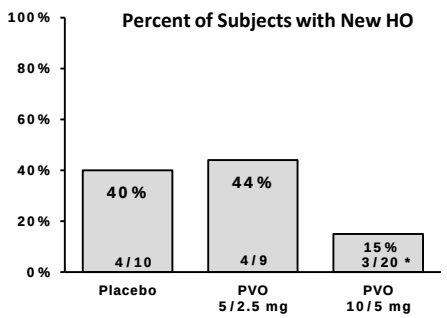
Most subjects (68%) reported at least four symptoms; pain (95%), stiffness (75%), and swelling (70%) were the most commonly reported.

The majority (90%) used steroids to treat flare-up symptoms.

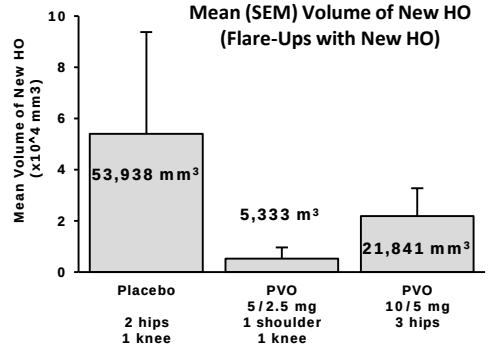
Results: Decrease in Heterotopic Ossification with Palovarotene Treatment

Primary endpoint was the proportion of responders (subjects with no or minimal new HO by x-ray) at Week 6: PLACEBO = 88.9%, PVO 5/2.5 mg = 88.9%, PVO 10/5 mg = 100%. X-ray was not sufficiently sensitive to detect new HO.

The results presented below are based on low-dose CT at Week 12.

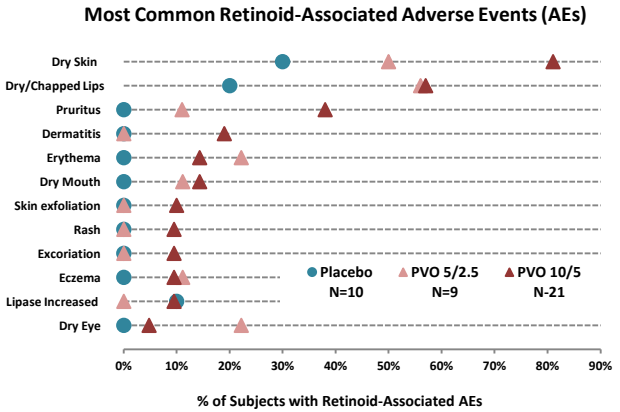


* Excludes one subject who was <80% compliant



Fewer subjects in the 10/5 mg regimen (65%) had new HO versus placebo at Week 12 (trend test p=0.0837).

There was a non-statistically significant reduction in mean HO volume of 60% in the 10/5 mg regimen versus placebo at Week 12.



Dry/Chapped Lips includes MedDRA preferred terms "Lips Dry" and "Lips Chapped"; Pruritus includes preferred terms "Pruritus" and "Pruritus Generalized".

Dose-related increases in retinoid-associated AEs were observed; most were mild or moderate in severity.

There were no discontinuations or other safety signals observed.

There was no effect of palovarotene on patient-reported functional outcomes in this short-term treatment study.

Urine and serum biomarkers (cartilage, bone, and inflammatory) did not predict flare-up outcome.

Conclusions

- Episodic treatment of a flare-up with palovarotene 10/5 mg resulted in a lower rate of HO occurrence and a reduction in HO volume.
- Palovarotene was well tolerated (no subjects discontinued treatment); retinoid-associated AEs can be treated prophylactically in most subjects.
- Results support the efficacy and tolerability of palovarotene as a potential treatment for FOP and its continued evaluation.
- Additional dosing regimens are being evaluated in the palovarotene Phase 2 program to determine the optimized regimen to be studied in a Phase 3 confirmatory study.

The authors thank the patient community, the International FOP Association who fostered their participation, and the clinical research coordinators and teams.

Presented at the Annual Meeting of the American Society for Bone and Mineral Research, 8-11 September 2017, Denver, CO