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

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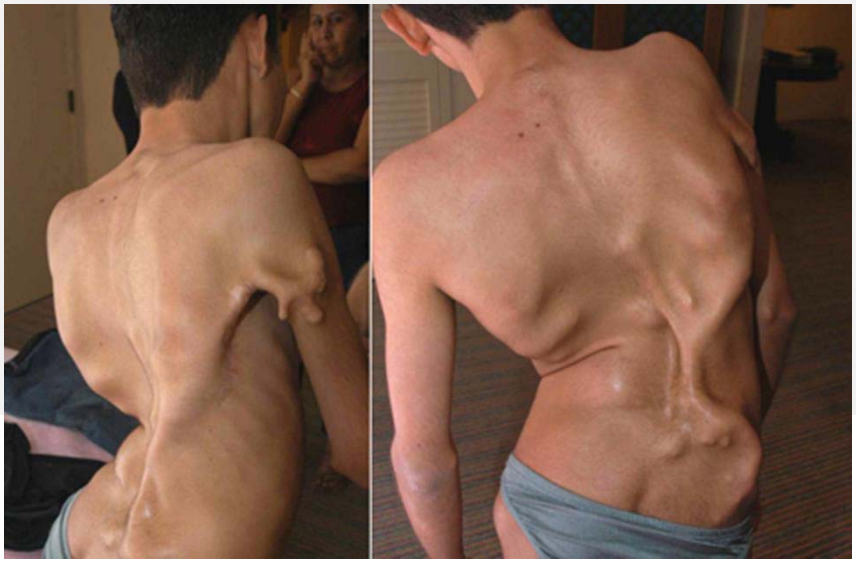
Fibrodysplasia Ossificans Progressiva (FOP) (OMIM #135100)

- Congenital disease caused by a single point mutation in the Acvr1/ALK2/BMP Type I receptor – 97% of patients have same mutation (R206H)
- Ultra-rare disease; prevalence of 1.3 per million (Baujat, 2017)
- Uncontrolled new bone formation often preceeded by ”flare-ups”
- No available therapies (steroids and NSAIDs used as palliative treatments)
- Immobility by mid-twenties

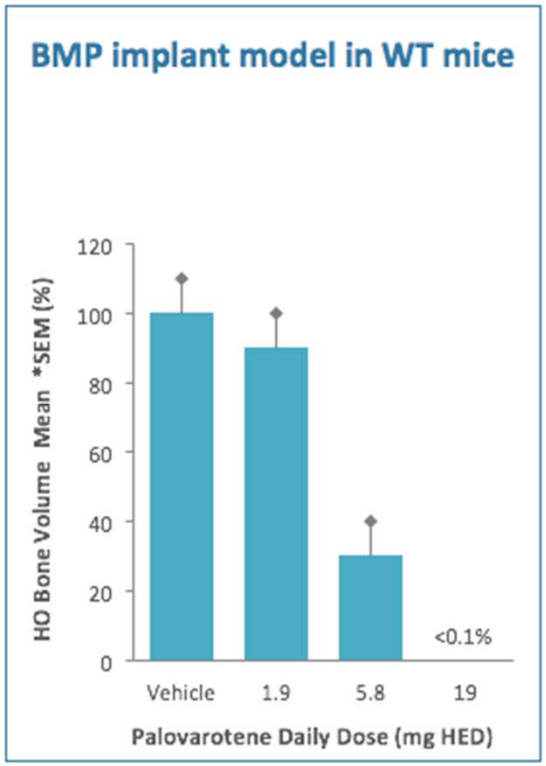
  (Connor, 1982)
- Premature death in 40’s

  (Kaplan, 2010)

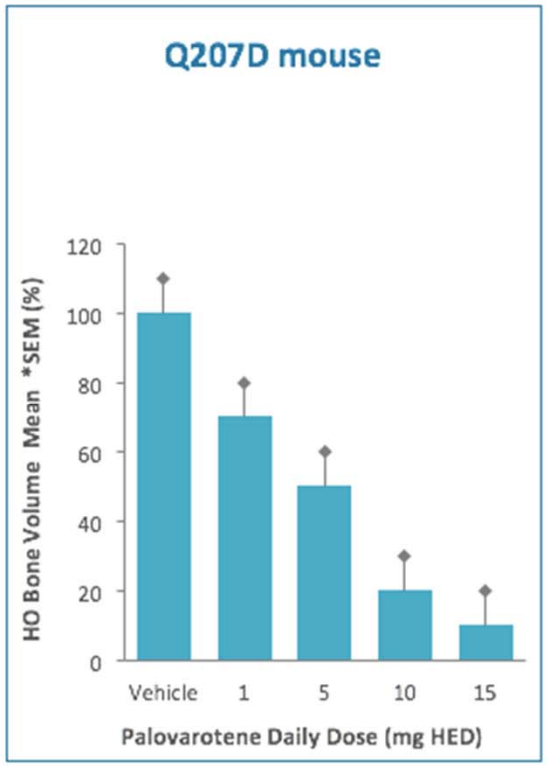


Palovarotene

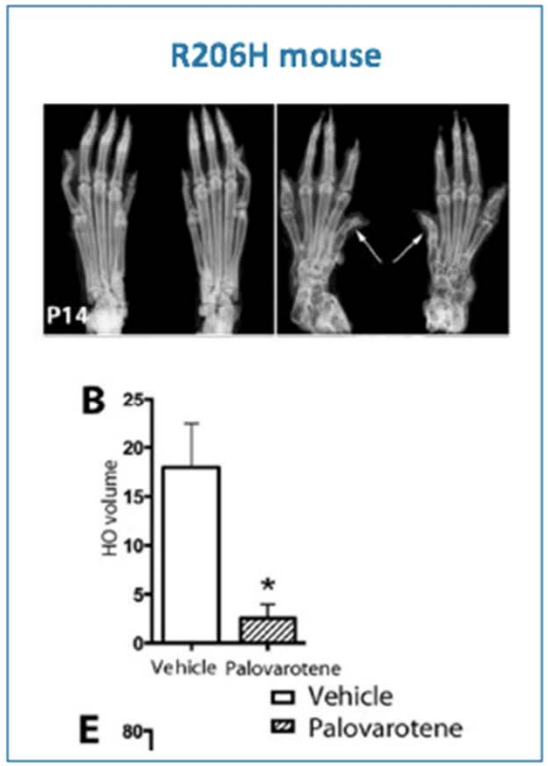
- An orally bioavailable retinoic acid receptor gamma (RARγ) agonist
- Demonstrated dose-dependent reductions in HO formation in three different mouse models



Shimono, 2011



Clementia data



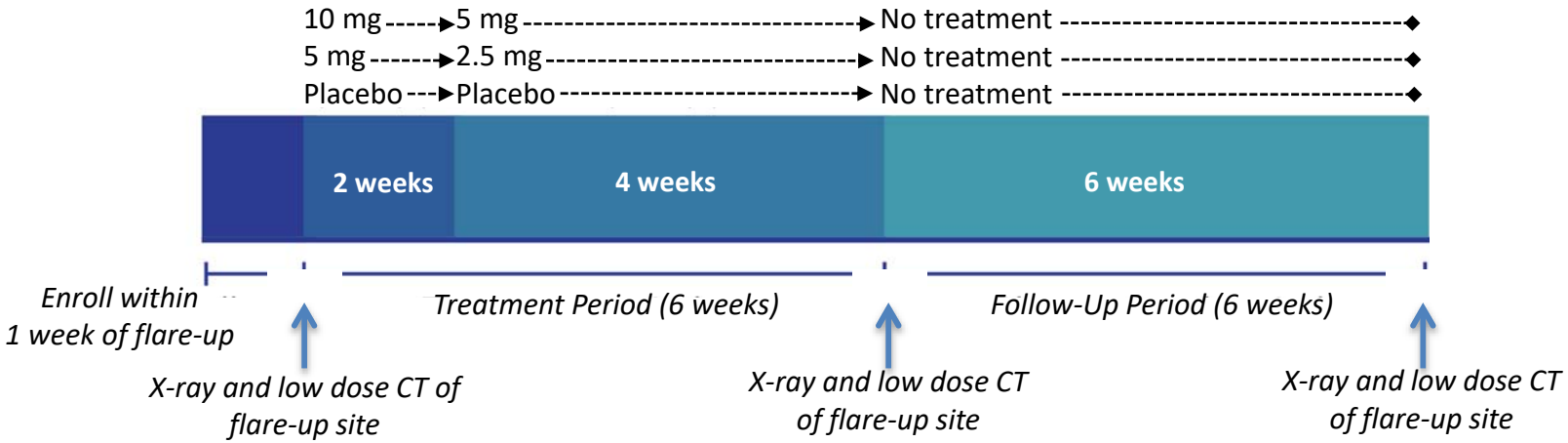
Chakkalakal, 2016

Primary Objective & Main Eligibility Criteria

- **Primary objective:** to evaluate whether palovarotene reduces HO formation relative to placebo in subjects with an active flare-up
- **Main eligibility criteria:**
  - Males and females at least 6 years old (and ≥20 kg) with clinically diagnosed FOP and R206H mutation
  - Onset of at least two of six classic symptoms of a flare-up (pain, swelling, erythema, decreased range of motion, stiffness, and 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



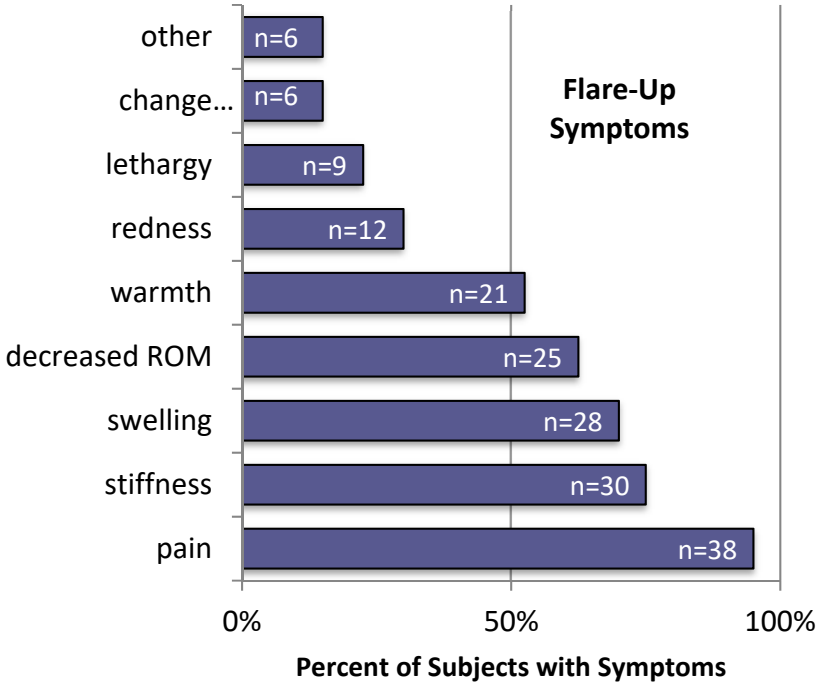
- Doses adjusted according to weight in skeletally immature subjects
- Incidence and volume of new HO based on a Global Read process using pre-specified, standardized procedures (readers blind to treatment)

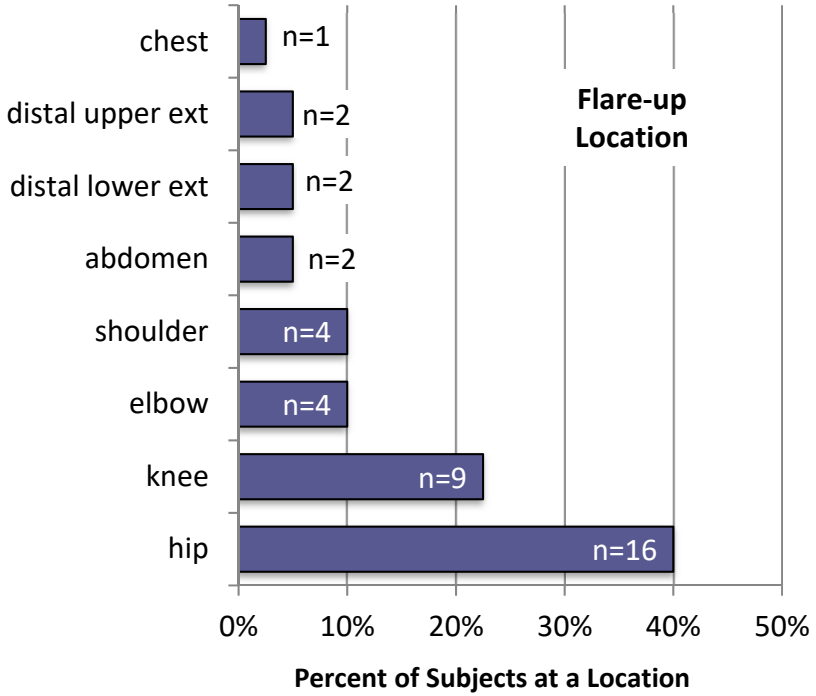
Demographics and Baseline Disease

		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)

- Overall mean age was 21 years (range of 7 to 53 years)
- Demographics were similar across treatment groups
- All subjects completed the study

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

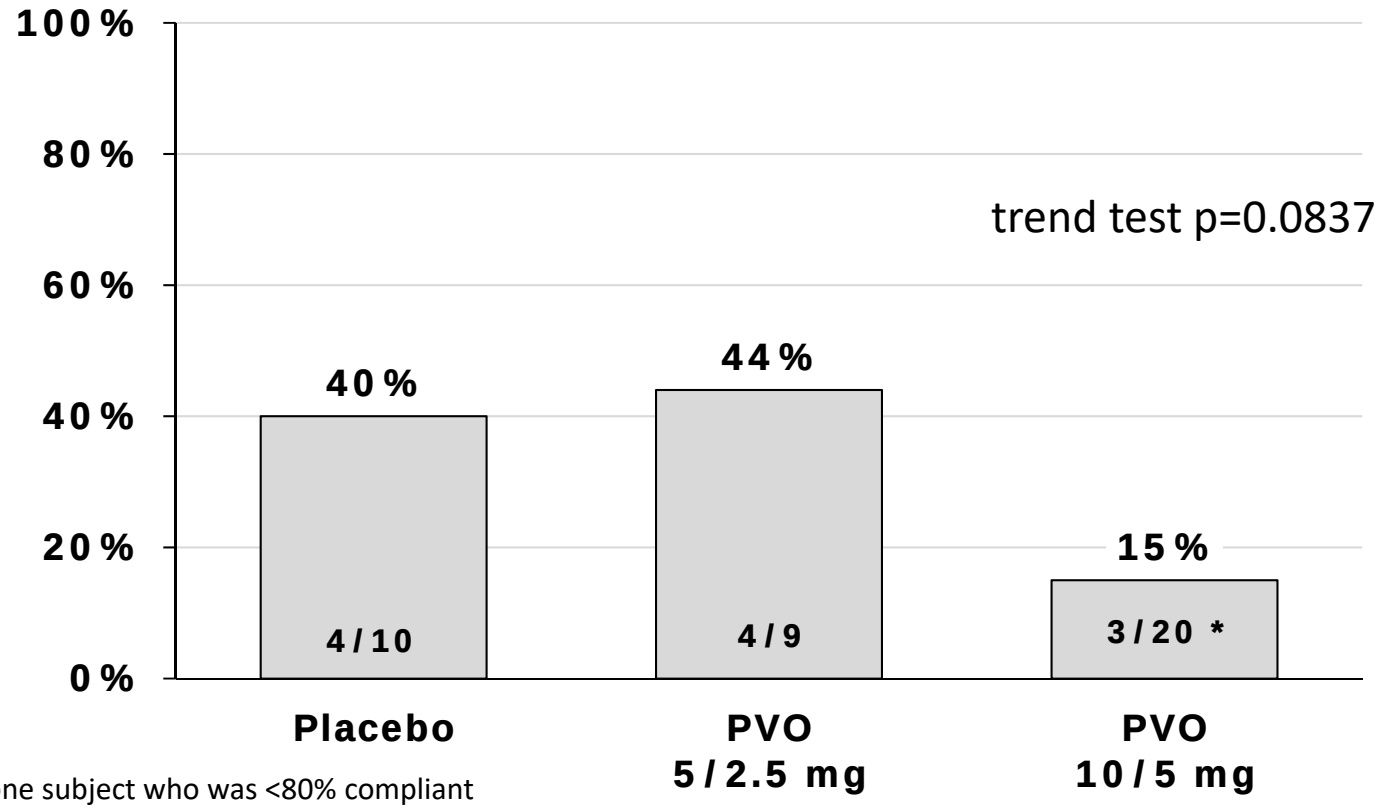
Results: Primary Endpoint

- Primary endpoint: incidence of responders (subjects with **no or minimal new HO** by x-ray) at Week 6 demonstrated that x-ray was not sufficiently sensitive to detect new HO

- The following slides shows the incidence and volume of **any new HO** by low-dose CT scan at Week 12

65% fewer subjects in the 10/5 mg regimen had new HO versus placebo

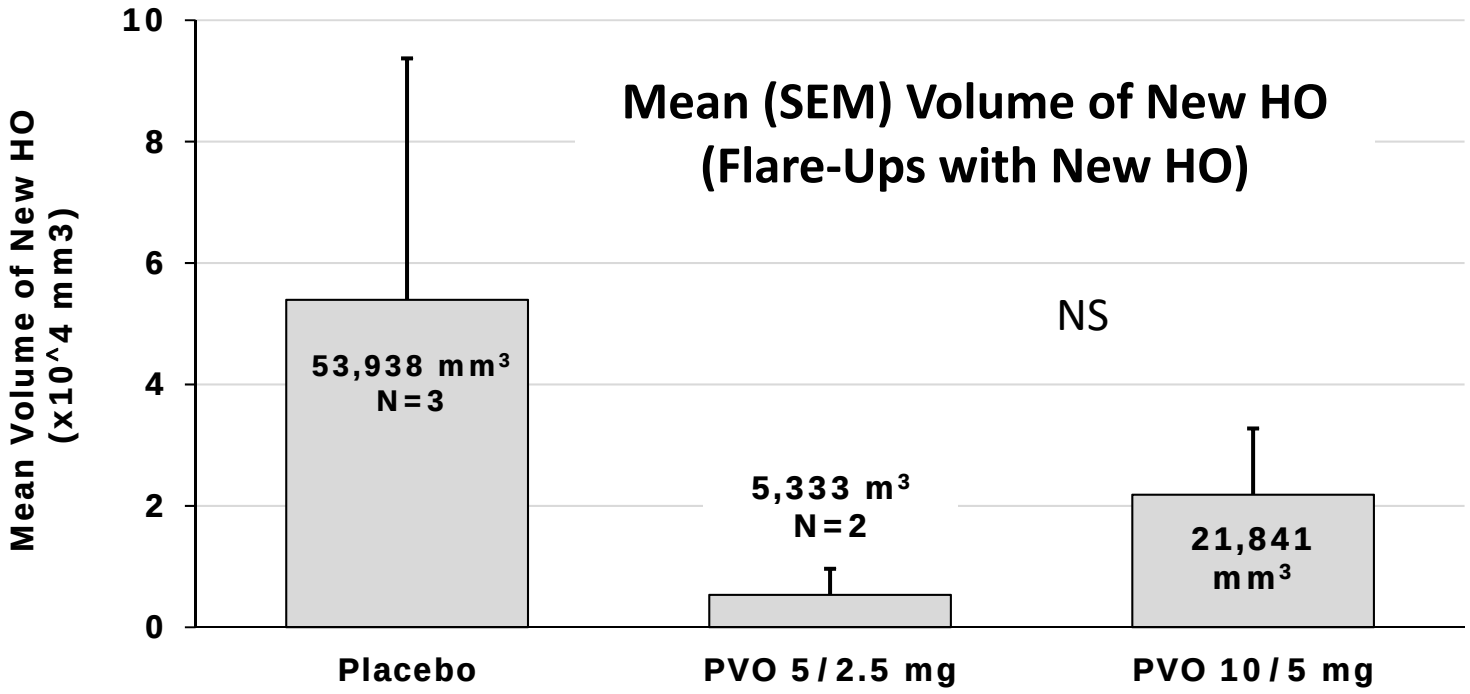
Percent of Subjects with new HO by Low-Dose CT Scan at Week 12



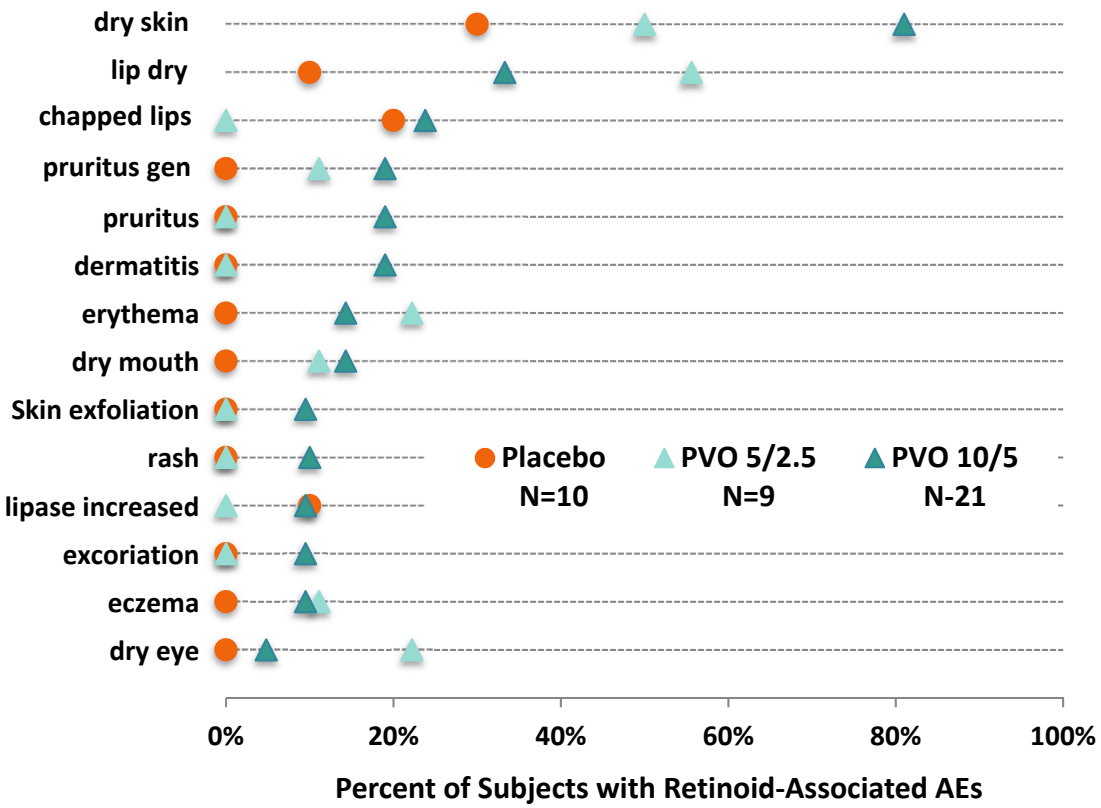
* Excludes one subject who was <80% compliant

60% reduction in mean HO volume in the 10/5 mg regimen versus placebo

New HO Volume by Low-Dose CT Scan at Week 12



Safety: Retinoid-Associated Adverse Events



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

There were no discontinuations

No other safety signals observed

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 relative to placebo
- Palovarotene was well tolerated; 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 were evaluated in the palovarotene open-label extension study
- The optimal regimen is being evaluated in the Phase 3 MOVE study, to be initiated 2017

Acknowledgements

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