Palovarotene Reduces New Heterotopic Ossification in Fibrodysplasia Ossificans Progressiva

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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) that leads to restricted movement, physical disability, and early death.

Palovarotene (PVO), an orally bioavailable retinoic acid receptor gamma agonist, has demonstrated dose-dependent reductions in HO formation in a number of injury-based mouse models of HO. PVO is an investigational drug under evaluation for its safety and efficacy in clinical studies. This analysis of clinical data, derived from the Phase 2 interventional studies (NCT02190747 and NCT02279095 [NCT02979769 in France]) and a natural history study (NHS; NCT02322255), evaluated the ability of different PVO treatment regimens to reduce new HO formation as assessed by low dose computed tomography (CT) of the flare-up site 12 weeks after onset.

Clinical Data Sources

A total of 148 prospectively assessed flare-ups with evaluable HO volume data were obtained from subjects with FOP (due to the R206H mutation). Flare-ups (excluding those in the jaw and upper were located in appendicular or axial body regions back) and characterized by two or more symptoms (pain, swelling, stiffness, decreased range of motion, redness, or warmth). The analysis groups included:

Comparator Group

- Thirty-nine untreated flare-ups from the NHS
- Ten placebo-treated flare-ups

Palovarotene Treatment Groups

- Forty-eight flare-ups treated with the PVO 10/5 mg regimen (10 mg for 2 weeks followed by 5 mg for 4 weeks; 6 weeks total treatment)
- Eighteen flare-ups treated episodically with the PVO 20/10 mg regimen (20 mg for 4 weeks followed by 10 mg for 8 weeks; at least 12 weeks total treatment)
- Thirty-three flare-ups treated with the PVO chronic/flare-up regimen (5 mg daily with increased dosing for an eligible flare-up to 20 mg for 4 weeks followed by 10 mg for 8 weeks or longer; at least 12 weeks total treatment)

Statistical Analyses

The volume of new HO at Week 12 was compared between palovarotene- and placebo/untreated subjects. Comparisons utilized ANOVA with 95% bias-corrected and accelerated (BCa) bootstrap CIs, and approximate p-values. Covariates were selected based on analysis of untreated NHS flare-ups and placebo-treated flare-ups in the palovarotene studies.

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Demographics and Flare-Up Characteristics

		Placebo/ Untreated	PVO 10/5 mg	PVO 20/10 mg	Chronic/ Flare-Up
Number of subjects		41	27	12	23
Age (years)	Mean ±SD	17.6 ±10.5	23.3 ±9.5	13.6 ±7.3	25.0 ±8.4
	Median (range)	14.0 (4-53)	22.0 (9-44)	10.5 (7-34)	25.0 (13-46)
Males	n (%)	20 (49)	14 (52)	4 (33)	8 (35)
Number of imaged flare-ups		49	48	18	33
Treated with steroids	n (%)	41 (84)	44 (92)	15 (83)	30 (91)
Baseline edema	n (%)	26 (62)	15 (44)	12 (71)	22 (69)
Flare-up symptoms	Mean ±SD	3.8 ±1.8	4.0 ±1.5	4.5 ±2.1	4.0 ±1.6
	Median (range)	4.0 (1-8)	4.0 (2-8)	4.0 (2-9)	4.0 (2-8)
≥4 symptoms	n (%)	26 (53)	28 (58)	10 (56)	21 (64)
Symptoms	Pain, n (%)	43 (88)	47 (98)	18 (100)	31 (94)
	Swelling, n (%)	37 (76)	34 (71)	12 (67)	25 (76)

- **The youngest subject treated in the Phase 2 studies was 7 years old; the youngest subject with flare-up imaging was 4 years old (in the NHS).**
- **Most flare-ups were treated with steroids.**
- **The majority of flare-ups had baseline edema (as assessed by MRI or US), except for the 10/5-mg palovarotene regimen.**
- **Most flare-ups were characterized by at least four symptoms; pain and swelling were the most common.**
- **The most frequent flare-up locations were at the hips and shoulders.**

Safety of Palovarotene

Treatment-Emergent Adverse Events

Treatment-Emergent Adverse Events (TEAE) MedDRA higher level term	Placebo (N=10)	5 mg (N=46)	10/5 mg (N=27)	20/10 mg (N=36)
Subjects with at least one TEAE	**100%**	**98%**	**100%**	**94%**
Lacrimal disorders	0%	9%	19%	19%
Diarrhea	10%	26%	15%	8%
Nausea & vomiting symptoms	40%	33%	33%	28%
Oral dryness & saliva altered	10%	39%	67%	47%
Oral soft tissue disorders	20%	15%	26%	22%
Febrile disorders	10%	13%	7%	22%
General signs & symptoms	30%	44%	52%	64%
Upper respiratory tract infections	0%	48%	30%	31%
Non-site specific injuries	0%	30%	19%	22%
Skin injuries	0%	26%	15%	36%
Joint related signs & symptoms	60%	50%	56%	36%
Musculoskeletal & connective tissue pain & discomfort	30%	44%	37%	56%
Headache	30%	20%	33%	22%
Urinary abnormalities	10%	11%	33%	19%
Alopecias	0%	33%	4%	28%
Dermal & epidermal conditions	40%	76%	89%	75%
Dermatitis & eczema	0%	24%	26%	22%
Erythemas	0%	24%	22%	53%
Exfoliative conditions	0%	15%	7%	44%
Pruritus	0%	37%	52%	67%
Rashes, eruptions, & exanthems	0%	30%	15%	39%

- **There were dose-related increases in adverse events (AEs); most were mild or moderate in severity.**
- **One subject discontinued for an AE (infected toe).**
- **Ten of 35 subjects had at least one dose-reduction, mainly due to retinoid-associated AEs; most (68%) during 20-mg dosing.**
- **Serious AEs were reported by 11 subjects administered palovarotene (three possibly related: FOP flare-up, myoclonus, and ankle fracture). There were no deaths.**
- **There were no apparent effects on laboratory or ECG findings; or on growth in skeletally immature subjects.**

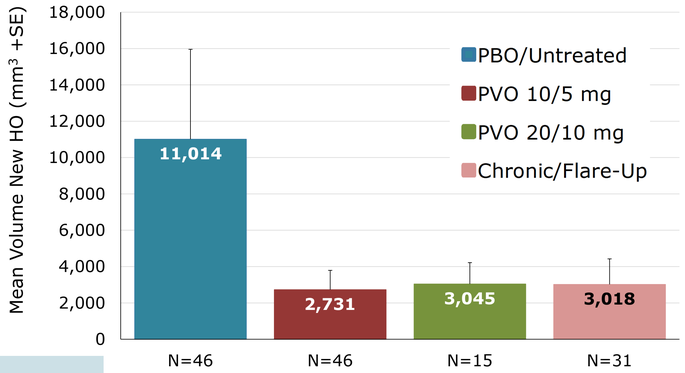
Palovarotene Reduced New HO Volume and the Incidence of Flare-Ups With New HO

Incidence of Flare-Ups with New HO

	Placebo/ Untreated	PVO 10/5 mg	PVO 20/10 mg	Chronic/ Flare-Up
All evaluable flare-ups	17/49 (35%)	14/48 (29%)	7/17 (39%)	7/33 (21%)
Flare-ups w/ baseline edema	11/26 (42%)	9/15 (60%)	6/12 (50%)	6/22 (27%)

Denominators are the number of evaluable flare-ups at 12 weeks.

Mean Volume of New HO at Week 12



N = number of flare-ups with evaluable HO volume at Week 12.

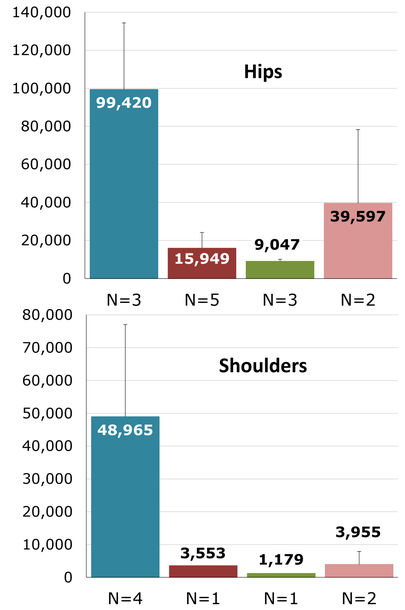
Statistical Results for New HO Volume Analyses

Method	Group	Treatment Effect Estimate	95% CI	p-value[1]
ANOVA with BCa bootstrap and covariate adjustment[2]	PVO 20/10 mg	-12597	-27379, -2253	0.02
	PVO 10/5 mg	-9084	-20622, -203	0.05
	Chronic/Flare-up	-8326	-21736, 2873	0.16
ANOVA with BCa bootstrap	PVO 20/10 mg	-7969	-20129, 858	0.09
	PVO 10/5 mg	-8222	-20033, 275	0.06
	Chronic/Flare-Up	-8090	-20452, 2093	0.12

1 P-values are approximated based on the BCa bootstrap confidence intervals.

2 Covariates included are gender, steroid use, age, and flare-up location (hip versus non-hip).

Mean Volume at Week 12 in Flare-Ups with New HO (Hip and Shoulder Locations Only)



N = number of flare-ups with evaluable HO volume at Week 12 in flare-ups with new HO.

Conclusions

- **Episodic administration of palovarotene at the time of a flare-up resulted in meaningful reductions in new HO volume (>70%) relative to untreated flare-ups. In spite of small sample sizes not powered for statistical significance:**
  - **✓The reduction with the episodic 20/10-mg regimen was statistically significant (p=0.02).**
  - **✓Flare-ups with baseline edema had poorer outcomes following the 10/5-mg regimen compared to the chronic/flare-up regimen.**
- **Palovarotene was tolerated; dose-related increases in AEs were observed; retinoid-associated AEs can be treated prophylactically in most subjects.**
- **Results support further evaluation of palovarotene as a potential treatment for FOP that that could change the trajectory of the disease.**
- **The impact of the chronic/flare-up regimen on whole body CT HO volume is being evaluated in the Phase 3 MOVE Trial (NCT03312634).**

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