Palovarotene Reduces New Heterotopic Ossification in Fibrodysplasia Ossificans Progressiva

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Background and Objectives
Fibrodysplasia Ossificans Progressiva (FOP) [OMIM #131000] 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 FOP. 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 [NCT02979719 in France] and a natural history study (NHS); NCT03232225), 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.

Demographics and Flare-Type Characteristics

<table>
<thead>
<tr>
<th>flare type</th>
<th>Placebo/untreated</th>
<th>PVO 10/5 mg</th>
<th>PVO 20/10 mg</th>
<th>Chronic/flare-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palovarotene</td>
<td>27%</td>
<td>29%</td>
<td>21%</td>
<td>27%</td>
</tr>
<tr>
<td>Placebo</td>
<td>35%</td>
<td>35%</td>
<td>30%</td>
<td>29%</td>
</tr>
<tr>
<td>untreated</td>
<td>35%</td>
<td>35%</td>
<td>30%</td>
<td>29%</td>
</tr>
</tbody>
</table>

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, altered range of motion, redness, or warmth). The analysis groups included:

- Thirty-nine untreated flare-ups from the NHS.
- Ten placebo-treated flare-ups.
- Eighteen flare-ups treated episodically with the PVO 20/10 mg 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).
- 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)
- Thirty-three 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)

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. There were dose-related increases in adverse events (AEs); most were mild or moderate in severity.

Conclusions
- Palovarotene was well 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 could change the trajectory of the disease.

The authors wish to thank the patient community, the International FOP Association who shared their experiences, and the clinical research coordinators and teams who managed the study.